

## Clinical Trials Update

### AD-1 Trial Update

Depression continues to be the most difficult phase of bipolar illness to eliminate. Despite the use of many different types of available pharmaceuticals, the first 258 patients in the Stanley Foundation Bipolar Network (SFBN) to be followed prospectively for one year (on average) continued to have depressive symptoms for about four months (121 days) per year compared with about 1½ months (44 days) of manic symptoms. Two-thirds of the patients continued to have substantial impairment from their bipolar illness, whereas only one-third were only mildly ill or completely well.

#### SFBN Antidepressant Trial (AD-1)

In the SFBN, as reported in previous BNN issues, many patients are currently enrolled in a 10-week, placebo-controlled trial (AD-1) of three different antidepressants with different mechanisms of action as adjuncts to mood stabilizers: bupropion (Wellbutrin®), sertraline (Zoloft®), and venlafaxine (Effexor®). Those patients who respond well enough to one of the three antidepressants may enter a 1-year continuation phase. In a previous BNN issue (Vol. 6, Issue 2, 2000) we reported that in 100 randomized trials, 12% showed hypomanic or manic switches in the acute phase, and another 12% switched in the continuation phase. We also reported that overall antidepressant response was about 33%.

Randomized comparison of these three antidepressants has now been completed in 175 acute (10-week) trials in 127 patients, although the results have not yet been unblinded to assess each drug separately. Over 50% (67/127) responded well enough to enter a 1-year continuation to determine the persistence of the antidepressant effect (episode prevention) and the liability for inducing mania (a significant risk with antidepressant treatment).

#### Hypo/Mania Induction Rate

In the acute phase, switching into hypomania or mania has been observed in 32 (18.3%) of 175 antidepressant exposures when these agents were added to ongoing treatment with one or more mood stabilizers (Post et al., 2001; *Bipolar Disorders*, in press). Only one-half (about 9%) of these cases represented episodes with more than mild hypomanic symptoms, i.e., of moderate or greater severity.

In the continuation phase, another 20.5% of the patients showed switches into either hypomania (11%) or mania (9.5%). Thus, significant dysfunction from mania was observed in 12.6% of the patients in the acute trials and in another 9.5% in the continuation phase trials. These episode switching totals in mania (22.1%) and hypomania (23.6%) suggest that some caution continues to be required in the use of these and related second-gen-

eration antidepressants in bipolar illness. It should also be noted that these switch rates are slightly higher than the rates reported after only the first 100 trials. The data suggest that even when these three antidepressants are used in conjunction with mood stabilizers, one in five bipolar outpatients will experience a manic episode.

#### Antidepressant Response Rate

Acute antidepressant response to these agents was observed in approximately 50% of the patients acutely and in another 43% in the continuation phase. Together with the moderate switch rate data noted above, these randomized controlled data continue to suggest that, as with the first-generation tricyclics and monoamine oxidase inhibitors (MAOIs), the second-generation serotonin selective reuptake inhibitors (SSRIs) (represented by sertraline), dopamine and norepinephrine-active antidepressants (represented by bupropion), and the mixed serotonin/norepinephrine reuptake inhibitors (SNRIs) (such as venlafaxine) have some switch liability, even when used in conjunction with mood stabilizers. However, whether this rate is higher than the rate expected from the natural course of illness remains to be determined.

*(Continued on page 2)*

### BNN CHANGES

**Publication Schedule:** The BNN will be published three times a year (Spring, Summer, and Fall), instead of quarterly, beginning with this issue. There will be no Winter 2000 issue. We will try to expand the content of the newsletter to cover the same amount of material.

**Contact Information:** The Stanley Foundation Bipolar Network is no longer operating a 1-800 number to call and request the BNN. If you would like to request a subscription or change your address, please do so by calling (301) 435-2529, or contact us using the information on page two.

### In This Issue:

**Publication Update:**

*NDMDA Consensus Conference on mood disorders in children and adolescents.....3*

**Meeting Highlight:**

*Second European Stanley Foundation Conference on Bipolar Disorder.....4*

**Life Chart Highlight:**

*Antidepressant response with switches into hypomanias and mania.....6*

### Preliminary Schema for Antidepressant (AD) Use in Depression Breaking Through One or More Mood Stabilizers (MS)

#### I. (A). Non-rapid cycling

Add AD

#### (B). Rapid cycling or

##### polyphasic episode

- Add 2nd MS, especially lamotrigine
  - Add 3rd MS
    - Add AD

#### (C). Adjuncts for:

##### Sleep, Anxiety, Agitation:

- High potency benzodiazepines
- Gabapentin

##### Memory:

- Donepezil
- Calcium channel blocker?

##### Alcohol:

- Naltrexone
- Acamprosate

#### II. If Non-response to MS + AD

- Lithium Augmentation
- Thyroid Augmentation
- Switch AD
  - Add Lamotrigine
    - MAOI
      - Electroconvulsive Therapy
      - Vagus Nerve Stimulation

#### III. Antidepressant Adjuncts

- Sleep Deprivation
- High Lux Light Therapy
- Omega-3 Fatty Acids
- Ascorbate
- Folate

## Clinical Trials Update

(Continued from page 1)

### Treatment Alternatives

Response rates and switch rates to the individual drugs require further direct study. One promising alternative approach is with the drug lamotrigine (Lamictal®). As noted previously in the *BNN*, response rates of about 50% have been observed in blind monotherapy trials (Calabrese et al., 1999; *J Clin Psychiatry* 60: 79–88; Frye et al., 2000; *J Clin Psychopharmacol* 20: 607–614), with low rates of switching into hypomania or mania in each study (Calabrese et al., 5.4%; Frye et al., 6.1%). One way of sequencing some of the initial alternative options is outlined in the table above. The main difference in this suggested approach is that it is based on the patient's prior course of illness and rapidity of cycling. In those patients without a rapid cycling pattern, an antidepressant would be added to the mood stabilizer regimen (because of the low risk of a manic switch). In those with more rapid or continuous cycling frequencies, the addition of another mood stabilizer would be recommended (because of the higher risk of switching and cycling acceleration with antidepressants in these patients). If this did not prove effective, an antidepressant and, subsequently, other adjunctive approaches as noted in the table, could then be added. ■

## Research Update

(Continued from page 3)

also document a 10-fold increase risk for BPD in boys and girls with ADHD relative to age- and gender-matched control subjects without ADHD.

