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Bipolar Network News

CLINICAL TRIALS UPDATE

We are in the process of analyzing and reporting the basic demographic data of the first 200+ Network patients. We have found that many bipolar patients have substantial morbidity from the illness despite the range of existing treatments and that, in many instances, bipolar illness co-occurs with other axis I disorders. For example, 61% of the males and 39% of the females have some substance abuse difficulties, and those who do have a higher incidence of a history of alcoholism and drug abuse in their first-degree relatives.

Thirty-seven percent of the males and 53% of the females in the Network have an associated anxiety disorder, and the presence of anxiety disorders is associated with patterns of illness progression in terms of either increasing cycle acceleration or having more severe episodes over time. Those with comorbid anxiety disorders also have more current suicidality (11%) compared with those without anxiety disorders (4%). These data are convergent with data from many other studies indicating that severe anxiety and agitation are risk factors for suicide.

Thus, anxiety symptoms should be treated with appropriate medications, and one is fortunate to have a variety of approaches that can specifically deal with comorbid anxiety symptoms in bipolar illness. These include both the traditional and the newer antidepressants, as well as the high-potency benzodiazepines lorazepam (Ativan®) and clonazepam (Klonopin®), and likely many of the anticonvulsant mood stabilizers as well. Drs. Keck and McElroy, for example, have reviewed the literature suggesting that valproate (Depakote®) has substantial anti-panic effects. Carbamazepine (Tegretol®) decreases anxiety in proportion to its blood levels in patients with epilepsy, and promising data are emerging for lamotrigine (Lamictal®) and gabapentin (Neurontin®).

It is interesting that those patients with a history of eating disorders also show a pattern of worsening course of illness in terms of either cycle acceleration or more severe episodes, and they, too, have a higher incidence of alcoholism and drug abuse in first-degree relatives. These data on comorbidity will soon be reported by Dr. McElroy.

Dr. Trisha Suppes will be publishing the general presentation of the patient demographics in the Network, and Gabriele Leverich has submitted a paper on the basic methodology of the Network.

Initial open Network studies of lamotrigine (Suppes et al., 1998, unpublished data) and olanzapine (McElroy et al., 1998, unpublished data)

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Data from the first 200+ Network patients:

Summary:	
BP I (191)	81%
BP II (39)	17%
BP NOS (4)	2%
Female	55%
Male	45%
College Degree	48%
Married	43%
History of:	
Psychosis	61%
Dysphoric Mania	59%
Rapid Cycling	53%
Substance Abuse	32%
Alcoholism	27%
Positive Family History for:	
Depression	59%
Alcoholism	49%
Bipolar Illness	41%
Drug Abuse	28%
Suicide	22%
Schizophrenia	8%
Age at onset of:	
Depression	
(First Symptoms)	21 yrs
(First Treatment)	31 yrs
Mania	
(First Symptoms)	25 yrs
(First Treatment)	34 yrs

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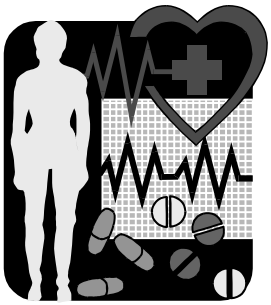
show promising effects in about 50% of treatment-refractory bipolar patients, and further exploratory studies and more formal clinical trials are being designed for these and a series of other new potential treatment interventions, including the anticonvulsants topiramate (Topamax®) and tiagabine (Gabatril®). ■



Bipolar Network News

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The *BNN* is published four times a year by the Stanley Foundation Bipolar Network, an international group of individuals with bipolar disorder together with their mental health care providers who participate in research studies investigating the long-term course of bipolar disorder. The goal of the Network is to improve the understanding of bipolar disorder and develop better treatment strategies to manage this illness.

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MEETING THE CHALLENGE OF TREATING REFRACTORY BIPOLAR ILLNESS

Robert M. Post, M.D.

Reprinted from the Editorial in the
Journal of Bipolar Disorder 1998; 1(2): 29-30

The problem of refractory bipolar illness deserves special recognition, because an increasing percentage of bipolar patients are now shown consistently to be less than adequately responsive to lithium carbonate—the only approved agent for the long-term prevention of the illness. Response-rate failures in many systematic and community samples are 70–80% over 2–3 years' follow-up despite allowance of adjunctive antidepressant and antimanic augmentation strategies.[1] In parallel, over the past 25 years we have seen a rising need for increased numbers of medications at discharge from our clinical-research unit at the National Institute of Mental Health (NIMH); the average number of medications (which used to be less than one) now exceeds three, with a range of one to six.[2] Rational polypharmacy and combination-therapy strategies need to be utilized increasingly in the various subgroups of patients who have now been identified as particularly lithium-refractory, including those with a greater number of prior episodes, a pattern of rapid cycling, a pattern of depression-mania-well interval (D-M-I) as opposed to M-D-I, a history of comorbid substance abuse or a negative family history for bipolar illness in first-degree relatives, as well as patients with dysphoric mania and a variety of other common patterns of illness.[3]

The Need for Research

Although a large number of second- and third-generation antidepressants have now been utilized in systematic clinical trials in unipolar depression, they remain virtually untested in bipolar depression; their relative assets and liabilities—not only in acute treatment, but also in the long-term prevention of depression without inducing manic episodes—are unknown. Studies of the comparative prophylactic efficacy of the mood stabilizers lithium, carbamazepine, and valproate (and their potential clinical and biological predictors of response) are likewise virtually absent, as are dose-finding studies for optimal therapeutics in the different bipolar syndromes.

Thus, more than in any other medical subspecialty, the clinician is left essentially without a systematic database upon which to make rational decisions about mono- and combination therapy. The problem will only be exacerbated by the newly emerging third-generation putative mood-stabilizing agents (such as lamotrigine and gabapentin) and the atypical neuroleptics, and the lack of knowledge about their appropriate place in the therapeutics of the refractory bipolar patient, particularly for augmentation strategies. Whereas the pharmaceutical companies that produce lamotrigine and olanzapine are interested in controlled clinical trials directed at obtaining Food and Drug Administration (FDA) approval, such trials—as Brodie[4] and others have emphasized—are rarely clinician- or patient-friendly. In fact, for the epilepsies, lamotrigine and gabapentin have been approved as adjunctive agents; no drug in psychiatry has yet been approved for this purpose.

