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Review Article

An overview of recent findings of the Stanley Foundation Bipolar Network (Part I)

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Aim and Methods: Selected recent findings of the Stanley Foundation Bipolar Network are briefly reviewed and their clinical implications discussed.

Results: Daily prospective ratings on the NIMH-LCM indicate a high degree of residual depressive morbidity (three times that of hypomania or mania) despite active psychopharmacological treatment with a variety of modalities including mood stabilizers, antidepressants, and benzodiazepines, as well as antipsychotics as necessary. The rates of switching into brief to full hypomania or mania during the use of antidepressants is described, and new data suggesting the potential utility of continuing antidepressants in the small group of patients showing an initial acute and persistent response is noted. Bipolar patients with a history of major environmental adversities in childhood have a more severe course of illness and an increased incidence of suicide attempts compared with those without. Preliminary open data suggest useful antidepressant effects of the atypical antipsychotic quetiapine, while a double-blind randomized controlled study failed to show efficacy of omega-3 fatty acids (6 g of eicosapentaenoic acid compared with placebo for 4 months) in the treatment of either acute depression or rapid cycling. The high prevalence of overweight and increased incidence of antithyroid antibodies in patients with bipolar illness is highlighted.

Conclusions: Together, these findings suggest a very high degree of comorbidity and treatment resistance in outpatients with bipolar illness treated in academic settings and the need to develop not only new treatment approaches, but also much earlier illness recognition, diagnosis, and intervention in an attempt to reverse or prevent this illness burden.

Robert M Post[a], Gabriele S Leverich[a], Lori L Altshuler[b], Mark A Frye[b], Trisha M Suppes[c], Paul E Keck Jr[d], Susan L McElroy[d], Ralph Kupka[e], Willem A Nolen[e], Heinz Grunze[f] and Jorg Walden[g]

[a] Stanley Foundation Bipolar Network and Biological Psychiatry Branch, NIMH, NIH, DHHS, Bethesda, MD, USA, [b] UCLA Ambulatory Clinical Research Center and VA Medical Center, Los Angeles, CA, USA, [c] University of Texas-Southwestern Medical Center, Dallas, TX, USA, [d] University of Cincinnati College of Medicine, Cincinnati, OH, USA, [e] Altrecht Institute for Mental Health, University Medical Center, Utrecht, The Netherlands, [f] Psychiatrische Klinik der LMU, Munich, Germany, [g] Zentrum fur innovative Therapie bipolarer Storungen am Universitatsklinikum, Freiburg, Germany

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Corresponding author: Robert M Post, MD, Biological Psychiatry Branch, Bldg 10, Room 3S239, 10 Center Drive, MSC-1272, Bethesda, MD 20892-1272, USA.
Fax: 301 402 0052; e-mail: robert.post@nih.gov

The Stanley Foundation Bipolar Network (SFBN) involved four sites in the United States and three in Europe, as described in detail elsewhere (1, 2). All sites used a core methodology with an emphasis on longitudinal ratings and follow-up with the National Institute of Mental Health-Life Chart Methodology (NIMH-LCM^{TM}) (3, 4). Ratings on the Young Mania Rating Scale (YMRS) (5), the Inventory of Depressive Symptomatology (IDS) (6, 7), and the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP) (8) were also completed on each patient. Subjects were recruited from local outpatients near each site and included all those with a bipolar diagnosis on the Structured Clinical Interview for DSM-IV (SCID); patients with concomitant active substance abuse requiring additional treatment in another setting were excluded.

In addition to careful longitudinal description of the illness (1, 9), its comorbidities (10), and response to naturalistic treatment, clinical studies were conducted at several levels of methodological

control. As of the end of 2002, the SFBN was no longer funded as a separate entity, although several individual drug studies at specific sites continue to be supported by the Stanley Medical Research Institute (SMRI).