"The high comorbidity between BPD and CD [*Conduct Disorder*] is not surprising considering that juvenile mania is frequently mixed (dysphoric) and commonly associated with 'affective storms,' with prolonged and aggressive temper outbursts.... Although limited, a recent literature documents a significant overlap between BPD and ODD [*Oppositional Defiant Disorder*]."

**Thomas J. Spencer, Joseph Biederman, Janet Wozniak, Stephen V. Faraone, Timothy E. Wilens, and Eric Mick,**

Massachusetts General Hospital and Harvard Medical School

"*Parsing Pediatric Bipolar Disorder from its Associated Comorbidity with the Disruptive Behavior Disorders*"

"A meta-analysis of all available placebo-controlled trials ( $n = 12$ ) of tricyclics (TCAs) in patients between 6 and 18 years concluded that the difference between active treatment and placebo is too small to be clinically significant.... Thus, at this time, SSRIs are the initial medication choice in this age group.

"More than 400 case reports and small trials have been reported on the treatment of bipolar children and adolescents.... Positive reports have been published for lithium, divalproex, and carbamazepine; however, many reports have been based on retrospective chart reviews and small open-label studies... few placebo-controlled trials for bipolar, manic or mixed, in children and adolescents have been conducted."

**Graham J. Emslie and Taryn L. Mayes,**

University of Texas Southwestern Medical Center

"*Mood Disorders in Children and Adolescents: Psychopharmacological Treatment*"

"To date there are six controlled studies of CBT [*Cognitive Behavioral Therapy*] interventions with children. All are school-based studies of children with self-reported (but not with diagnosed) depression. Five of the six support the efficacy of CBT in reducing depressive symptoms. There is considerable variation in the nature of the CBT interventions.

"There are nine controlled or comparative studies of CBT for adolescent depression, seven of which found CBT efficacious at the end of acute treatment. Most include adolescents with diagnosed depressive disorders, and only one was conducted in a school setting.

"IPT [*Interpersonal Psychotherapy*] has demonstrated efficacy in two controlled trials, but long-term follow-up data are not yet available.

"...there is a question about whether CBT, medication, or combined treatment is more efficacious with depressed teenagers or with certain subgroups of these young people."

**John F. Curry,** Duke University Medical Center

"*Specific Psychotherapies for Childhood and Adolescent Depression*"

## Bipolar Network News

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The *BNN* is published three times a year by an international group of investigators working with patients with bipolar disorder to better understand the long-term course and treatment of the illness. The 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 editor, and do not necessarily represent the views of the Stanley Foundation or the National Institute of Mental Health. For any comments or suggestions you may have, or to be placed on the mailing list, please contact us at:

### Bipolar Network News

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## Research Update

### NDMDA Consensus Conference: "The Unmet Needs in Diagnosis and Treatment of Mood Disorders in Children and Adolescents"

Published in *Biological Psychiatry*, Vol. 49, Number 12, June 15, 2001



"A recent National DMDA [*Depressive and Manic-Depressive Association*] survey of people with bipolar disorder indicated that the average length of time from onset of symptoms to correct diagnosis was 10 years.

"The National DMDA-sponsored conference on "Unmet Needs in Diagnosis and Treatment of Mood Disorders in Children and Adolescents" was organized with a goal of formulating a consensus statement that would be perceived as a strongly worded 'call to action,' and with the hope that the various interdependent organizations and individuals with the knowledge and ability to effect change would contribute in their area in answer to the call."

**Lydia Lewis**, National DMDA

*"Unmet Needs in Diagnosis and Treatment of Mood Disorders in Children and Adolescents"*

"An area that we pediatricians are called upon more and more is to treat mood disorders.... ADHD is also aligned with mood disorders and is the most common neurobehavioral disorder of childhood. Earlier it was a condition treated only by child psychiatrists, but now it is treated also by pediatricians who have been chosen by patients as there is such a long wait for them to see a child psychiatrist.

"...because of the shortage of child psychiatrists, some pediatricians are treating depression with antidepressant medication under the supervision of adult psychiatrists."

**Dr. Ordean L. Torstenson**, Pediatric Generalist

*"The Treatment of Mood Disorders in Children and Adolescents by General Pediatricians"*

"Research over the past 2 decades...has clearly demonstrated that children are capable of experiencing episodes of depression that meet standard DSM-IV criteria for major depressive disorder (MDD).

"Epidemiologic studies estimate the prevalence of depression is 2% in children...and 5 to 8% in adolescents.... Within 5 years of the onset of MDD, 70% of depressed children and adolescents will experience a recurrence.

"Despite similarities in the clinical picture and longitudinal course of MDD in children, adolescents, and adults...there are notable differences in the neurobiological correlates and treatment response of depressed patients in these different age cohorts that warrant careful consideration. Most notably, depressed children and adolescents do not show evidence of hypercortisolemia as is frequently reported in adults...and depressed children and adolescents fail to respond to tricyclic antidepressants..."

**Joan Kaufman, Andres Martin, Robert A. King, and Dennis Charney**,  
Yale University Department of Psychiatry

*"Are Child-, Adolescent-, and Adult-Onset Depression One and the Same Disorder?"*

"Community epidemiologic surveys of self-reported depression symptom scales find that between 20 and 50% of children and adolescents exceed conventionally established adult cut points for clinically significant depression.... Point prevalence estimates of major depression based on diagnostic interviews are considerably lower than the rates based on self-report depression symptom scales—in the range

of 1%...to 6%.... The discrepancy between self-report symptom scores and diagnostic interview classifications might be explained by overreporting of mild mood difficulties or by the fact that a substantial proportion of young people might suffer from subthreshold depression.

"Uncertainty regarding the prevalence of mania among children and adolescents is due to divergence of opinion about whether youngsters with maniclike symptoms should be counted and, if so, the criteria by which they should be defined as cases.

"...parental psychopathology is the strongest predictor of the subsequent onset of child and adolescent depression and mania, although parental mania is much more specific in predicting offspring mania...than is parental depression in predicting offspring depression."