Study-Design Controversies

What clinicians and patients need are comparative and crossover studies, allowing rational judgments for individual therapeutics in the non-responsive patient. Such crossover studies are shunned generally by the regulatory approval agencies and the NIMH, and by other academic committees which have, mistakenly, adopted the attitude that only FDA-sanctioned designs (rather than what is actually needed in the field) are acceptable and/or fundable. Bipolar illness is particularly open to this and additional design controversies because of its pleomorphic and comorbid presentations of both manic and depressive episodes, ensuring that the homogeneous populations required by classic FDA-approved designs are difficult to acquire.

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LIFE CHART HIGHLIGHT

Late onset rapid cycling bipolar II disorder, with emphasis on prophylactic treatment with two mood stabilizers

Drs. Grard W. Akkerhuis and Willem A. Nolen M.D., Ph.D.

From the Utrecht, Netherlands site which is pioneering level III studies (i.e., randomized open trials in community settings).

The patient presented in this Life Chart Highlight is a 54 year-old woman, who became depressed for the first time when she was 50 years old (September 1993), a few months after she had moved with her family to a new house. Shortly after moving, and a week before her husband's 50th birthday, she attempted suicide and was hospitalized for 4 months. Initially she was treated with the selective serotonin reuptake inhibitor (SSRI) fluvoxamine (Fevarin®/Luvox®). However, depressive symptoms remained and her medication was switched to the tricyclic antidepressant (TCA) nortriptyline (Nortrilen®/Pamelor®), also without success. Even after her discharge from the hospital her depression stayed at the same level, so lithium was added in March 1994.

In May 1994, 4 months after starting the TCA and 2 months after starting lithium, she became hypomanic for the first time and began cycling with a very regular pattern: episodes of moderately severe depression lasting 3 to 4 weeks, alternating with 3- to 4-week episodes with mild hypomanic symptoms. She called these latter episodes her "good periods", because she was very cheerful, could do a lot of work and had increased self-esteem. Her diagnosis then became bipolar II disorder.

In October 1994 her thyroid levels were found to be too low, possibly because of an adverse effect of lithium. Lithium was stopped and levothyroxine (T_4) (Synthroid®/Thyrax®/Eltroxin™) was added. Subsequently she became more agitated and in November 1994 she was hospitalized for the second time. In addition to the nortriptyline she was given haloperidol (Haldol®), and soon thereafter she switched into a severe depression. The nortriptyline dose was increased to 150 mg/day and, after another hypomania, lithium was added again.

Although the cycling pattern had not stopped, she was discharged from the hospital in February 1995. Her cycling pattern then became very regular and she could almost foretell her "bad" and "good" periods. Every day she noted her mood in her diary, and when she entered the SFBN naturalistic follow-up study in March 1995, we had no difficulty in making a retrospective life chart of the past 2 years of her illness.

According to our algorithm (Goodwin and Nolen, 1997, *Int J Psych Clin Pract* 1:S9–S12) for the treatment of rapid cycling, we decided to discontinue the antidepressant. We did so because we realized that the depressive episodes were not her only problem—the recurrent rapid cycling pattern was even more important. In other words, our approach became not the acute but the prophylactic treatment of her depressions, in order to prevent further episodes.

However, omitting the antidepressant did not slow down her cycling pattern. Therefore, a second mood stabilizer, valproate (Depakine®/Depakote®), was added. From that moment on (June 1996), the rapid cycling slowed, her depressive episodes vanished and the hypomanic episodes did not reappear. As can be seen from her life chart (Fig. 1A, 1B), she has been almost completely stable for more than 1 year and she feels like she did before her illness began in 1993.

It can be hypothesized that the rapid cycling pattern in this patient was induced by the TCA nortriptyline (see *BNN* Vol. 2, Issue 4; and Post et al., 1997, *CNS Drugs* 8: 352–365). Antidepressant-induced hypomania and mania have also been studied by Dr. Lori Altshuler at the National Institute of Mental Health (NIMH)(Altshuler et al., 1995, *Am J Psychiatry* 152: 1130–1138). Dr. Altshuler's study showed that 35% of longitudinally-observed patients had a manic episode that was likely to be antidepressant-induced. Moreover, rapid cycling was associated with antidepressant treatment in 25% of the patients referred to the NIMH.

Thyroid malfunctioning (in this case possibly due to treatment with lithium) may also have played a role. Although the literature is inconsistent, it is hypothesized that decreased thyroid function is associated with an increased risk for rapid cycling. The treatment of our patient shows that after stopping the antidepressant her depressions did not worsen. With the combination of two mood stabilizers and thyroid hormone she completely recovered (see Fig. 2).

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NIMH Study Participation Clinical Center, Bethesda, MD

rTMS

Depressed patients who wish to participate in a protocol to evaluate repeated transcranial magnetic stimulation (rTMS) of the brain should contact Dr. Andy Speer at (301) 402-2293.

Lamictal®/Neurontin®

Patients wishing to be screened for the Lamictal®/Neurontin® protocol (see *BNN* Vol. 3, Issue 4) should call (301) 496-6827.

PTSD

Patients with post-traumatic stress disorder interested in volunteering for a randomized clinical trial to evaluate the potential efficacy of repeated transcranial magnetic stimulation (rTMS) over the right frontal cortical area—with a month of either low frequency treatment or sham treatment and a crossover to the other phase—should contact Dr. Una McCann at 301–402–2947.