As illustrated in Fig. 1, at the apex of the methodological pyramid (Level I) were double-blind studies. These studies included a comparison of three different antidepressants – bupropion, sertraline, and venlafaxine – as adjuncts to mood stabilizers in those patients whose depression broke through ongoing treatment (11). A second study probed the double-blind addition to mood stabilizers of omega-3 fatty acids [eicosapentaenoic acid (EPA)], 6 g versus placebo for 4 months, with an 8-month open continuation. One hundred twenty-one patients were randomized to EPA versus placebo for either treatment-refractory depression (n = 59) or cycling (n = 62). The antidepressant effects of modafinil versus placebo are also being evaluated as adjunctive treatment for residual depression and low energy states.

At the base of the pyramid (Fig. 1), open case series (Levels III–V) allowed systematic collection of clinical data about drugs used as naturalistic add-on treatments. Should positive results be observed, more controlled clinical trials could follow. For example, the observations of the preliminary efficacy of topiramate for weight loss in an open case series (12) were followed by a randomized comparison of topiramate with another putative weight loss agent (sibutramine), so that these two drugs could be directly compared at Level II (i.e. in randomized, but not blind, trials). Other anticonvulsants have been assessed for their potential mood stabilizing properties, including gabapentin (13), lamotrigine (14), tiagabine (15), zonisamide (S.L. McElroy, unpublished data), and levetiracetam (R.M. Post, unpublished data). These anticonvulsant studies will be reviewed in a separate article (16). Because the atypical antipsychotics were initially Food and Drug Administration (FDA)-approved for schizophrenia, olanzapine (17) and quetiapine (18) have also been explored as potential antimanics and mood stabilizers with a particular focus on their antidepressant properties.

Depressive morbidity and antidepressant treatment

Morbidity and clinical outcome

In the first 258 patients to be followed prospectively and rated daily on the LCM for a period of 12 consecutive months, a wide range of outcomes and the existence of considerable residual morbidity was observed. Patients had been on an average of 4.1 medications (often one or two mood stabilizers in combination with a variety of other adjunctive antidepressant, antipsychotic, or anxiolytic agents). Quite disappointingly, more than 25% of these patients were ill for more than 75% of the year (Fig. 2) (19). Of these patients, 6.6% had ultra-rapid as well as ultradian cycling occurring throughout the year; 9.3% had rapid and ultra-rapid patterns with depression predominating; 3.9% had mania predominating; and 7% had chronic extended depression. Of the entire population, 40.3% remained intermittently ill despite treatment. Of these patients, 9.7% had recurrent major depressions with full-blown manias interspersed; 19% had recurrent major depressions with intermittent hypomanias; 5.8% had no manias; and 5.8% had only intermittent manic episodes without prominent depressions.

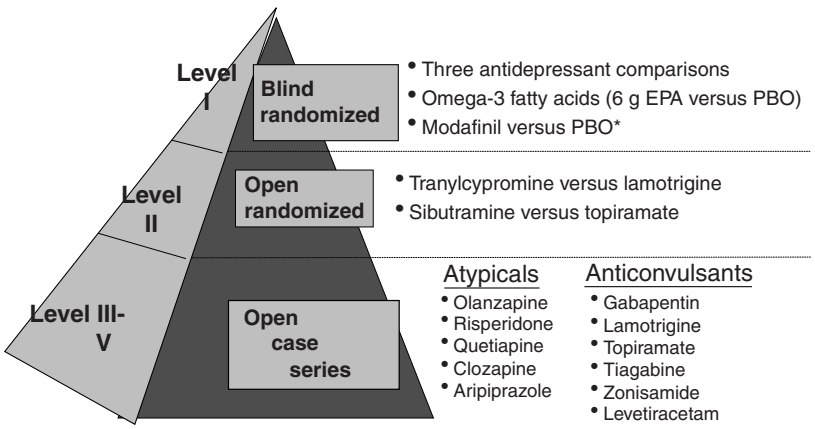

Fig. 1. Clinical studies in the Stanley Foundation Bipolar Network at multiple levels of methodology and control. PBO = placebo.