**Ronald C. Kessler, Shelli Avenevoli, and Kathleen Ries Merikangas**,

Harvard Medical School and Yale University School of Medicine  
*"Mood Disorders in Children and Adolescents: An Epidemiologic Perspective"*

"...children may be better off as research subjects than as patients, particularly when the treatments being used have not been examined in well-designed studies that are relevant to the particular children involved.

"Standard treatments should not be assumed to be safe or effective if they have not been subject to well designed studies. Examples abound of long established treatments that were later abandoned when shown to be harmful or ineffective.

"Research involving children with mood disorders should generally offer a reasonable prospect of benefit to all those involved, unless the risks are minimal. While federal regulations require that 'benefit' be restricted to medical benefits, from an ethical perspective there may be indirect benefits that could outweigh the burdens."

**Norman Frost**, University of Wisconsin Medical School Program in Bioethics  
*"Ethical Issues in Research and Innovative Therapy in Children with Mood Disorders"*

"Reliable assessment of depression in children requires gathering information from both the parent and child, as well as from all other available information. The methodology for obtaining information from the child must be adapted to reword and better obtain information in those domains that are inherently difficult for children, including questions about internal affect state and questions requiring judgment. Because child depression is highly comorbid with other psychiatric disorders, including anxiety, attention-deficit/hyperactivity disorder (ADHD), and conduct disorder (CD), it is imperative that these and other psychiatric disorders be simultaneously assessed. "

**Neil D. Ryan**, University of Pittsburgh  
*"Diagnosing Pediatric Depression"*

"A consistent and bidirectional overlap between BPD and ADHD has been reported in the literature. Systematic studies of children and adolescents with a diagnosis of BPD show that rates of ADHD range from 60% to 90% in pediatric patients with mania.... Studies of ADHD

*(Continued on page 2)*

## Meeting Highlights



Second European Stanley Foundation Conference on Bipolar Disorder  
Amsterdam, The Netherlands, September 21–22, 2000

In the last issue of the *BNN*, we featured highlights of the satellite symposium on bipolar disorder in children and adolescents held in Rotterdam, The Netherlands, September 20, 2000. In this issue, we present highlights of the larger Second European Stanley Foundation Conference on Bipolar Disorder, of which the satellite symposium was a part.

### Anticonvulsants

Dr. B. Amann et al. from the University of Munich and University of Freiburg, Germany, found in two

separate studies that slow-release **valproate** (Depakote®) administered once daily was an adequate and well-tolerated treatment for both acute mania and continuation therapy. One group of 11 acutely manic patients and another group of 10 subsyndromal patients recovering from mania benefited just as much from once-a-day dosing as from twice-

a-day dosing. Once-a-day treatment could help increase compliance, particularly in mania, and smooth the transition from acute to continuation therapy.

- Even regular valproate can be given in a single nighttime dose for most individuals.

Dr. Y. Bersudsky and colleagues at the Mental Health Center, Beersheva, Israel, performed a double-blind controlled trial of the anticonvulsant diphenylhydantoin (also called **phenytoin**) for five weeks versus placebo in patients with mania or schizoaffective mania. All patients received haloperidol (Haldol®) as well.

In 30 patients who have completed the study, significant therapeutic benefit for phenytoin over placebo was found on three different rating scales, beginning on week three.

A number of investigators reported results from studies of the drug **topiramate** (Topamax®). Dr. H. Grunze et al. from the University of Munich and the University of Freiburg, Germany, conducted an on-off-on study of adjunctive topiramate in 10 manic patients. Topiramate was given in conjunction with mood stabilizers for 10 days, then discontinued for six days, and then reintroduced, in doses from 25–200 mg/day. Eight of 10 patients showed a good antimanic response during the initial trial, seven patients got worse when topiramate was discontinued, and all seven improved with the reintroduction of topiramate, demonstrating clear therapeutic efficacy.

- These data provide additional support for the potential antimanic and mood stabilizing effects of topiramate, first suggested from the open case studies of adjunctive topiramate in the scientific literature.

Dr. R. McIntyre and colleagues at the Centre for Addiction and Mental Health, Toronto, compared **topiramate** (50–300 mg/day) to **bupropion SR** (Wellbutrin®, 100–400 mg/day) for eight weeks as adjuncts to mood stabilizers in 26 bipolar outpatients with major depression. Both bupropion SR and topiramate showed a significant reduction in depressive symptoms and were not statistically different from each other. No patients switched into a manic episode on either treatment.

- These preliminary results suggest that topiramate may have comparable antidepressant

activity to bupropion SR, a remarkable finding if replicated.

Dr. G. Sachs and co-workers at Massachusetts General Hospital did a retrospective chart review of all patients who had received **topiramate** at their bipolar clinic, and who had at least one follow-up visit. Fourteen patients fit the criteria, 13 of whom had at least one comorbid condition and eight who had rapid cycling. Patients on average were receiving three concomitant drugs. Eleven patients were on topiramate for more than two weeks, and of those, four had decreased severity of bipolar illness, and eight had clinically significant improvement in their primary comorbid condition. Four patients experienced an average weight loss of nearly 30 pounds. Adverse side effects led to eventual discontinuation of topiramate in five patients, and two patients discontinued treatment themselves because of lack of efficacy.

Dr. E. Vieta et al. of the University of Barcelona, Spain, performed a study of adjunctive **topiramate** for six weeks in 21 patients with bipolar disorder who were considered resistant to treatment with lithium, carbamazepine (Tegretol®) and valproate. Nine patients were manic, six depressed, three hypomanic, and three mixed. Six of the 21 patients discontinued the study, but only one due to adverse side effects. After six weeks, the mean dose of topiramate was 158 mg/day. Six patients were considered responders to topiramate, although none of the patients with depression were responders. Ten patients experienced moderate weight loss.

- The lack of acute antidepressant response is similar to that observed in the SFBN by McElroy et al. (2000; *Biol Psychiatry* 47: 1025–1033)

(Continued on page 5)

## Meeting Highlights

(Continued from page 4)

### Atypical Antipsychotics

A variety of new data on the medications olanzapine (Zyprexa®) and risperidone (Risperdal®) were presented.

Dr. R. Baker and co-workers from Lilly Research Laboratories and Harvard Medical School found that in two inpatient double-blind, randomized trials investigating the efficacy of **olanzapine** for acute mania, worsening of mania occurred more often on placebo than on olanzapine, in contrast to previous reports in open trials that olanzapine induced or exacerbated mania.