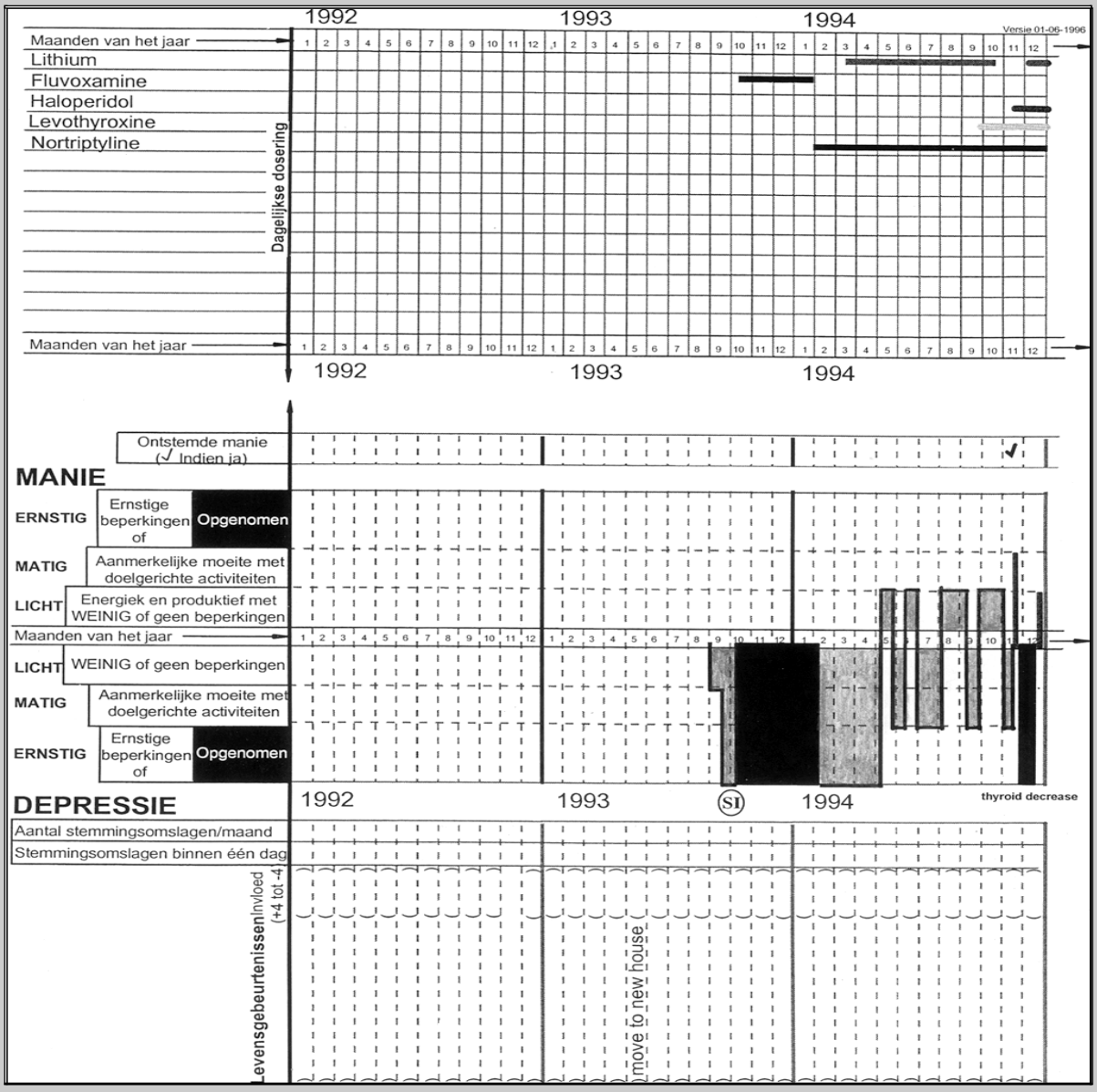

Figure 1A: Onset of depression 5 months after a move: cycling on lithium and nortriptyline

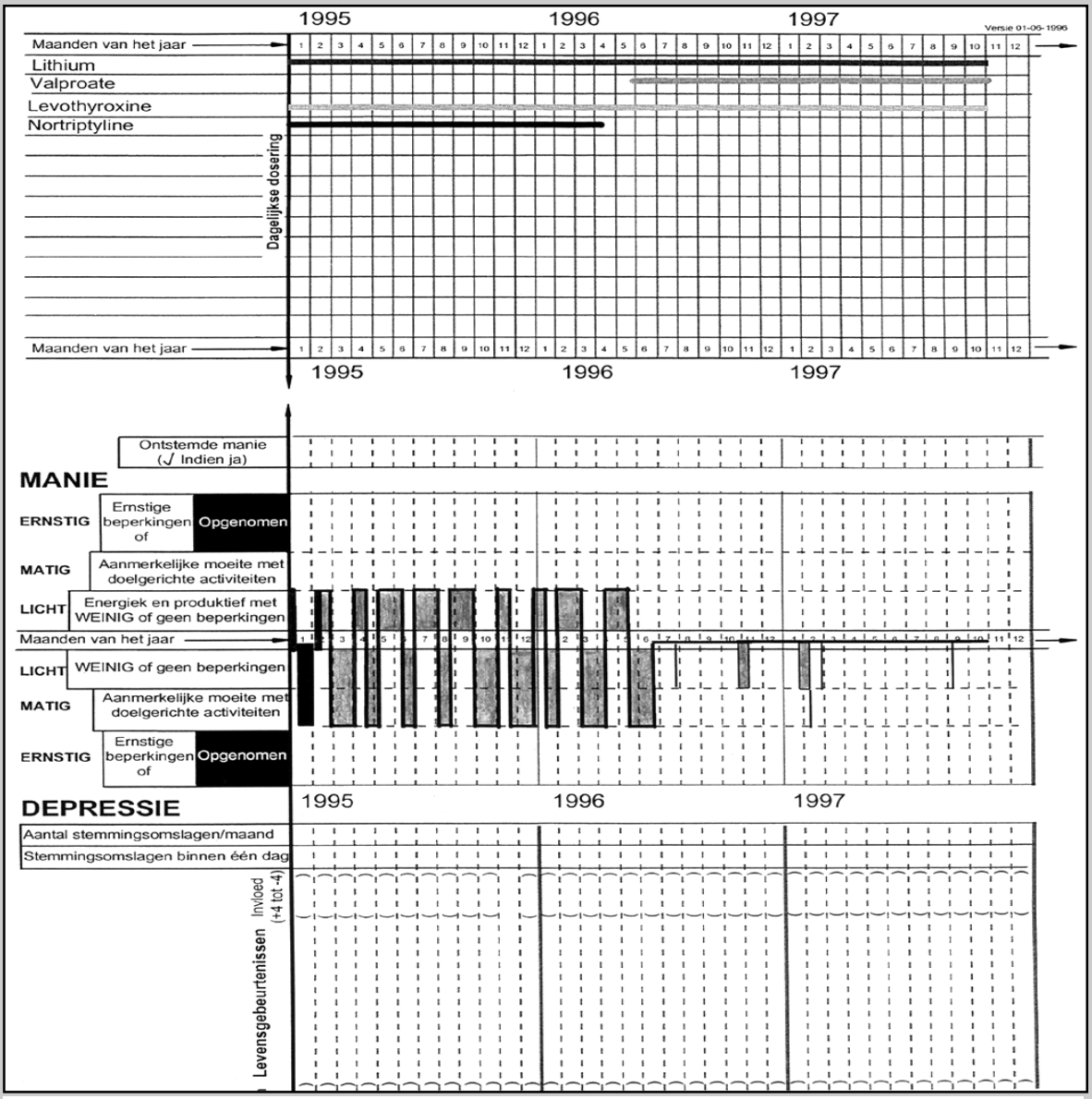

Figure 1B: Response to lithium and valproate (after discontinuation of nortriptyline)