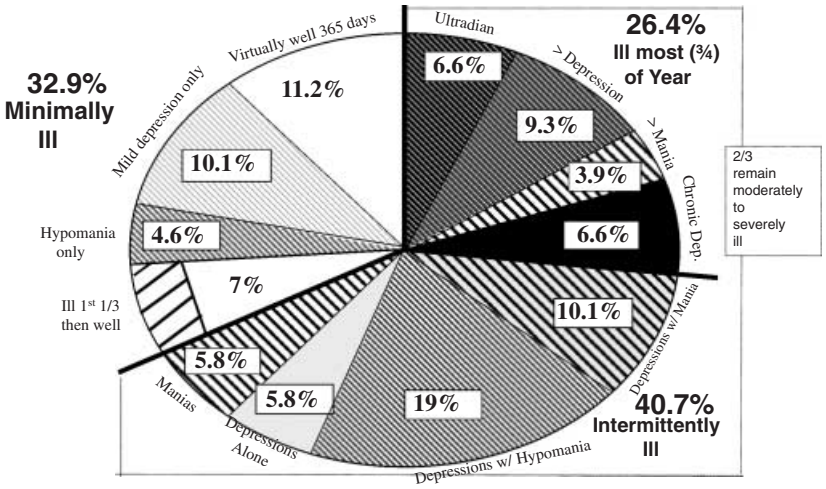

Fig. 2. Patterns of illness in 258 patients in the Stanley Foundation Bipolar Network intensively treated and rated daily for 1 year.

As illustrated in Fig. 2, one-third (33%) of the patients had minimal degrees of illness for the year. Of these 33%, 7% had a moderate to major episode of mania or depression in the first third of the year and then were virtually well thereafter; 4.7% of the patients had only mild hypomanias predominating; 10.1% had only mild depressions; and only 11.2% were virtually well for the entire year.

In the entire group, patients averaged 40 days of hypomania or mania per year and 121 days of depression per year despite treatment with mood stabilizers in 97% of patients, antidepressants in 53% of the patients, benzodiazepines in 49% of the patients, atypical antipsychotics in 21% of the patients, and typical antipsychotics in 17% of the patients.

These data are highly convergent with the reported experience in a variety of other academic centers that indicate that long-term outcome in patients with bipolar I and bipolar II illness who seek care in academic settings is not as benign as previously surmised (20–27). Our data re-emphasize that refractory breakthrough depression is often a greater problem than mania in the long-term treatment of bipolar illness, including patients with bipolar I illness who comprised 76% of our patient group.

Randomized comparison of bupropion versus sertraline versus venlafaxine

Given these types of clinical observations, acute and long-term comparisons of three different widely-used antidepressants (which had not been systematically compared in patients with bipolar illness) were studied on a double-blind, randomized basis. Bupropion, sertraline, and venlafaxine were studied for 10 weeks in an acute, randomized trial as adjuncts to mood stabilizers. Non-responders (minimally improved or worse on the CGI-BP) at the end of the 10-week trial were re-randomized, whereas apparent and possible responders were offered the opportunity of an intended 1 year of continuation treatment. In a total of 127 patients, we observed results of 175 acute antidepressant trials since many patients were re-randomized to a second drug when they did not respond to the first antidepressant. An earlier report on the first 64 patients in the cohort is published (11).

We present an interim update involving all three antidepressant drugs as a class because the full study has not yet been unmasked. Bupropion (IR or SR) was given to a maximum of 450 mg/day, sertraline to 200 mg/day, and venlafaxine (IR) to 375 mg/day. The first 27 patients were randomized in an unblinded fashion before matched placebos were made available from each pharmaceutical company who generously donated free medications. The next 100 were randomized on a blind basis. The response rate and switch rates were relatively similar in the open randomized and blind randomized portions of the study; therefore, they are considered here in a combined fashion.

