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March 1999

Bipolar Network News

Clinical Trials Update

Principal investigators from the 5 Stanley Foundation Bipolar Network sites along with representatives from the Data Coordinating Center in Bethesda attended a Network meeting at the Los Angeles site from March 4-6, 1999. The UCLA and VA consortium site in Los Angeles represents the second largest number of patients of any site in the Network, which now includes 467 patients. The meeting was very successful from many perspectives and generated much new data and excitement. Among the highlights were the following findings:

Thyroid Data

Dr. Ralph Kupka from the Utrecht site presented Network data on thyroid antibodies from the largest cohort of patients with bipolar illness yet studied (n=224), to our knowledge. Initial data indicated a 28% incidence of thyroid antibodies in our bipolar patients compared with much lower rates (<10%) in unipolar patients and normal volunteers. Although a previous investigator (Oomen et al., 1996; *Clin Endocrinol* 45: 215–223) suggested a possible link between thyroid antibodies and rapid cycling, this link is not evident in our sample to date. The increase in thyroid antibodies could be related to direct evidence of thyroid dysfunction itself (although this was not evident from the assays of triiodothyronine [T_3], thyroxine [T_4] and thyroid-stimulating hormone [TSH]), or could be representative of some other type of immune dysfunction with central nervous system consequences that remain to be further explored.

Dr. Peter Whybrow, Chairman of the Department of Psychiatry at UCLA, and Dr. Michael Bauer, a visiting scientist from Berlin, Germany, also presented new thyroid data. Their data suggested that very high doses (400-500 µg/day) of T_4 (Synthroid®) beyond the normal dose range for replacement therapy was effective in more than 50% of patients (both unipolar and bipolar depressed) who had failed multiple previous therapies. In general, there was an all or none response, with some patients showing complete remission and other patients showing little clinical improvement or change in status. Despite the high doses of T_4, patients demonstrated remarkably good tolerance and no decrease in bone density, with some patients showing tolerable levels of symptoms usually associated with hyperthyroidism, such as tachycardia (an average increase in pulse rate of 10 points), palpitations, sweating, etc. These data parallel and extend those of several other groups and Dr. Whybrow's earlier data (1994; *Acta Med Austriaca* 21: 47–52) that such high dose thyroid treatment could be a useful augmenting strategy in improving both manic and depressive phases in rapid cycling bipolar patients.

Valproate and PCOS

Final arrangements for a study of the possible relation of valproate (Depakote®) to the development of polycystic ovary syndrome (PCOS) were completed with investigators and endocrinologists at the Los Angeles site. Isojarvi et al. (1993; *N Engl J Med* 329: 1383–1388) have reported that valproate was the most highly incriminated of the anticonvulsant drugs in a study that found a higher incidence of PCOS in epilepsy patients treated with long-term therapy. In those patients, effects were related to dose and duration of valproate treatment. However, PCOS is more common in epileptic patients than in many

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other patient populations, and it is not yet clear whether valproate might also cause this problem in psychiatric patients because no patients with this syndrome have been observed or reported to date.

PCOS involves menstrual irregularities, increased body hair (hirsutism) because of increased levels of testosterone, and increased size of the ovaries because of multiple cysts (which can be detected with a magnetic resonance imaging [MRI] scan of the ovaries). There is some uncertainty as to whether insulin resistance that has been reported in association with the syndrome is due to weight gain that might occur nonspecifically with any drug, or is more specifically linked to valproate.

Bipolar Network News

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The BNN is published 4 times a year by the Stanley Foundation Bipolar Network, an international group of investigators who, together with patients with bipolar disorder who participate in research studies, investigate the long-term course and treatment of bipolar disorder. The goal of the Network is to improve the understanding of bipolar illness and develop better strategies for treatment.

We welcome any comments or suggestions you may have. For communication or to be placed on the mailing list, please contact us at:

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Females Taking Valproate (Depakote®) Sought

The Bipolar Network is therefore interested in obtaining blood samples from female patients who have been on long-term valproate or lithium treatment to assess whether there is any evidence for possibly developing PCOS. Women wishing to participate in such a study should call their nearest Stanley Foundation Bipolar Network site (see page 11). It is preferable for blood to be drawn after an 8–12 hour fast and specifically on days 4–7 of the menstrual cycle, although days 1–3 are also acceptable. Valproate has now surpassed lithium as the most widely utilized treatment for bipolar illness; therefore, it is very important that the potential complication of PCOS in psychiatric patients be determined. Volunteers who wish to contribute to this investigation would be most appreciated.

Omega-3 Fatty Acid Trial

Details were completed for the initiation of our Network omega-3 fatty acid trial (see previous BNNs). Bipolar patients wishing to participate in a 4-month study of an add-on, randomized omega-3 fatty acid (eicosapentaenoic acid [EPA], thought to be the active compound) versus placebo trial should contact their nearest Bipolar Network site (see p. 11). After the 4-month randomization, all patients become eligible for open omega-3 treatment for another 8 months.