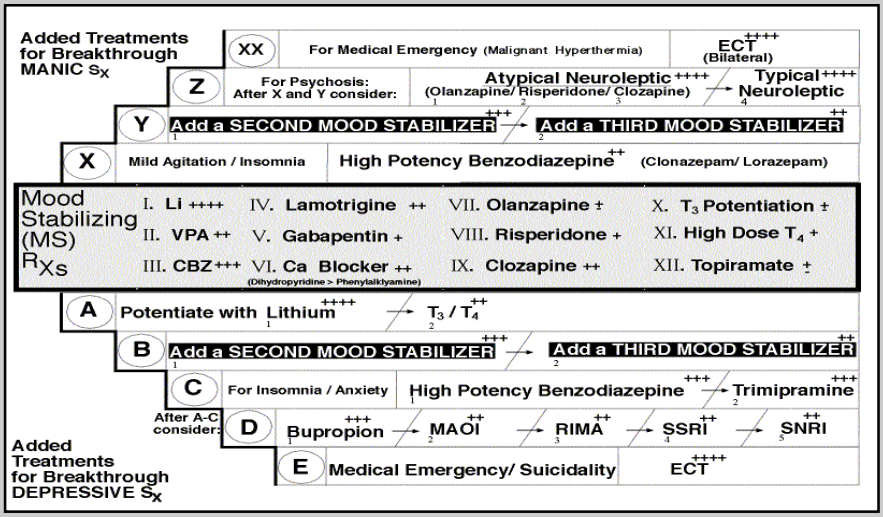

Figure 2: Treatment algorithm for rapid and ultra rapid cyclers

MEETING HIGHLIGHT

American College of Neuropsychopharmacology (ACNP)
36th Annual Meeting, December 8–12, 1997

Founded in 1961, the ACNP is a professional organization of some 600 leading scientists. The principal functions of the College are research and education in neuropsychopharmacology.

The 1997 ACNP meeting continued the unfortunate trend of having many more symposia focused on schizophrenia than bipolar illness, despite their approximately equal incidence in the general population (1%). As in the past two ACNP meetings, the panels and symposia related to schizophrenia numbered more than 12, whereas only 1 or 2 were directly relevant to bipolar illness.

We raise this issue not to undercut the work in schizophrenia, but only to emphasize that bipolar illness continues to be markedly understudied and underfunded relative to schizophrenia, revealed not only in the grants portfolio of the National Institute of Mental Health (NIMH) (see *BNN* Vol. 1, Issue 3; and Vol. 3, Issue 1), but also in the scientific investigations of one of the most prestigious U.S. psychopharmacology meetings of the year.

Elsewhere (p. 2) we have reprinted an editorial from the *Journal of Bipolar Illness* that Dr. Post wrote on the issues facing us in the study of and funding for treatment-refractory bipolar illness. In that editorial, Dr. Post makes the case that the National Alliance for the Mentally Ill (NAMI) has already suggested, that there be a national plan for studies on bipolar illness, just as there was for schizophrenia a decade ago. The national plan for schizophrenia completely revitalized the field and has resulted in a most productive and creative outburst in the better understanding and development of new treatments for that illness. A similar effort now appears necessary for bipolar illness.

Despite the lack of robust focus on bipolar illness, several exciting new approaches to bipolar illness were presented. These findings and others pertinent to schizophrenia and depression are selectively highlighted here:

New Treatment Approaches

● Dr. Andrew Stoll et al. reported positive therapeutic effects of approximately 9 grams of omega-3 fatty acids per day compared with an olive oil control group in patients blindly randomized to these two approaches. The patients were bipolar patients refractory to existing prophylactic regimens that were held constant. Only 1 of 15 patients relapsed in the omega-3 fatty acid group, whereas 7 of 15 patients relapsed in the olive oil control group. The investigators found these findings so statistically remarkable that they terminated the study early, based on the very positive differential effect already observed.

Ed. note: If these findings are replicated by others, they would suggest the possible clinical relevance of omega-3 fatty acid supplementation for a subgroup of refractory bipolar patients, particularly those struggling with depressive breakthroughs. The Network is designing a protocol to rapidly acquire further data in this regard.

● Drs. Mark Corrigan and Dwight Evans presented data on pramipexole, a dopamine agonist, in the treatment of major depression. In the course of previous studies of this agent—which is now approved for the treatment of Parkinson's disease—they observed that many patients, even some of those who did not improve remarkably in terms of their motor symptoms, were nonetheless substantially improved in mood. The present study design consisted of 5 parallel treatment groups: pramipexole (0.37 mg, 1 mg, or 5 mg) versus fluoxetine (20 mg) or placebo for 8 weeks in patients with major depression. On the Hamilton Depression Rating Scale 1 mg of pramipexole was superior to placebo at the .05 level of significance, whereas the .375 mg dose and fluoxetine were both superior to placebo at the .10 level. For the Clinical Global Impressions (CGI) and Beck Depression Inventory measures, only the pramipexole 1 mg group demonstrated superiority to placebo.

Ed. note: Pramipexole is of considerable interest because it is a direct dopamine agonist that not only stimulates traditional dopamine D2 receptors involved in parkinsonism, but also D3 receptors which are heavily represented in the limbic system and its modulation of emotion. The Stanley Foundation Bipolar Network will be conducting Level III & IV studies (open randomized and open assigned) of this D3 agonist in bipolar depression to see whether it is also effective in this group. The dosage must be titrated extremely slowly towards that of 1 mg/day because nausea, vomiting, somnolence, and dizziness are the most frequent side effects.

● Dr. Maricio Tohen presented data comparing olanzapine with placebo in a double-blind study of acute mania, with 70 patients in each group. Olanzapine was statistically superior to placebo on most measures; scores on the Young Mania Rating scale dropped 10.3 points compared with 4.9 points on placebo. There was a statistically significantly greater number of responders on olanzapine (48.6%) versus placebo (24.2%; $p < .004$).