Approximately 50% of the 127 patients responded (CGI 'much' or 'very much' improved) in the acute 10-week phase and 43.8% of the 67 patients who entered continuation were also considered responders. Data on a total of the 193 patients who were randomized are currently being analyzed. As illustrated in Table 1, 12.6% of the patients switched into hypomania or mania with some dysfunction (i.e. mania ratings reaching at least

Table 1. Rate of switch during antidepressant treatment (bupropion, sertraline, venlafaxine, augmentation of mood stabilizers) as a function of total number of patients

	Acute			Continuation		
Switch	Open (n = 27)	Blind (n = 100)	Total (n = 127)	Open (n = 12)	Blind (n = 55)	Total (n = 67)
Brief hypomania	3.7%	6%	5.5%		3.6%	3%
Recurrent brief hypomania	11%	12%	11.8%	8.3%	18.2%	16.4%
Hypomania	11%	13%	12.6%	8.3%	23.6%	20.9%
Mania	14.8%	12%	12.6%	33.3%	14.5%	17.9%
Total Hypo/Mania only	25.8%	25%	25.2%	41.6%	38.1%	38.8%

n = number of patients.
An extension of Post et al. (19).

moderate severity on the LCM) during the acute trial, and another 12.6% into hypomania (seven or more days of mild ratings on the LCM). Similarly, 17.9% of the 67 patients switched into a hypomanic to manic episode during the 1 year intended continuation and another 20.9% switched into hypomania, i.e., seven or more days of mild mania with little or no dysfunction on the LCM.

It is noteworthy that the LCM allows assessment of brief bursts of hypomania (BH) (only mild ratings on the LCM for <7 days) or recurrent brief hypomania (RBH) (more than one of these short episodes). This range of severity/duration of an episode from BH or RBH to hypomania/mania observed during antidepressant treatment could, in part, account for some of the wide variation in rates of switching reported in the literature. If one discounts the BH, RBH, and hypomanic switches (which by DSM and LCM definition do not involve functional impairment), the total switch rate into mania with some dysfunction (i.e. more than mild manic ratings on the LCM) of 12.6% acutely and 17.9% in continuation needs to be viewed with some caution. Whether or how much this would exceed the natural switch rate (on placebo) cannot be ascertained from these data.

In the continuation phase, however, such switch rates might not be unexpected in an outpatient cohort with 42% reporting a past history of rapid cycling and 38% having this confirmed prospectively (R. Kupka, unpublished data). In the confirmation phase, another 30% of the presumptively responsive patients dropped out prematurely because of a recurrence of a depressive episode. Counting manic, depressive, and administrative drop outs, only a relatively small percentage (19.2%) of the 67 patients were successful in completing an entire intended 1 year of antidepressant continuation. Switch rates as a function of the total number of antidepressant trials rated (175 acute trials and 73 continuation trials) are presented in Table 2.

Length of antidepressant treatment

An ongoing debate in the literature has been on how long antidepressants should be maintained in those bipolar patients successfully responding to them. Altshuler et al. (28) reported in a retrospective chart review that of those patients responding to antidepressants for at least 2 months, there was a better outcome in those who continued their antidepressants compared with those who discontinued them. Sixty-eight percent of the 25 patients who stopped their antidepressant relapsed into another depression within the first year, compared with only 32% of the 19 patients who continued on their antidepressants. This better outcome for depressive relapse came without an increase in manic relapses (which occurred in 25% of those who stopped their

Table 2. Rate of switch during antidepressant treatment (bupropion, sertraline, venlafaxine, augmentation of mood stabilizers) as a function of total number of antidepressant trials

	Acute			Continuation		
Switch	Open (n = 37)	Blind (n = 138)	Total (n = 175)	Open (n = 12)	Blind (n = 61)	Total (n = 73)
Hypomania	8.1%	9.4%	9.1%	8.3%	21.3%	19.2%
Mania	10.8%	8.7%	9.1%	33.3%	13.1%	16.4%
Total			18.2%			35.6%

n = number of clinical trials.

antidepressants versus 20% who continued on the antidepressants). These preliminary data from an uncontrolled (non-randomized) chart review suggest that within the subgroup of patients who respond well to antidepressants and remain stable for the first 2 months of treatment, antidepressant continuation may be preferable to discontinuation.