Dr. R. Baker and colleagues also investigated the efficacy of **olanzapine** in bipolar patients with depressive symptoms during mania in the same two studies noted above. Response to mood stabilizers can be different in patients with mania versus patients with depression during mania. In these studies, olanzapine was significantly superior to placebo in improving both manic and depressed symptoms. Worsening of depression was not significantly different between olanzapine and placebo.

Dr. J. Frazier from Harvard Medical School and colleagues conducted a study of **olanzapine** monotherapy (2.5–20 mg/day) in 23 juvenile bipolar patients (ages 5–14) with mania or mixed symptoms. Sixty-one percent of patients responded, and 22 (96%) of 23 completed the study. Clinically significant increases in weight occurred in some patients, however.

Dr. M. Namjoshi et al. at Lilly Research Laboratories conducted a 1-year study of **olanzapine** in mania, investigating the clinical, humanistic, and economic aspects of the drug. Patients with mania were randomized to either placebo or olanzapine for three weeks, and then were all given olanzapine for 49 weeks. Patients had a statistically significant improve-

ment in (clinical) symptoms over the 49-week period, statistically significant improvement on several dimensions of a scale used to measure humanistic outcome, and saved an average of \$900/month compared to the year before olanzapine therapy.

Dr. Namjoshi and co-workers also conducted a 6-week trial comparing **olanzapine** with placebo in patients who had been treated with lithium or valproate for at least two weeks before the study, and who were required to stay on these drugs during the olanzapine trial. Patients treated with olanzapine had statistically significant greater improvements in mania than patients on placebo, and greater improvements on six different scales of a rating instrument used to rate quality of life.

Dr. M. Tohen of Lilly Research Laboratories and Harvard Medical School, along with colleagues from a variety of universities, performed several studies with olanzapine. A three-week, double-blind study of **olanzapine** (5–20 mg/day) versus **valproate** (500–2500 mg/day) in hospitalized manic patients showed a statistically significant greater improvement on olanzapine.

Dr. R. Licht and fellow scientists at the Stanley Bipolar Center in Denmark performed a 4-week trial of **risperidone** (6 mg) versus the antipsychotic **zuclopenthixol** (Clopixol®) in 14 patients with mania. Ten of 14 patients completed the study, and all achieved at least a 75% reduction on the primary mania rating scale used. Five of the patients were treated in conjunction with a mood stabilizer.

Dr. F. Petty (University of Texas Southwestern Medical Center), Dr. G. Sachs (Massachusetts General Hospital), and Dr. C. Bowden (University of Texas Health Sciences Center) conducted a multicentre, 3-week, double-blind study comparing adjunctive **risperidone** (1–6 mg/day) with placebo in 158 manic bipolar patients with or without psychotic

features. Risperidone was added to either lithium or valproate. Both patient groups (with or without psychotic features) showed improvement in total mania rating scale scores, indicating that risperidone-related improvement in manic symptoms is not due solely to its antipsychotic effects. In this same patient sample, Drs. Bowden and Sachs reported that risperidone was well-tolerated compared with placebo with regards to adverse side effects.

Dr. M. Reinares and fellow researchers at the Bipolar Disorders Program in Barcelona, Spain, looked at 20 bipolar I and bipolar II patients, who were euthymic for at least six months and treated with antipsychotics. Eleven patients had been treated with **risperidone**, and nine with typical antipsychotics. In neuropsychological testing, patients on risperidone showed more cognitive flexibility and better occupational functioning than those treated with conventional antipsychotics.

Dr. E. Vieta et al. of the University of Barcelona, Spain, and the Spanish Group for the Study of Risperidone in Affective Disorders, conducted a 6-month study of the efficacy and safety of **risperidone** in conjunction with mood stabilizers in patients with mixed mania. Thirty-one patients participated in the open study; the mean risperidone dose was 4.2 mg/day. After the second week of treatment, highly significant improvements were seen in all outcome measures with risperidone. After four weeks, 74% of the patients on risperidone were classified as responders. At the end of the 6-month study, 71% were without symptoms or only mildly ill, with no reports of tardive dyskinesia; only 16% of the patients discontinued the study. A larger study by the same

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*“Patients treated with olanzapine had statistically significant greater improvements in mania than patients on placebo, and greater improvements on six different scales of a rating instrument used to rate quality of life.”*

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(Continued on page 8)

## Life Chart Highlight

Antidepressant response with switches into recurrent brief hypomanias (RBH) and then mania.

As noted in “Clinical Trials Update” (page one), the Stanley Foundation Bipolar Network (SFBN) is conducting a 10-week, placebo-controlled trial (AD-1) of three different antidepressants as adjuncts to mood stabilizers—bupropion (Wellbutrin®), sertraline (Zoloft®), and venlafaxine (Effexor®)—with a 1-year continuation phase for good responders. Here we present two different life charts from patients who volunteered to enter the double-blind, randomized trial. The study results remain blinded until recruitment is completed.

### Life Chart Patterns

As illustrated in figure 1, the (blinded) antidepressant was added with good effect, but recurrent brief hypomanias (RBH) emerged (8/30 through 9/27), although they appeared to resolve spontaneously. However, 10 weeks after starting the antidepressant, a more severe mania began, and the antidepressant was discontinued.

In figure 2, antidepressant treatment was associated with periods of hypomania, but in this case, they resolved spontaneously. Thus, some of the switches into hypomania discussed on page one may not be problematic.

Joffe and colleagues recently reported that in a study of patients randomized to receive the addition of either paroxetine (Paxil®) or a second mood stabilizer (lithium or valproate) to their current mood stabilizer, the rate of switch did not differ. Paroxetine was better tolerated than the second mood stabilizer, however. What predicted a switch into mania or hypomania with either approach was the history of a mania directly

preceding the depression, i.e., a biphasic episode or the mania-depression-well interval (M-D-I) pattern.

### Duration of Antidepressant Treatment

Altshuler et al. found that in those bipolar patients doing well after two months following the addition of an antidepressant, further continuation of the antidepressant was associated with a lower rate of relapse into depression (35–40%) than when the antidepressant was discontinued (relapse rate of 67%). The SFBN has replicated these findings virtually identically in another 83 patients and, like the original study, found no increased risk of switch into mania (about 20%) in those who continued on their antidepressant compared with those who stopped taking it.