Ed. note: Given the fact that this atypical neuroleptic is better tolerated than the typical neuroleptics (with their proclivities for acute parkinsonian side effects and a longer-term risk of tardive dyskinesia), these new data speak strongly to the potential utility of this and other atypical neuroleptics in the management of acute mania. This would be potentially even more important in prophylaxis, in which the liabilities of the typical neuroleptics (unsatisfactory side-effects profiles and risk of tardive dyskinesia) would be more problematic. It should be noted that the side effect of weight gain on olanzapine can be difficult for some individuals.

Clinical Findings

● Dr. Alan Swann et al. reported on another in a growing series of studies by different investigators that the occurrence of a large number of affective episodes prior to

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starting lithium prophylaxis was associated with a poor response to lithium. In many of these studies, 3 or 4 episodes appear to be the limit; if patients experienced this many episodes prior to beginning lithium prophylaxis, they were likely to be nonresponders.

Ed. note: The implication of these studies appears quite clear: patients should not subject themselves to multiple episodes prior to beginning lithium prophylaxis. If they do, it is highly likely that lithium will not be effective, as reported by many others (Sarantidis and Waters, 1981, *Prog Neuropsychopharmacol* 5: 507–510; Gelenberg et al., 1989; *N Engl J Med* 321: 1489–1493; Markar and Mander, 1989, *Br J Psychiatry* 15: 496–500; O'Connell et al., 1991, *Br J Psychiatry* 159: 123–129; Winokur et al., 1993, *Arch Gen Psychiatry* 50: 457–465; Denicoff et al., 1997, *J Clin Psychiatry* 58: 470–478).

● Dr. Sarah Lisanby (with Dr. Sackeim's group at Columbia) reported on the retrograde memory effects of electroconvulsive therapy (ECT). Based on a structured interview covering memories up to four years prior to ECT, she found that patients demonstrated significant amnesia one week post-ECT on items related to both personal and impersonal productivity, and in the detail and richness of impersonal memories. Two months after ECT, memory returned to baseline values for all subscales except impersonal memory productivity and recent impersonal memory richness.

Ed. note: This study represents one of the best assessments of the type and duration of memory loss produced by ECT, indicating that impersonal memory (i.e., memory less likely to be emotionally encoded) was more vulnerable to the amnesic effects of ECT than memory related to personal details. The persisting effect of ECT for 2 months on this subscale helps validate many patients' subjective sense of impaired memory for extended periods of time following a series of ECT.

● Dr. Ron Crystal from the Rockefeller Institute amazed everyone with his demonstration of the potential of a biologic bypass procedure using molecular biology and gene transfer techniques. In pigs who had had their coronary arteries completely ligated, Dr. Crystal was able to insert a specific neurotrophic factor (vascular endothelial growth factor or VEGF) into these animals such that they grew a new coronary artery. The growth factor was delivered by an adenovirus vector expressing complementary DNA for VEGF. This VEGF glycoprotein is specific for the endothelium and does not activate fibroblasts such that it results in new growth of only what you want to grow, in this case new coronary artery vessels.

Ed. note: Although clinical applications are still a long way away for patients with occluded coronaries, and even farther away for similar gene therapy feats in patients with neuropsychiatric illness, such a magical demonstration allows one to hypothesize about the potential resetting of deficient or overactive neural systems using gene therapy in patients with psychiatric illness, in order to avoid episode recurrence or exacerbation.

Imaging Studies

● Dr. Wayne Drevets reported on a replication of his data that left prefrontal metabolism using positron emission tomography (PET) was inversely correlated with the severity of Hamilton depression ratings, whereas metabolic activity in the amygdala was directly correlated with severity of depression. He extended these findings with the observation that not only was a particular area of the anterior cingulate gyrus (just under the anterior part of the corpus callosum, i.e., the subgenual anterior cingulate) particularly low metabolically, but there also was a remarkable deficiency in the number of glial cells in this area of brain. *Ed. note:* Did they die by apoptosis, i.e., preprogrammed cell death?

● Dr. Grazyna Rajkowska reported a 14% decrease in the average cortical thickness of the orbital frontal region of the brain in patients with major depressive disorder compared with controls. The glial cell densities were not decreased in this study, but neuronal size and the densities of large neurons were significantly below normal, and densities of large glial cells were reduced in some layers.

Ed. note: These studies form a growing number indicating that major depression is not only associated with a host of biochemical and neuroendocrinological alterations, but also with changes in the size of the brain and endocrine organs.

● Interestingly, Dr. Bob McCarley reported a decreased left anterior grey matter in first degree relatives of patients with bipolar illness and unipolar illness.

● Dr. Terence Ketter reported that normal volunteers who self-induced a depressed mood for 30 minutes by recalling sad memories showed decreases in glucose metabolism in the amygdala as measured by fluorodeoxyglucose (FDG**)** PET. These findings are particularly striking in relation to the findings of George et al (while at the NIMH) that a similar but more brief sadness induction caused increases in blood flow as measured with 0^{15} water (George et al., 1995, *Am J Psychiatry* 152: 341–351; George et al., 1996, *Biol Psychiatry* 40: 859–871). Because the normal volunteers in Dr. Ketter's study seemed to have induced a more lasting depressed mood over a period of 30 minutes, it was suggested that this might be the reason for the decreased metabolism, whereas the more brief sadness induction of George et al. may yield increases in blood flow in some of these same areas of the brain.

Ed. note: Whether it is the differential nature of the two inductions (sustained mood versus brief emotion) or differences in the techniques for assessing brain activity (blood flow versus metabolism) remains for further study. In either case, these data continue to implicate the amygdala and related brain structures in the medial part of the temporal lobe as important to both normal and pathological emotion modulation.

● Dr. Anna Rose Childress, working with Dr. Chuck O'Brien and others in Philadelphia, reported on limbic substrates of conditioned or cue-induced cocaine craving, in which their studies using PET demonstrated limbic increases and basal ganglia decreases in regional cerebral blood flow (rCBF) during cocaine craving induced by a cocaine video. Interestingly, some of the same limbic substrates found to be abnormal in affective illness, such as the amygdala and anterior cingulate gyrus, are the areas that showed increases during cocaine craving induced in cocaine users by watching the video. This pattern did not occur in volunteers without such a cocaine history.