To further examine the reliability of these findings, we assessed the 549 patients who had been on antidepressants in the SFBN and had a positive response (remaining well for at least 2 months), as in the initial Altshuler et al. (28) study. Of the 84 (15%) patients who qualified as being well for 2 months (i.e. minimally or not ill on the CGI-BP), 41 had continued on their antidepressants and 43 had discontinued them (presumably on the basis of patient and physician preference as discontinuation of antidepressants had been the recommended practice). There were no significant differences in demographics or in prior illness characteristics between the two groups. Again, the rate of relapses into depression was substantially different: 70% of those who discontinued antidepressants versus 36% who continued on them relapsed into a depression (29). As in the first study, no significant difference was seen in the rate of switch into mania in the group who continued (7%) versus discontinued (18%) antidepressant medication.

Although a prospective randomized design is necessary to confirm these two preliminary open case series based on naturalistic treatment, their initial interpretation would suggest the potential utility of continuation antidepressant treatment in the small subgroup of bipolar patients who have done well for several months with adjunctive antidepressant medication. However, only 15% of all of the patients exposed to adjunctive antidepressants met criteria for 2 months of response to be observed in this study. The others had already switched into mania, or failed to respond adequately or tolerate the antidepressant. These new data raise questions about the advisability of the general recommendation in bipolar depression to discontinue antidepressants as soon as possible because of fear of an increased rate of switching into mania.

Course of illness characteristics and comorbidity

Association with early environmental adversity

Leverich and associates have assessed the relation between early traumatic life events and the course of bipolar illness in a cohort of 631 patients (30) for whom detailed demographic and course of illness variables were available from a patient questionnaire (2). Those who experienced early extreme stressors in their childhood or adolescence (i.e. physical or sexual abuse) had an earlier onset of bipolar illness, a more adverse course of illness, more Axis I, Axis II, and Axis III comorbidities, and an increased incidence of serious suicide attempts (30).

A subgroup of 373 of these patients were followed for a mean of 2.8 years with prospective ratings; the patients with a history of early physical or sexual abuse who reported increased illness severity prior to Network entry also experienced increased time ill and percentage of time depressed, as well as increased severity of depression on the IDS.

In our series of 631 bipolar patients, we found that the age of onset of first symptoms meeting diagnostic criteria was 19.4 years, but the age of first treatment was 29.2 years (30). Disappointingly, the duration of time untreated was significantly longer for those with a history of these early extreme environmental adversities compared with those without such a history. These data suggest the importance of recognizing those with this relatively poorer prognostic factor (i.e. report of the experience of physical or sexual trauma) and, accordingly, intervening earlier, before the potential future cascade of negative illness and life events unfolds (i.e. increased severity of depression; rapid and ultrarapid cycling; suicide attempts; and Axis I, II, and III comorbidities and loss of social supports). We acknowledge that this clinical perspective assumes a causal relationship that has not been demonstrated (as we used only correlational analyses); such clinical intervention, however, would be supportable in any case. This view is further bolstered by the recent observations of Nemeroff (personal communication, April 2003) that cognitive behavioral therapy (CBT) was more effective in unipolar depressed patients with a history of early trauma, whereas in those without such a history, the combination of an antidepressant with CBT was superior to either modality alone.

The SFBN data provide some empirical support for the theoretical formulations of the occurrence of stress and episode sensitization in bipolar illness (31, 32), which have already received considerable validation in unipolar illness (33–35). The data are convergent with the view that the occurrence of some types of stressors during initial periods of development may lead to lasting behavioral and neurochemical alterations in preclinical models (36, 37), and clinically to a more fulminant course of affective illness, although causal mechanisms cannot be directly inferred from the clinical data.

There also appears to be an interaction of genetic vulnerability and environmental stressors

affecting the onset of bipolar illness. A family history of affective illness in first degree relatives and the occurrence of early environmental adversities each influenced age of onset and together they had additive effects and were associated with the earliest age of illness onset (30). An alternative interpretation of these data could be that children with more genetic vulnerability could have an earlier age of onset (which is not adequately recognized as an illness) and this behavior could elicit aberrant behavior from others.