### Therapeutic Implications

Although these open naturalistic observations remain to be confirmed in prospective randomized studies, they do provisionally suggest that the prior recommendation of discontinuing antidepressants in bipolar patients as soon as possible should be reevaluated. Rather, if one is doing well following the addition of an antidepressant, it may be advisable to continue treatment in order to decrease the risk of the occurrence of a subsequent depression. This current reformulation is consistent with the general conservative treatment principle in bipolar illness: if one’s mood is stable, do not alter the treatment regimen; if it is not, one should continue to seek changes and alternatives that might be more effective. ■



#### ■ What is a life chart?

A life chart is a method to systematically track and monitor one’s retrospective and prospective course of illness and treatment.

#### ■ What is the purpose of creating a life chart?

With daily entries, a graphic representation of the course of illness and response to treatment is built. It can be easily shared with treatment providers or family members and becomes a continuous and permanent record.

#### ■ How is a life chart constructed?

Patients rate their mood and functional impairment on a scale, which is converted to a chart. Manic episodes are coded above and depressive episodes below a date line that signifies baseline (or euthymic) mood. Treatments are coded above the manic episode range, and other comorbidities and stressors are noted below the depressive episode range.

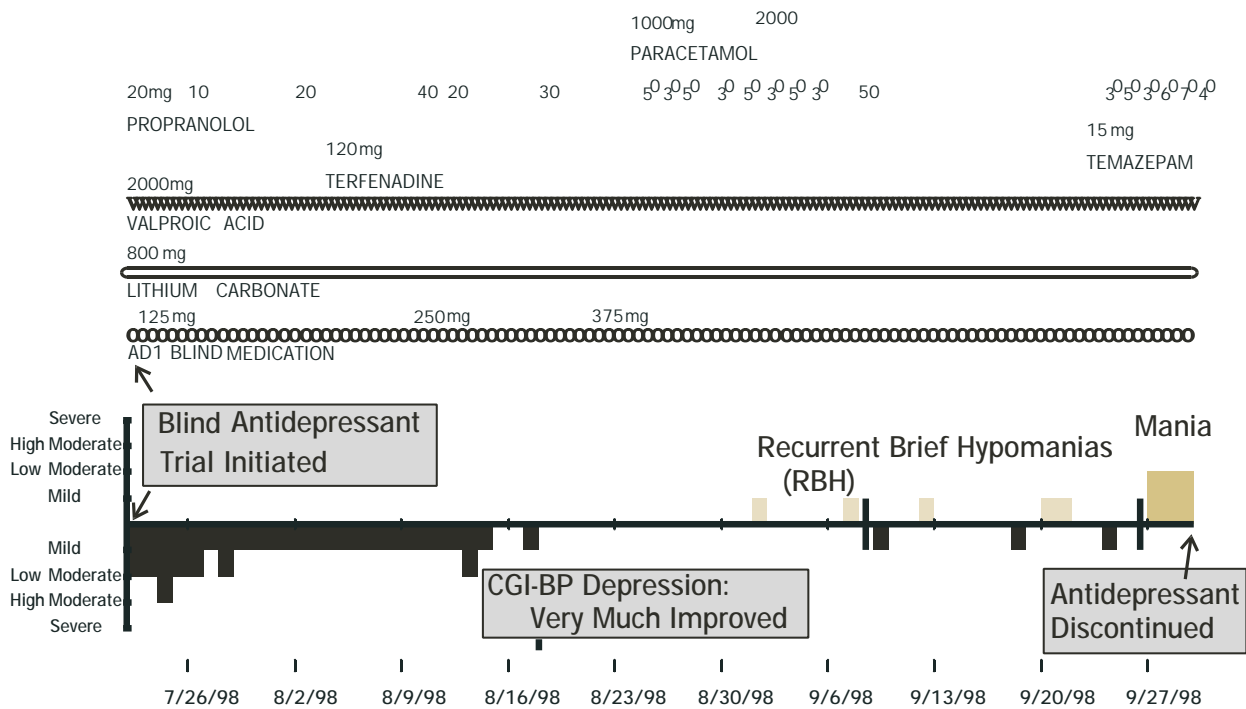
#### ■ How do I get a life chart?

Please contact the National Depressive and Manic-Depressive Association (NDMDA) at:

#### NDMDA

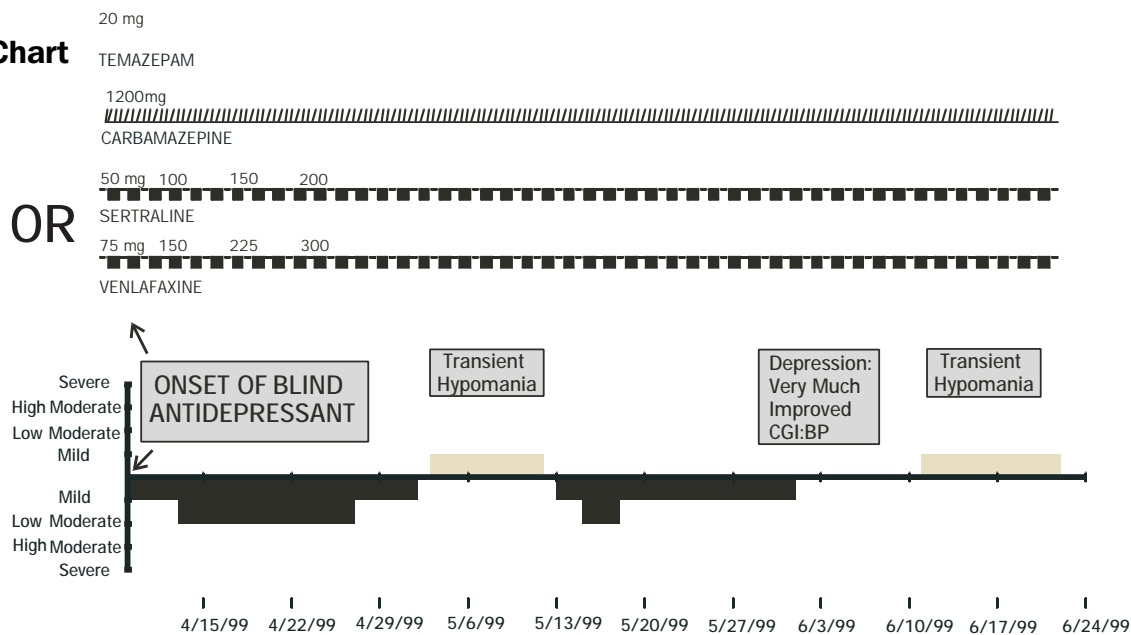
730 N. Franklin St.  
Suite 501  
Chicago, IL 60610  
1-800-826-3632  
www.ndmda.org

### Prospective Life Chart



**Figure 1:** Prospective life chart showing an antidepressant-related switch into recurrent brief hypomania and then mania, whereby the antidepressant was discontinued.