Ed. note: The convergence of some of the neural substrates involved in the regulation of cocaine craving and mood may ultimately be linked to the very high

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comorbidity of substance abuse disorders (such as cocaine) in patients with bipolar illness.

● Dr. Roger Pittman reviewed the brain imaging literature on post-traumatic stress disorder (PTSD), indicating that there are convergent data in a number of studies that indicate increased right anterior limbic and frontal blood flow metabolism in PTSD victims during recall of their trauma. At the same time, there are differences and much needs to be learned about the pathophysiology of this neurobiologically-based illness and its therapeutics.

Ed. note: Drs. Una McCann and Beth Osuch at the NIMH in Bethesda are recruiting patients with PTSD for a randomized clinical trial to evaluate the potential efficacy of repeated transcranial magnetic stimulation (rTMS) over the right frontal cortical area, with a month of either low frequency treatment or sham treatment and a crossover to the other phase. **Patients with PTSD interested in volunteering for such a study should contact Dr. McCann at 301–402–2947.**

Biochemical Studies

● Dr. Husseini Manji continued his remarkable series of studies comparing the gene induction profile of lithium and valproate with the idea that common actions of these two drugs might be related to their effects in bipolar illness. He demonstrated that both of these drugs increase binding to a certain part of DNA called the activator protein 1 (AP-1) site, and possibly as a consequence of this, increase BCL-2 in gene transcription.

Ed. note: This is important because BCL-2 prevents neuronal cell death by apoptosis (preprogrammed cell death). These agents also have a common site of action on a complex molecule called GSK-3, that affects the binding of the transcription factor c-jun. C-jun is involved in the transcription control of a variety of chemicals and cellular functions, including replication and cell death. If these common processes can be further delineated, it may be possible to more specifically target them for therapeutics.

● Dr. De-Maw Chuang from the Biological Psychiatry Branch, NIMH, presented new evidence on how lithium might exert some of its actions through a unique and previously undiscovered pathway. He found that lithium blocks calcium influx through the N-methyl-D-aspartate (NMDA) glutamate receptor—an action also shared by carbamazepine and possibly valproate. This action of lithium may be related to its ability to prevent age- and stress-related cell death in the cerebellar granular cell culture preparation, as well as in hippocampal cell cultures.

Ed. note: It would be tantalizing to consider the possible relation of lithium's preventing the apoptotic (cell suicide) programs of single cultured neurons in a petrie dish, as well as preventing and normalizing the suicide rate in patients with bipolar illness who choose to remain on maintenance treatment with this agent. There are more than 10 billion neurons in each individual's brain, and double that number of glial cells. Moreover, each neuron may have up to 10,000 synapses, indicating that the human brain is a little more complex than single cells in culture. And yet, lithium is capable of preventing suicide in both instances. One would dismiss the notion that there could be any commonalities between the two processes if it were not for some of the new mathematics of chaos theory which, among other things, indicate that there are replications upon replications of similar processes at multiple levels of magnitude of consideration or visualization of a given process. That is, in many objects or processes, "self similarity" at multiple levels of analysis appears to be the rule.

● Dr. Terence Ketter also reported decreased prefrontal N-acetyl aspartate (NAA) in his study of bipolar patients. These findings are of interest in relationship to earlier reports of Dr. Danny Weinberger and his team that NAA, which is a marker of neuronal loss, is also reduced in this area in schizophrenic patients. ■

Caution for patients starting lamotrigine: go slowly

Lamotrigine is associated with a 5–10% incidence of a rash. In some 1 in 500 instances the rash can proceed to a very severe, life-threatening form where the skin starts to slough off.

It is thought that starting the drug very slowly—one pill/day (25mg) for 2 weeks and then 2 pills/day (50mg), with increases by 50mg/week thereafter—will further decrease the likelihood of this side effect.

If one is taking valproate (Depakote®)—which approximately doubles lamotrigine blood levels—the rate should be slowed by ½ accordingly.

Carbamazepine (Tegretol®) reduces lamotrigine levels by ½, so patients taking carbamazepine can titrate their dosage twice as fast.

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Within the Stanley Foundation Bipolar Network, protocols have been developed to gain more information about optimal strategies to treat patients with different illness patterns and phases (see *BNN* Vol. 3, Issue 1). A series of antidepressant, antimanic, and anticycling protocols will hopefully inform us as to which treatments are most optimal and may also increase our knowledge to make our treatment algorithms more evidence-based. ■

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As evidenced by the 1989 and 1994 NIMH-sponsored meetings on bipolar illness, almost no design or study has been deemed acceptable, fundable or feasible in the past 15 years.[5,6] Despite the problem of the under-study of bipolar illness (even in the face of growing evidence of its increasing morbidity, disability, costs and treatment refractoriness), solutions have not been forthcoming; in fact, the field has regressed, only one treatment study being funded in the USA this year.

Possible Solutions

A variety of different solutions may be available:

- Studies on the long-term therapeutics of bipolar illness should be declared an orphan area and given special attention and priority relief. Such a change in emphasis on schizophrenia research was accomplished with The National Campaign for Schizophrenia in the 1970s, increasing availability of funding and stimulating an entire new generation of much-needed research in that field. Only with such a National Campaign for Bipolar Illness will the impasse of the past two decades be overcome.
- Committees reviewing grants for the pharmacotherapeutics of bipolar illness should be given the minutes of the 1989 and 1994 NIMH meetings so that a broader consideration of patient populations and design options that are acceptable and/or fundable will be included in their deliberations. A quota should be established and a certain number of bipolar grants funded. 'Design flaws' should be corrected if feasible, but methodological purity and controversy should no longer be reasons to eliminate an entire field of study.
- Alternative design options that are physician-friendly should be sought, together with those that specifically focus on the generation of new data on complex combination therapies and their relative efficacy.
- Similarly, strategies enabling better definition, construction and study of the comparative efficacy of current idiosyncratic clinical algorithms should be given extra consideration.
- In this regard, a portion of the large NIMH set-aside for services research should be specifically targeted for this bipolar population, even though this research rarely focuses on diagnostic entities. Bipolar patients form an increasing percentage of the neglected, homeless, and jailed populations in the USA, as well as a grossly underserved population in the current counterproductive managed-care system of discouraging and limiting regular visits and optimal long-term prophylaxis.
- The watchdogs of managed care should be given new guidelines so that, as in diabetes and other chronic medical disorders, the diagnosis of bipolar illness does not require an endless series of renewals for certification of the need for long-term follow-up and prophylaxis. These should be mandated as part of the standard of care, and the long-term cost-effectiveness of excellent and intensive early and sustained illness management should be recognized and fostered. The guidelines revolution will help to some extent in this regard.
- Conversely, one should recognize that over-reliance on guidelines constructed on the basis of expert opinion and 'best guess' are an inadequate substitute for systematic investigative approaches to the therapeutics of this illness in NIMH-sponsored clinical trials, as well as in services research. In fact, one should be careful to avoid premature closure and the misuse of such guidelines actually to limit treatment options.
- A new round of lobbying efforts by academic and advocacy groups, together with a National Campaign for Bipolar Illness, should enable the field to leap forward in the near future, particularly with the emergence of a host of new potential treatments for bipolar illness in almost all of its therapeutic categories. Multiple new agents are available as putative mood stabilizers, antidepressants, antimanics and atypical neuroleptics, and promising investigational approaches include second-messenger targeted drugs, dietary supplements such as inositol and choline, and even alternatives to electroconvulsive therapy such as repeated transcranial magnetic stimulation of the brain.