Three arms of the study are available so that patients who are on at least one mood stabilizer with: 1) depression (not responding to drugs available in our earlier protocols), 2) inadequately controlled mania, or 3) cycling, will be eligible for participation. As noted in previous issues of the BNN, Stoll et al. (1999; *Arch Gen Psychiatry* 56: 407–412) showed highly promising improvement in a small group of refractory bipolar patients who were randomized to omega-3 fatty acids (9 grams) or olive oil. Dr. Stoll's study received wide attention in the popular press and we hope to assess whether these findings will be substantiated in a much larger group of patients.

New Treatment Trials

Fifty-six Bipolar Network patients have been studied with open, add-on topiramate (Topamax®) treatment, showing promising effects of topiramate in mania and cycling, with less clear effects on the depressive phase of the illness. Topiramate appears to be well tolerated, including a possible positive side effect of mild to moderate weight loss in a substantial percentage of patients.

Data from the newest adjunctive anticonvulsant, tiagabine (Gabatril®), were also discussed at the meeting; initial data have shown both the therapeutic possibilities and the risks of this drug, which selectively potentiates the major inhibitory neurotransmitter system in the brain (gamma-aminobutyric acid [GABA]) by blocking its reuptake (i.e., inactivation) in the nerve terminal. Although several patients have shown clinical improvement with the addition of tiagabine, two patients without a history of prior seizures suffered seizures while taking this drug. Because of this potentially serious side effect, we are currently putting this agent on hold for general studies in the Network, and will only consider using tiagabine in a clinical trial in patients who have failed many other available treatment options and who clearly understand the potential risk of seizures.

As noted in the last issue of the BNN, 3 new Bipolar Network double-blind drug trials will begin soon. A randomized open comparison of olanzapine (Zyprexa®) and quetiapine (Seroquel®) will be available for patients requiring antipsychotic augmentation. These two drugs have been explored in patients with schizophrenia, but their relative efficacy and side effects have not been systematically studied in bipolar patients, al-

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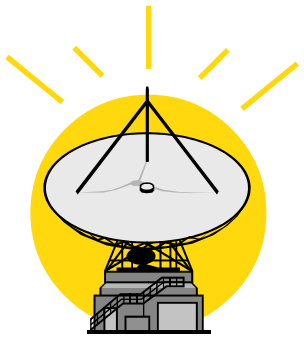
Meeting Highlights



"Are schizophrenia and bipolar disorder one disease or two?"

Stanley Foundation Satellite Symposium
International Congress on Schizophrenia Research
Sante Fe, New Mexico, April 17, 1999

Dr. A. Jablensky, from the University of Western Australia, opened the symposium with a historical perspective on the central question: **"Are schizophrenia and bipolar disorder one disease or two?"** Dr. Jablensky noted that Dr. Kraepelin initially distinguished schizophrenia (dementia praecox) from manic-depressive illness, believing the two were distinct entities, but he was open to the idea that the two could share common risk factors, genes, and pathophysiological processes. Kraepelin's concept of dementia praecox was more consistent with the notion of mental weakening or aberration, rather than what we now consider the more classic type of memory loss proceeding to confusion and disorientation in Alzheimer's dementia.

Dr. E. Fuller Torrey, of the Stanley Foundation, spoke on the **"epidemiological comparison of schizophrenia and bipolar disorder,"** highlighting the overwhelming evidence from 100 studies that there is an increased incidence of late winter and early spring births of people who later develop schizophrenia, suggesting a potential infectious etiological agent. Eight of 9 studies in bipolar disorder also show an excess of winter births. In addition, individuals born in cities are approximately 1.65 times more likely to acquire schizophrenia compared with those born in rural locations (with a similar increased risk for bipolar disorder). All of this evidence is consistent with a possible infectious agent in the pathophysiology of the major psychiatric illnesses (see Drs. Buka and Yolken, below). Dr. Torrey postulated the concept of "manicdephrenia," in which people could have a genetic predisposition to either manic-depressive illness or schizophrenia, and could develop either pathological process depending on the timing and neural location of the insult.

Dr. D. Wildenauer, of the University of Bonn, reviewed the evidence of **"whether schizophrenia and affective disorder share susceptibility genes,"** concluding that possible shared hot spots for both illness vulnerabilities were localized on similar areas of chromosomes 10, 13, 18, and 22, although the evidence is far from conclusive. He indicated that there was a 5.3 times increased risk of concordance for bipolar disorder in monozygotic versus dizygotic twins, suggesting a strong genetic component, as well as a 4.9 times increased risk for diabetes, a 2.8 times increased risk for schizophrenia, a 2.4 times increased risk for heart disease, and most interestingly, a 2.3 times increased risk for tuberculosis, which is not generally thought of as a genetic illness.

Ed. Note: These data are consistent with the notion presented by Dr. Yolken (below) that even for infectious agents, there may still be a considerable interaction of susceptibility genes and environmental processes, both of which could influence vulnerability to stressors or infectious agents.