### Prospective Life Chart



**Figure 2:** Prospective life chart showing transient hypomania during blinded antidepressant augmentation.

## Meeting Highlights

(Continued from page 5)

group in 541 patients with schizoaffective disorder (bipolar type) or bipolar disorder with mania, hypomania, or mixed symptoms also showed highly significant improvement in patients taking mood stabilizers in conjunction with risperidone; after six months, 76% of the patients were classified as responders.

Dr. L. Yatham of the University of British Columbia, Vancouver, Canada, also performed a double-blind study of **risperidone** versus placebo in conjunction with mood stabilizers (lithium, valproate, or carbamazepine). In 150 patients in a manic or mixed episode, risperidone showed significant improvement over placebo in those with and without psychotic features, and was generally well-tolerated.

*“The average age for a definitive diagnosis of bipolar disorder was 36.2 years, which was 12.5 years from the first symptoms to a definitive bipolar diagnosis, and 6.6 years from first manic or hypomanic episode to definitive diagnosis.”*

## Course and Treatment

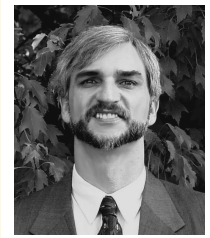
Dr. F. Akdeniz and colleagues from Ege University, in Izmir, Turkey, investigated the **effects of pregnancy and postpartum period** on the course of illness in 72 women with bipolar disorder. Two psychiatrists blind to the course of illness took the childbirth history, and two other psychiatrists prepared a retrospective life chart of the illness of each patient. Of the 72 women, 39 (54%) experienced onset of the illness after the childbearing was completed; the onset of the illness was during the postpartum period in 14 (19%) of the women; four (6%) with illness onset before childbearing experienced no episodes during pregnancy or postpartum; and 15 (21%) with onset before childbearing experienced episodes during either pregnancy or postpartum. These in-

vestigators concluded that postpartum episodes were associated with: (1) early age of onset of the illness; (2) the prior frequency of episodes; (3) the occurrence of episodes during pregnancy; (4) the presence of episodes during the first postpartum period; and (5) a history of the premenstrual syndrome.

Dr. G Akkerhuis et al. from University Medical Centre Utrecht, The Netherlands, conducted a retrospective study of the **diagnosis of bipolar disorder in 55 Dutch patients** from the Utrecht site of the Stanley Foundation Bipolar Network. They found that the average age of onset of first symptoms was 23.7 years, and the average age of the first manic or hypomanic episode was 29.5 years. The average age for a definitive diagnosis of bipolar disorder was 36.2 years, which was 12.5 years from the first symptoms to a definitive bipolar diagnosis, and 6.6 years from first manic or hypomanic episode to definitive diagnosis. Predictors for a diagnostic delay were: (1) early illness onset; (2) a history of sexual abuse; and (3) older birth cohort, whereas early contact with a psychiatrist or physician predicted a shorter delay.

Dr. K. Denicoff of the NIMH, Bethesda, and colleagues examined the relation between **prior course of illness, neuropsychological functioning, and neuroanatomic structures** in bipolar disorder. Forty-nine euthymic bipolar I or II patients were given neuropsychological tests to assess various cognitive functions. A life chart was also constructed for each patient to assess duration and severity of illness variables and episode frequency. Twenty-six of these patients also received a magnetic resonance imaging (MRI) scan. Statistical analysis showed that several different measures of a more severe course of prior illness (e.g., longer duration and greater number of affective episodes and hospitalizations) were associated with poorer cognitive performance on tests of abstraction, attention, and memory, even when patients were

## Investigator Spotlight



**Dr. Gary S. Sachs**

### Background:

- M.D., University of Maryland, School of Medicine
- Residency in Psychiatry, Massachusetts General Hospital

### Current Position:

- Director, Harvard Bipolar Research Program
- Principal Investigator, Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

### Key Research Areas:

Recurrent mood disorders, psychopharmacology, chronobiology, treatment effectiveness

### Selected Key Studies:

- Clonazepam in Bipolar Disorder
- Bupropion vs. Desipramine in Bipolar Depression
- Omega-3 Fatty Acids in Bipolar Disorder

### Career Summary:

Dr. Sachs has pioneered in the study and treatment of patients with bipolar disorder. He authored the Expert Consensus Guidelines Series for Bipolar Disorder (*Postgrad Med* 2000; Apr: 1–104). His development of “contracts” for future treatment if a patient should become manic are a model for the field. His leadership with Dr. Thase of the STEP-BD program is truly outstanding.

euthymic. Results from the MRI showed that a longer and more rapid-cycling prior course of illness was associated with significantly **larger**

(Continued on page 9)



## Meeting Highlights

(Continued from page 8)

volumes of the temporal lobes as well as the third ventricles, and a **larger** right hippocampal volume was also associated with poorer neuropsychological functioning.

Dr. Denicoff and Stanley Foundation Bipolar Network associates also assessed **morbidity** in 202 patients followed for one year in the Network. Of the 202 patients, 77% were bipolar I, 18% bipolar II, 3% bipolar Not Otherwise Specified (NOS), and 2% schizoaffective, bipolar type. Patients were interviewed monthly and administered the prospective Life Chart Methodology to rate their mood daily. A large percentage (51%) of the group had a history of rapid cycling. Despite optimal treatment with mood stabilizers and adjunctive medications, 19% of the patients were hospitalized in the prospective year, 14% became psychotic, and 43% experienced dysphoric mania. Patients experienced an abnormal manic or depressive mood on 49% of the days. Thus, patients remained symptomatic on about half the days in the year with an average of 10.7 weeks of moderate or greater degrees of depressive dysfunction.