Only with a concerted effort and the resumption of systematic NIMH-funded clinical investigations of this host of agents alone and as part of complex combinations will the optimal therapeutics of bipolar illness be placed on a more secure evidentiary database and lead to better early detection, treatment, and amelioration of this potentially deadly disorder.

References

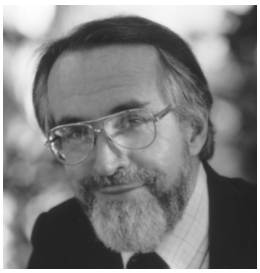
1. Goldberg JF, Harrow M, Sands JR. Lithium and the longitudinal course of bipolar illness. *Psychiatr Ann* 1996; 26: 651–658.
2. Frye MA, Ketter TA, Leverich GS, *et al.* The increasing use of polypharmacy for refractory mood disorders: twenty-five years of study. *APA New Research Program and Abstracts* 1996; 151–152 (abstract).
3. Post RM, Ketter TA, Pazzaglia PJ, et al. Rational polypharmacy in the bipolar affective disorders. *Epilepsy Res* Suppl 1996; 11: 153–180.
4. Brodie MJ. Antiepileptic drugs, clinical trials, and the marketplace. *Lancet* 1996; 347: 777–779.
5. Prien RF, Potter WZ. NIMH Workshop Report on treatment of bipolar disorder. *Psychopharmacol Bull* 1990; 26: 409–427.
6. Prien RF, Rush AJ. National Institute of Mental Health Workshop Report on the Treatment of Bipolar Disorder. *Biol Psychiatry* 1996; 40: 215–220. ■

Early Intervention Initiative (E.I.I.) Protocol

Children whose parents both have affective illness (at least one bipolar) are being sought as potential candidates to enter a clinical trial to determine if treatment instituted at first symptoms can prevent the development of full-blown illness. Depakote® will be compared to placebo with careful monitoring. Those showing no improvement will be offered open treatment with either lithium or gabapentin (Neurontin®).

Protocol enrollment will not be possible for 6 months to 1 year, but those potentially interested should call Emily Fergus at (301) 496-6827, or write to: E.I.I., c/o Stanley Foundation Bipolar Network, 5430 Grosvenor Lane, Suite 200, Bethesda, MD 20814.

AROUND THE NETWORK



E. Fuller Torrey, M.D.

Chair, Stanley Foundation Awards Program
Chair, Stanley Foundation Research Program
on Serious Mental Illnesses

Persistent. Creative. Iconoclastic. Indefatigable. These are words commonly used to describe Dr. E. Fuller Torrey, chair of both the Stanley Foundation Awards Program and the Stanley Foundation Research Program on Serious Mental Illnesses. Dr. Torrey is on a mission to better understand and treat the serious mental disorders, particularly schizophrenia and bipolar illness.

Dr. Torrey was born in Clinton, New York and spent his childhood there. He completed his undergraduate work at Princeton University, where he was graduated magna cum laude. He attended medical school at McGill University, received a Master of Arts degree in anthropology from Stanford University, and trained in psychiatry at the Stanford University School of Medicine. He practiced general medicine in Ethiopia for two years as a Peace Corps physician and in the South Bronx in an Office of Economic Opportunity Health Center. Dr. Torrey's dedication to patients was obvious from the beginning—he was a family doctor in the Indian Health Service for a large sector of Alaska, and the only physician for many hundreds of miles. His range of medical treatment covered treating the common cold and minor surgical procedures to delivering babies and responding to major traumas.

In 1970 he joined the National Institute of Mental Health (NIMH) and rapidly rose to a position where he was overseeing a dozen wards at St. Elizabeth's Hospital. However, attacked for his outspoken views on the seriously mentally ill and unhappy with the pace of progress in understanding the serious mental disorders, Dr. Torrey resigned his position in 1985 to pursue research and foster better public awareness of mental illness by presenting his unique scientific themes in a series of books, now numbering 15 (16 and 17 are in progress). These books have ranged from *The Death of Psychiatry* (1974) to the popular *Surviving Schizophrenia* (1983), which is now in a third edition. His study of schizophrenic and bipolar twins has become a classic in the field, revealing effects of the environment beyond those of the usually assumed role of genetic inheritance *(Schizophrenia and Manic Depressive Disorder: The Biological Roots of Mental Illness as Revealed by the Landmark Study of Identical Twins,* 1995*)*.

From the beginning, Dr. Torrey was interested in the possibility that viruses might be implicated not only in causing the major central nervous system disturbances of meningitis and encephalitis, but also in causing developmental vulnerabilities predisposing to schizophrenia and bipolar illness, through their more subtle forms of infection. He has amassed a wealth of evidence indicating that a seasonal occurrence of births in the winter and spring are associated with not only schizophrenia, but also with bipolar illness, suggesting that this season of increased viral infection might be linked to the increased incidence of these illnesses. Consistent with this idea is the observation that in the southern hemisphere, in which winter peaks in July and August, more people with schizophrenia and bipolar illness are born in these months than in any other months.

Dr. Torrey has followed the scientific history of the increased incidence of schizophrenia and linked it to increased urbanization and to the increased popularity of cats as household pets. He has raised the possibility that feline-carried viruses might be related to this increased incidence of schizophrenia.