Factors associated with suicidal attempts

Variables contributing significantly to the occurrence of suicide attempts in our population are longitudinally schematized in Fig. 3 (38). These variables overlap greatly with illness and other factors associated with early environmental adversity and are illustrated within the circle in Fig. 4. The reported frequency/severity of abuse was also positively related to increased suicidal acts. The occurrences of physical and sexual abuse were also additive in their association with subsequent suicidal acts, i.e., 57.4% in the presence of both compared with a 25% rate of prior serious suicide attempts in those without either adversity. Each type of abuse was associated with an approximate 15% increase in incidence of suicide attempts (to about 40%) compared with baseline. Interestingly, the occurrence of these early environmental stressors appeared to be associated with: a subsequent occurrence and accumulation of later stressors; a

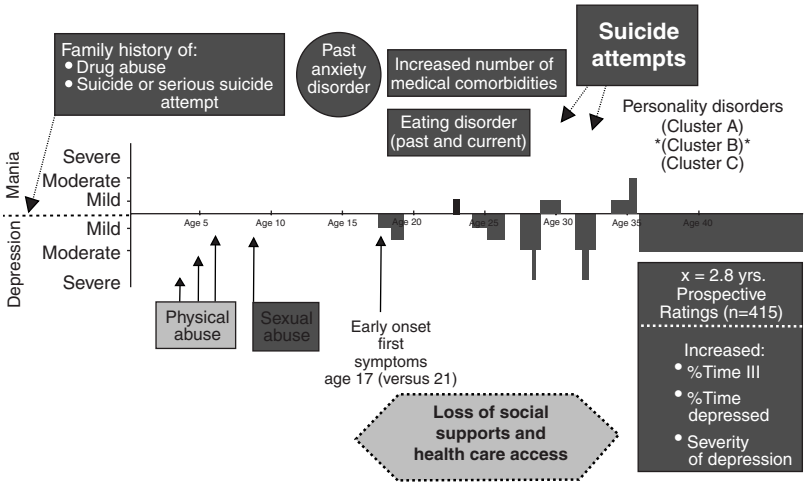

Fig. 3. Schema of factors associated with suicide attempts in 632 patients with bipolar illness in the Stanley Foundation Bipolar Network.

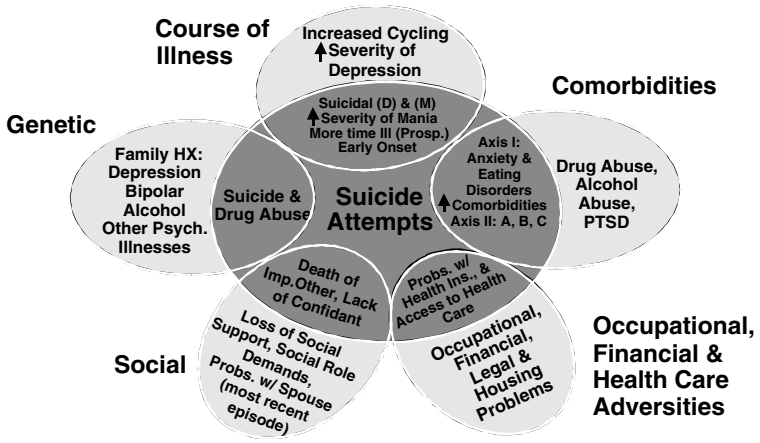

Fig. 4. Overlapping factors associated with physical and sexual abuse and suicide attempts in bipolar illness.

lack of social supports; and lack of access to medical care (30, 38).

Gender effects on alcoholism

Frye et al. (39) examined substance abuse and comorbidity in men and women in the SFBN. Although he found the expected two to threefold increased risk for alcoholism in men with bipolar illness compared with the general population, a strikingly high (more than sevenfold) risk for alcohol abuse/dependence was observed in women in the SFBN compared with the general population. In women, but not men, there was an association between an increased incidence of depressive episodes and alcohol use and abuse. These data again suggest the importance of early intervention in initial depressive occurrences and specifically inquiring about substance abuse in women with bipolar illness who might be attempting to treat their depression with a counterproductive substance.