Researchers at the University of Barcelona, Spain, examined the issue of **treatment noncompliance** in a sample of 200 euthymic bipolar patients. Dr. F. Colom and colleagues assessed treatment compliance and its clinical correlates in 200 bipolar patients in remission using compliance interviews, tests of plasma concentrations of mood stabilizers, and two structured interviews. Almost 40% of the patients were judged to be mildly or poorly compliant with treatment. Comorbidity with personality disorders was strongly associated with poor compliance, and poorly compliant patients had a higher number of previous hospitalizations, but reported fewer previous episodes than well compliant patients.

Dr. R. Licht et al. from the Stanley Bipolar Center in Risskov, Denmark, looked at the **2-year outcome** in 148 Danish bipolar patients who **began lithium prophylactic treatment** from 1993 to 1998. The patients had had at least two episodes within the last five years; the average age was 45.7 years, and 62% were women. In 89% of the cases, lithium was the only mood stabilizer given. During the 2-year follow-up, 22% of the patients had an episode recurrence that necessitated readmission to the hospital, and 20% discontinued treatment prematurely. An episode recurrence was independently associated with living alone and age below 45 years. Discontinuing treatment was associated with a history of substance abuse.

Increased risk of schizophrenia has been associated with season of birth, second trimester exposure in utero to influenza, urbanicity of place of birth, and some sibship (all siblings from one parental group) characteristics. Dr. P. Mortensen and co-workers of the Department of Psychiatric Demography, Aarhus, Denmark, sought to determine whether any of these **risk factors** were also associated with bipolar disorder. After investigating the case register in Denmark of all patients given a bipolar illness diagnosis (out of a database of 3.5 million people), none of the risk factors noted above were associated with increased risk for bipolar disorder. The only variables significantly associated with risk for bipolar disorder were a family history of bipolar disorder, other affective disorders, or schizophrenia, as well as parental loss during childhood.

Dr P. Mortensen and colleagues also examined a case register in Denmark of 10,242 patients with bipolar illness to determine whether or not **head injury was a risk factor for developing bipolar illness**. They found that head injury both during the last year before first admission to a psychiatric hospital and the period 1–5 years before first admission was associated with an

increased risk for bipolar illness. There was no association with head injury prior to the last five years before first admission and no association between central nervous system infections and bipolar illness. The risk for other bone fractures possibly reflecting general accident proneness was significantly increased during the last year before first admission, but not increased during the period 1–5 years before first admission.

Dr. T. Suppes and co-investigators from the Stanley Foundation Bipolar Network examined the **co-occurrence of hypomanic and depressive symptoms** in patients with bipolar disorder. Out of 10,560 observations in the Network, 788 (7.5%) met the criteria for hypomania, and of those, 488 (62%) also had concurrent depressive symptoms. In this large cohort of prospectively studied patients with bipolar disorder, depressive symptoms co-occurred with hypomania in the majority of patients, suggesting that dysphoric hypomania is a more common presentation of the illness than previously recognized.

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Dr. M. Tohen and colleagues in the McLean First-Episode Project (McLean Hospital, Belmont, Massachusetts) studied **syndromal and functional recovery** in 219 patients with major affective disorders and psychotic features. Syndromal recovery was determined using DSM-IV criteria for affective illness, and functional recovery was defined as gaining vocational and residential status equal or superior to baseline. Syndromal recovery was reached by 65%, 82%, 91%, and 97% of subjects by three, six, 12, and 24 months, respectively. The time-to-syndromal-recovery did not differ significantly by sex or initial illness

(Continued on page 10)

## Meeting Highlights

(Continued from page 9)

severity, but was shorter in patients who were bipolar, married, at least 30 years old at onset, without comorbidity, who were discharged after shorter hospitalization, and with less polypharmacy. Func-

tional recovery by six (32%) and 24 (37%) months was 2–2.5 times less likely than syndromal recovery. In fact, **63% of patients who had recovered syndromally had not recovered functionally by two years.**

Functional recovery was associated with older age-at-onset and shorter hospitalization.

Dr. E. Hoyer and investigators from the Department of Psychiatric Demography, Aarhus, Denmark, sought to identify **risk factors associated with suicide** in patients with bipolar disorder, and examined the records of all people in Denmark hospitalized for the first time because of bipolar disorder from 1973–1993. During the study period, 365 patients committed suicide and 95 (26%) of the suicides occurred during the first year after the first hospital admission for bipolar disorder. The risk of suicide was high immediately after admission and discharge. An increased risk of suicide was also associated with short duration of bipolar disorder, multiple admissions, male gender, and age. The study did not include patients treated solely as outpatients, and therefore conclusions are limited to those with the most severe illness.

### Comorbidity

Dr. E. Frank and co-investigators from the University of Pittsburgh School of Medicine and the Univer-

sity of Pisa, Italy, sought to determine the **clinical significance of lifetime panic spectrum symptoms** in the treatment of bipolar I disorder. The investigators believed that lifetime panic spectrum symptoms would be associated with higher levels of suicidal ideation and a poorer response to acute treatment in patients with bipolar I disorder. Forty-five patients completed a self-report measure of lifetime panic/agoraphobic spectrum symptoms. More than half of the patients reported panic spectrum features above a predefined clinical threshold, and these lifetime symptoms were associated with a history of more prior episodes of depression, higher levels of current depressive symptoms, higher levels of suicidal ideation, and an 18-week delay in acute treatment response. Patients with high scores were also more likely to be treated for depressed or mixed/cycling mood states versus pure mania. Even after controlling for the predominant mood state treated, the negative clinical implications of lifetime panic spectrum symptoms remained significant.

Dr. M. Frye et al. of the Stanley Foundation Bipolar Network examined the **lifetime prevalence rate of alcohol abuse comorbidity** and its subsequent course of illness in 267 patients in the Network. In this patient sample, 49% of men versus 29% of women reported a history of alcohol abuse or dependence, but the relative risk compared with the general population was much greater for women (six times) versus men (1.9 times). Bipolar women with a history of alcohol use were more likely than women without such a history to have a greater number of prior major depressive episodes, hospitalizations for depression, other psychiatric illnesses, and an ultra rapid cycling course of illness. None of these measures were more prevalent in the bipolar men with alcohol use than men without such history.