In addition to epidemiological studies, Dr. Torrey has pursued these themes with a variety of techniques and technologies including cerebrospinal fluid measures and other neurobiological approaches. Most recently, he and Dr. Robert Yolken founded the Stanley Foundation Neurovirology Laboratory at Johns Hopkins Medical Center. Exciting new work with molecular neurobiological techniques has begun to indicate a potential role of viral sequences inserted into the DNA of identical twins discordant for schizophrenia. Extra pieces of DNA not observed in the well twin were consistently found in the ill twin, suggesting the possibility of a viral infection. In addition, a number of other candidate sequences and mechanisms have been assessed in his cerebrospinal fluid studies and remain strong candidates for roles in either bipolar illness or schizophrenia.

Dr. Torrey's administrative responsibilities have been as ample and productive as his book writing. Early on, he was sought out by Ted and Vada Stanley of the Stanley Foundation (see *BNN* Vol. 3, Issue 4) to be its Chief Executive in the distribution of Stanley Foundation funds. Dr. Torrey began what is now one of the most successful grants programs in the country outside of the NIMH for providing grants to study etiological mechanisms and therapeutic approaches to bipolar illness and schizophrenia. Under his leadership, the number of grants funded has risen from 9 in 1989 to 98 in 1997, with the number of submissions also increasing remarkably—from 35 in 1989 to 278 in 1998.

Each potential Stanley Foundation grant is personally read by Dr. Torrey, summarized, and then distributed to committee members for further discussion; the grants are then ranked based on accumulated scores of all of the reviewers. Thus, a large number of grants are disbursed rapidly with a minimum of overhead cost to the Foundation and no overburdening paperwork for grantees.

For many years Dr. Torrey did the yeoman's work with added advice, recommendations, and finally, specific rankings from: Nobel Prize winner Julius Axelrod; one of the founding fathers of American biological psychiatry; Seymour Kety; one of

(Continued on page 11)

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the most outstanding and philanthropic behavioral neurologists interested in the interface with the major psychiatric illnesses, Janice Stevens; and Nobel Prize winner Carlton Gajdusek who discovered the mechanism of transmission and the cure for the formerly progressive, degenerative, and fatal neurological disorder kuru. More recently, Dr. Torrey has been joined by Bob Post, Bob Yolken, Carol Tamminga, Lou Bigelow, John Rush, Jeffrey Lieberman, and Mike Knable in rating and expediting the large number of Stanley Foundation grants. Remarkably, Ted and Vada Stanley are almost always in attendance, as is Laurie Flynn (Executive Director, National Alliance for the Mentally Ill), as non-voting observers and witnesses of what can be a most tumultuous process—attempting to reach agreement about which are the most novel and exciting grant proposals that are most likely to have a major impact from among the large number of outstanding proposals.

In addition to leading the Stanley Foundation grants program, Dr. Torrey initiated a Stanley Scholars program to foster apprenticeship in the teaching of young investigators by major figures in modern psychiatry. This program has been highly successful in fostering the career development of a whole new cadre of young investigators who have generated a wealth of new ideas and approaches to the etiology and therapeutics of the major mental disorders.

Dr. Torrey also initiated a major Stanley Foundation Bipolar Disorder Centers program with specific funding of very diverse programs throughout the U.S., in Pittsburgh, Bethesda, Boston, Baltimore, Cleveland, Detroit, Chicago, and Palo Alto. As described in previous *BNNs*, one of these, the Bethesda Stanley center, in collaboration with the NIMH and under the leadership of Dr. Robert Post, led to the establishment of the first Bipolar Treatment Outcome Network—a multi-center collaborative effort with five separate Network sites. The Network now daily follows more than 250 patients in a unique longitudinal fashion and enrolls patients in randomized clinical trials to develop new approaches to therapeutics. Network sites in Los Angeles, Dallas, Cincinnati, Bethesda, and Utrecht are involved in this collaborative network, with many other affiliated sites involved as well. Similarly, Dr. Torrey has endorsed a Stanley Foundation Early Intervention Initiative, that has established consensus on a core group of longitudinal assessment methods that should help facilitate early detection and intervention in child and adolescent bipolar illness.

Dr. Torrey was able to establish an active and expanding European centers program for schizophrenia and bipolar disorder, with special emphasis on finding countries and investigators in which small amounts of money would yield great rewards in terms of productivity. He also helped many of these centers conduct comparative studies of bipolar illness and schizophrenia.

In addition to establishing the Stanley Foundation Neurovirology Center, Dr. Torrey's most recent groundbreaking initiative has been the development of the Stanley Foundation Brain Bank which has already distributed brain autopsy specimens to more than 50 investigators; samples are being considered for distribution to as many as 100 different programs. These carefully collected samples have been matched for cause of death and post mortem delay before fixation and represent one of the best organized and well-characterized collections of its kind in the world. It now consists of brains of those with carefully diagnosed bipolar disorder, schizophrenia, unipolar depression/suicide as well as normal controls. These brain specimens are being made available to all investigators requesting access as long as they are willing to put the core data back into the Stanley data bank after primary publication. In this way, Dr. Torrey will be able to correlate and confirm neurobiological alterations in many different systems and have the best chance for discovering important primary pathophysiological mechanisms of these major psychiatric illnesses.

Dr. Torrey is married to an equally energetic and active science administrator, Barbara Torrey. His daughter recently gave birth to his first grandchild. Dr. Torrey's sister has dealt with schizophrenia for much of her adult life. This personal confrontation with the profound and tragic disabilities conveyed by this illness was undoubtedly important in Dr. Torrey's fervent pursuit of its causes, treatments, and cures. He has been unsparingly unselfish in fostering NAMI's efforts and has also founded the NAMI Research Institute.

Patients with serious mental disorders and their families, advocacy groups, and research investigators all owe a huge debt of gratitude to E. Fuller Torrey for his unceasing scientific and administrative efforts to help forge a new understanding and better approach to the therapeutics of serious mental illnesses. His unique partnership with Ted and Vada Stanley has greatly fostered and improved the identification, understanding, destigmatization, study, and treatment of bipolar illness and schizophrenia. The many new findings from Stanley Foundation-supported studies and programs, and those that will surely emerge from Dr. Torrey's Stanley Foundation Brain Bank, speak to Dr. Torrey's extraordinary contributions to the field of psychiatry. ■

Bipolar Network News
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