Correlates of obesity in bipolar illness

McElroy et al. (40) examined the clinical correlates of being obese or overweight in 644 SFBN outpatients (see Table 3). Particularly notable is the correlation of the basal metabolic index (BMI) at study entry and the number of previous exposures to psychotropic drugs known to be associated with weight gain. Given the increased recognition of the problem of overweight and obesity in the US population in general, and the vulnerability for such problems in bipolar patients in particular (because of medication profiles that often involve the liability of weight gain), careful attention to the potential medical consequences of this condition and possible interventions is of considerable importance. In addition to the substantial risk factor that depression poses for cardiovascular illnesses and fatalities, it appears to be a risk factor for obesity with its own potential for associated arthritis, hypertension, and diabetes.

Table 3. Clinical correlates of overweight and/or obesity in 644 Stanley Foundation Bipolar Network outpatients

Demographics
Male gender
Age
Income $\geq$ 20 000/year
Site location
Life style
Little or no regular exercise
Greater than three cups of coffee per day
Treatment
Basal metabolic index and current weight correlate with prior number of exposures to psychotropic drugs known to increase weight
Comorbidities
Axis I: Binge eating disorder (past and current)
Any history of eating disorder
Medical: diabetes, hypertension, arthritis

From McElroy et al. (40).

One is fortunate that of the available second- and third-generation anticonvulsants, some are weight neutral (lamotrigine, oxcarbazepine, and levetiracetam) and others have a positive side effect of weight loss (topiramate and zonisamide). Weight loss on these agents of about 0.33 lbs/week on average are approximately equivalent to loss on the FDA-approved weight-loss agent sibutramine. The emerging data from the SFBN on efficacy of the anticonvulsants in bipolar illness and their effects on the target comorbidity of obesity are reviewed in more detail in a following SFBN summary (16).

Preliminary comparison of quetiapine, risperidone, and clozapine

The atypical antipsychotic agents are being widely used in the US for bipolar illness as well as for schizophrenia in preference to typical antipsychotics with their associated risk of acute extrapyramidal side effects, acathesia, and longer-term problems with tardive dyskinesia in 20–40% of bipolar patients so exposed (41). It is also hoped that these agents will have a better profile of antidepressant efficacy and mood stabilization than the older drugs. In a preliminary examination of the series of 48 patients given quetiapine, 37 given risperidone, and 19 given clozapine, we have seen statistically significant drops in clinician depression ratings on the IDS in the first month and maintained thereafter on quetiapine, but not on similar add-on treatment with risperidone or clozapine (18). More detailed and systematic study is required of these initial data suggesting utility of quetiapine in the depressive phases of bipolar illness. These preliminary observations drawn from naturalistic treatment may provide the basis for more systematic evaluation of the antidepressant efficacy of quetiapine in relation to other atypical antipsychotics. McElroy and associates are examining the effectiveness of the atypical antipsychotic aripiprazole (which is weight-neutral) in both phases of bipolar illness. As a partial agonist at D_1, D_2, D_3 and $5HT_{1A}$ receptors, and a full antagonist at $5HT_2$ receptors, one hopes that aripiprazole will also have a positive antidepressant profile.

Thyroid disease and bipolar illness

Kupka et al. (42) reported an increased prevalence of thyroperoxidase antibodies in SFBN patients (28.3%, n = 226) compared with 3190 unselected inpatients in the Netherlands and a sample of that general population (14.2%, n = 252); Spencer et al. (43) found an incidence rate of 10.1% in 4453 patients in the US undergoing routine multiphasic health examinations. In the Kupka et al. study, the presence or absence of antithyroid antibodies was not associated with rapid cycling, but was associated with an increased risk for lithium-induced hypothyroidism. Females in the SFBN were at increased risk for hypothyroidism (22.8%) compared with males (11.6%). However, as reported in a more recent investigation (44), hypothyroidism was not associated with the presence or absence of rapid cycling, and the presence of antithyroid antibodies did not appear to be a potent predictor of clinical response or outcome (42). The pathophysiological mechanisms and clinical implications of this high incidence of thyroid auto antibodies deserve further study and are being further explored (R. Kupka et al., unpublished data).