- Clinicians should ask females with bipolar illness about substance abuse and develop treatment and prevention regimens accordingly!

G. Leverich and co-investigators from four other Stanley Foundation Bipolar Network sites presented data on **comorbidity** from almost 300 bipolar outpatients in the Network. Seventy-seven percent of these patients met criteria for a comorbid personality disorder, based on a self-report on the PDQ-4+. Patients with these personality disorders reported an earlier illness onset, experienced a longer time to first treatment, had been ill longer at study entry, experienced more severe episodes over time and decreased functioning between episodes, and reported a higher incidence of negative life events prior to both the first and the most recent episode.

Leverich et al. also examined the impact of **physical or sexual abuse** on the course of bipolar illness. A history of either early physical abuse (27%) or sexual abuse (28%) compared to patients without such a history, was associated with increased comorbidities, including drug and alcohol abuse, a history of increased medical comorbidities, earlier illness onset, faster cycling frequencies, and more negative life events prior to the first and most recent affective episode. Physical abuse was highly associated with increasing severity of mania and sexual abuse with an increased incidence of suicide attempts.

### Cognitive Functioning

Dr. J. Cavanagh and colleagues from the University of Glasgow, UK, performed a case control study examining **neuropsychological abnormalities in euthymic bipolar patients**. Euthymic bipolar patients were matched with healthy controls for age, sex, and premorbid IQ, and a neuropsychological battery of tests

(Continued on page 11)

## Meeting Highlights

(Continued from page 10)

of executive function and memory was given. The euthymic bipolar patients showed impairments in tests of verbal learning and memory compared to controls, and these impairments correlated with the number of manic episodes. These data suggest that neuropsychological abnormalities which may be of clinical consequence may increase as a function of the number of prior episodes.

Dr. J. Thompson et al. from the Stanley Bipolar Affective Disorders Centre, Newcastle Upon Tyne, UK, also studied **neuropsychological function in euthymic bipolar patients**, and found that these patients demonstrated a clear deficit in verbal learning, in generating words, and on other measures of executive function; these results suggest that residual cognitive impairments often persist, even after symptomatic recovery.

### Brain Structure

Dr. C. Ashton and coworkers from Royal Victoria Infirmary and Newcastle General Hospital, Newcastle Upon Tyne, UK, studied quantitative **electroencephalogram (EEG), cognitive performance, and magnetic resonance imaging (MRI) abnormalities** in young euthymic bipolar patients. Fifty euthymic bipolar patients and 26 controls underwent an MRI scan. Twenty-nine of the 50 patients also had an EEG recording and took a range of neurocognitive tests. They found that young bipolar patients have smaller left and right temporal lobe volumes than controls, mainly in females. Young bipolar patients also had an excess of MRI white matter lesions (as many have previously reported), a global increase in EEG power, and cognitive impairments.

Dr. D. Barbenel and colleagues used structural and functional MRI to investigate the **cingulate cortex** in euthymic bipolar patients. Subjects

performed a paced verbal fluency task, in each of three induced mood states, on the functional MRI. The verbal fluency task activated a neuroanatomical network involving the anterior cingulate cortex, dorsolateral prefrontal cortex, and other frontal structures, consistent with previous studies. The investigators did not find significant deactivation of the superior temporal gyrus with verbal fluency in bipolar patients. Specific comparison of verbal fluency activation across all mood states between patient and control groups highlighted functional deficits of the subgenual anterior cingulate in bipolar subjects.

Dr. B. Baumann and investigators from the Stanley Bipolar Center, Magdeburg, Germany, examined the **postmortem brains of non-elderly patients** with a primary mood disorder as compared to non-psychiatric controls, to determine the total number of neurons and the number of serotonergic neurons in the ventral, dorsal and caudal tier of the dorsal raphe. They found that the total number of neurons in the ventral complex of the dorsal raphe was reduced in patients with a primary mood disorder by about 20%, although no difference was found between bipolar disorder and major depression. Neuron numbers of the dorsal and caudal subnucleus did not differ between patients and controls. Doses of antidepressants showed no correlation with total neuron numbers in any part of the dorsal raphe, but a positive correlation with serotonergic neurons in the ventral complex of the dorsal raphe. The investigators concluded that the structural changes in the dorsal raphe may contribute to impaired serotonergic innervation of brain regions which are involved in the pathology of mood disorders, and that antidepressants appear to increase serotonergic function in the dorsal raphe of depressed patients.

Dr. A. Bertolino and researchers from the Clinical Brain Disorders and the Biological Psychiatry Branches of

the National Institute of Mental Health, Bethesda, Maryland, used proton magnetic resonance spectroscopic imaging (<sup>1</sup>H-MRSI) to study the **hippocampal area** in 17 patients with bipolar disorder and in 17 controls. They found a reduction in the ratios for N-acetylaspartate (NAA) / creatine + phosphocreatine and for NAA / choline-containing compounds in patients with bipolar disorder. They found no other significant effect of diagnosis or side, or their interaction in any other region. The researchers concluded that the selective reductions of NAA measures in the hippocampal area of patients with bipolar disorder suggest neuronal pathology in this area important in cognition and memory and add further evidence for its involvement in the pathophysiology of some of the defects in bipolar disorder. ■

### //www: bipolar

Websites with information on bipolar illness that may be helpful to you:

**www.nami.org**

National Alliance for the Mentally Ill

**www.ndmda.org**

National Depressive and Manic-Depressive Association

**www.narsad.org**

National Alliance for Research on Schizophrenia and Depression

**www.bpkids.org**

The Child and Adolescent Bipolar Foundation

**www.bpsso.org**

Bipolar Significant Others

**www.nimh.nih.gov/publicat/childmenu.cfm**

NIMH Child and Adolescent Mental Health

**www.clinicaltrials.gov**

NIMH Clinical Trial Database

**www.stepbd.org**

Systematic Treatment Enhancement Program for Bipolar Disorder

**www.edc.gsph.pitt.edu/stard**

Sequenced Treatment Alternatives to Relieve Depression

**www.ncbi.nlm.nih.gov/entrez/query.fcgi**

PubMed (National Library of Medicine)

**www.nih.gov**

National Institutes of Health

**www.bipolarnetwork.org**

Stanley Foundation Bipolar Network

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**Bipolar Network News**

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