Omega-3 fatty acids

Keck et al. have completed one of the last SFBN studies, a randomized comparison of the omega-3 fatty acid EPA (6 g) versus placebo for 4 months and then open treatment with EPA for 8 months. Disappointingly, EPA response did not exceed that of placebo in the 59 patients randomized for the treatment of acute depression or the 62 for rapid cycling (Keck et al., unpublished data). In addition to the positive results of the Stoll et al. (45) omega-3 study in bipolar patients, others have observed positive effects of adjunctive omega-3 fatty acids in depression with lower doses (1–2 g EPA) (46, 47). Whether 6 g EPA is too high a dose for effective treatment, or there are other factors pertaining to baseline or changed omega-3 fatty acid levels in different subgroups, will be explored.

Conclusions

In the 7 years of its existence, the SFBN has made progress in a variety of domains and accomplished many of its major goals as described in this and in a companion paper (16). Its core methodology is now widely accepted and used (1, 2, 8), not only by the SFBN sites, but also by other NIMH- and pharmaceutical industry-sponsored trials. The LCM (3, 4) has been validated against cross-sectional rating scales such as the YMRS, Hamilton Rating Scale of Depression (48), and IDS, as well as the Global Assessment of Function (GAF) scale (49, 50). This prospective daily rating of mood and behavior can accurately delineate the detailed course of illness and high incidence of rapid and faster cycling frequencies, and document the degree of response to treatment.

Using this methodology we have observed that two-thirds of our bipolar outpatients remain substantially affected by their illness (Fig. 2) despite intensive pharmacotherapy and excellent compliance. Depression emerges as a much greater problem of treatment-resistance than mania (19).

We have also identified a variety of clinical correlates of an adverse course of bipolar illness (30) and medically-serious suicide attempts (38). We have begun to assess how new treatment approaches can address the considerable morbidity that remains in the illness despite multi-modal treatment. More than 18 pharmacological agents have been examined in the Network. We have observed a variety of promising results in many instances, and in others, areas of caution and lack of positive results have been delineated. Even prior to the unblinding of the specific comparison of bupropion, sertraline, and venlafaxine, we have added information about the risk/benefit ratio for these newer antidepressants as a class (Tables 1 and 2). Preliminary observations from two highly convergent studies suggest that in the small subgroup of patients who respond and remain well on adjunctive antidepressants for at least 2 months, continuation of the antidepressant may be preferable to its discontinuation (28, 29).

Our overall results strongly recommend a re-orientation in the therapeutic approach to bipolar illness. It appears appropriate to reconceptualize bipolar illness as a highly recurrent, extremely pleomorphic, and potentially lethal medical disorder especially given the 25–55% incidence rate (the latter in the subgroup with a history of early abuse) of suicide attempts requiring medical attention prior to Network entry (38). With the average of a decade between first symptoms meeting diagnostic thresholds and first treatment (9, 30), the importance of intervening earlier in the illness course is re-emphasized, particularly given the high risk of adolescent and young adult bipolar patients acquiring other severe liabilities, such as comorbid alcohol and substance abuse. Many, but not all studies (51) have also indicated that those with a greater number of episodes prior to institution of

lithium prophylaxis are less likely to respond to lithium treatment (21, 23, 24, 27, 52–56). This same relationship of number of prior depressive episodes and poorer response has also been observed for lamotrigine (57). The SFBN now finds this is a poor prognostic factor for outcome in general and combination treatment (58).

Thus, considering the potential for considerable morbidity and even mortality in inadequately treated bipolar illness, one would hope that earlier illness detection and treatment with pharmacological and targeted psychotherapeutic techniques (59) could begin to ameliorate some of these adverse outcomes. We are very much indebted to Theodore and Vada Stanley of the Stanley Foundation and to E. Fuller Torrey, M.D. for having made this work of the SFBN possible. We hope that the continued fruits of these studies along with others in the field, such as the NIMH STEP-BD program (60), together with the renewed interest of the pharmaceutical industry, will have a positive impact on the treatment of bipolar illness and the ability of patients to achieve and sustain complete remission of their symptoms.

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