Dr. S. Buka, of the Harvard School of Public Health, spoke on the **"association of prenatal and perinatal complications with subsequent bipolar disorder and schizophrenia."** Dr. Buka presented exciting data from the National Collaborative Perinatal Study, which collected blood from mothers of 17,700 children born from 1959 to 1973. He followed these children until his research team had identified 100 individuals who eventually developed schizophrenia, 100 with bipolar disorder, and 200 controls (no psychiatric diagnosis). In the first group of subjects with psychosis studied, he found a 7-fold increased risk for maternal antibodies to herpes simplex virus type-2 (HSV-2), the agent etiologically involved in genital herpes. This finding did not likely relate to nonspecific genital infections, because there was no increased risk for antibodies to HSV-1, chlamydia, or the papilloma virus. In addition, he found a 4-fold increased risk of antibodies to toxoplasmosis virus in the mothers of children who later developed schizophrenia or affective psychosis. There was no evidence of infection in the umbilical cord blood, suggesting that the infants themselves were not infected. It is possible that mothers had been previously infected, and infections in the perinatal period reactivated the viral process, either in terms of cytokine or immune activation or viral replication. There was a dose/response relationship such that increased levels of antibody titer were associated with increased risk for psychosis in the offspring.

Ed. Note: These striking findings present some of the best controlled evidence to date of specific types of infectious agents potentially acting as vulnerability factors in the later development of the major psychoses. If these findings are replicated and extended, they could lead to primary and secondary preventive treatment measures in an attempt to reduce these risk factors.

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Life Chart Highlight

Apparent tolerance to gabapentin in an ultra ultra-rapid cycling patient

The patient whose illness course is illustrated in the figure at right is a 50 year-old single male with a 30-year history of bipolar disorder. His illness course has shown a general pattern of accelerating episode frequency. After the first biphasic episodes of hypomania and severe depression, the following eight episodes were isolated and intermittent, but his illness course progressed to rapid cycling in the late 1970s and ultra rapid cycling in the 1990s (see figure). A substantial number of mood fluctuations continued to occur, reaching moderate levels of severity for both mania and depression despite a variety of treatment interventions, including: lithium monotherapy, carbamazepine (Tegretol®) monotherapy, the combination of lithium and carbamazepine, the combination of lithium and valproate (Depakote®), and triple therapy with lithium, carbamazepine, and valproate. He was treated for breakthrough manic and depressive episodes with adjunctive medication including thioridazine, perphenazine (Trilafon®), and nortriptyline (Pamelor®).

In early 1997, episodes of mania and depression continued to break through treatment, despite combination therapy with valproate, carbamazepine, and lithium, along with as-needed augmentations of unimodal neuroleptics (perphenazine, thioridazine) and nortriptyline. However, with the addition of gabapentin (Neurontin®) to carbamazepine and lithium combination treatment, an approximately 10-month remission was achieved. Nevertheless, with continued drug administration, episodic depressions of mild and moderate severity began to break through and continued to do so despite a gabapentin dose increase from 600 to 2100 mg/day.

Tolerance to Other Agents

This patient and several others in our open case series suggest that tolerance may develop to the therapeutic effects of gabapentin even when it is used as an adjunct. Tolerance development has been preliminarily and anecdotally reported with the use of gabapentin for its anticonvulsant and anti-pain effects, and further systematic long-term follow-up studies are required in order to ascertain whether this case of apparent gabapentin tolerance occurs in a substantial number of bipolar patients.

Some loss of efficacy via tolerance might be expected because this phenomenon has been reported in 25–40% of National Institute of Mental Health patients initially responsive to lithium, carbamazepine, or valproate who were followed longitudinally, either retrospectively or prospectively. If tolerance does develop, various clinicians have suggested strategies of: 1) increasing the dose; 2) adding other drugs with different mechanisms of action; or 3) revisiting the initially effective drug at a later time. Each of these maneuvers has been observed to be useful in isolated examples, but more definitive prospective studies are required to address the issue of loss of efficacy and to ascertain whether these general principles are applicable to some or all drugs wherein tolerance development is a problem.

Gabapentin Background Data

In the NIMH double-blind, randomized, 6-week comparison of gabapentin, lamotrigine (Lamictal®), and placebo in monotherapy, the 52% response rate observed with lamotrigine was significantly better than that of either gabapentin (27%) or placebo (23%). However, when gabapentin was used as an adjunctive treatment to previously ineffective regimens of mood stabilizers in the case series of Young et al. (1997; *Biol Psychiatry* 42: 851–853), McElroy et al. (1997; *Ann Clin Psychiatry* 9: 99–103), and Erfurth et al. (1998; *J Psychiatr Res* 32: 261–264), as well as within the Network patients (Altshuler et al., 1999, in press), response rates between 50% and 70% have been reported.

Thus, gabapentin will probably not have much usefulness in monotherapy for treating refractory patients, but may have a greater role in the augmentation of other therapeutic approaches in bipolar outpatients, particularly because gabapentin has positive effects in social phobia, Parkinson's disease, epilepsy, and pain syndromes. Moreover, further attention should be given to the utility of gabapentin as an adjunctive medication, particularly given that many patients in the Network have a variety of comorbid anxiety disorders (42%) and social phobia (16%) as well as pain syndromes (Suppes et al., 1999; *J Affect Disord*, in press).

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Probable Response to Gabapentin and Subsequent Tolerance to its Antidepressant Effects

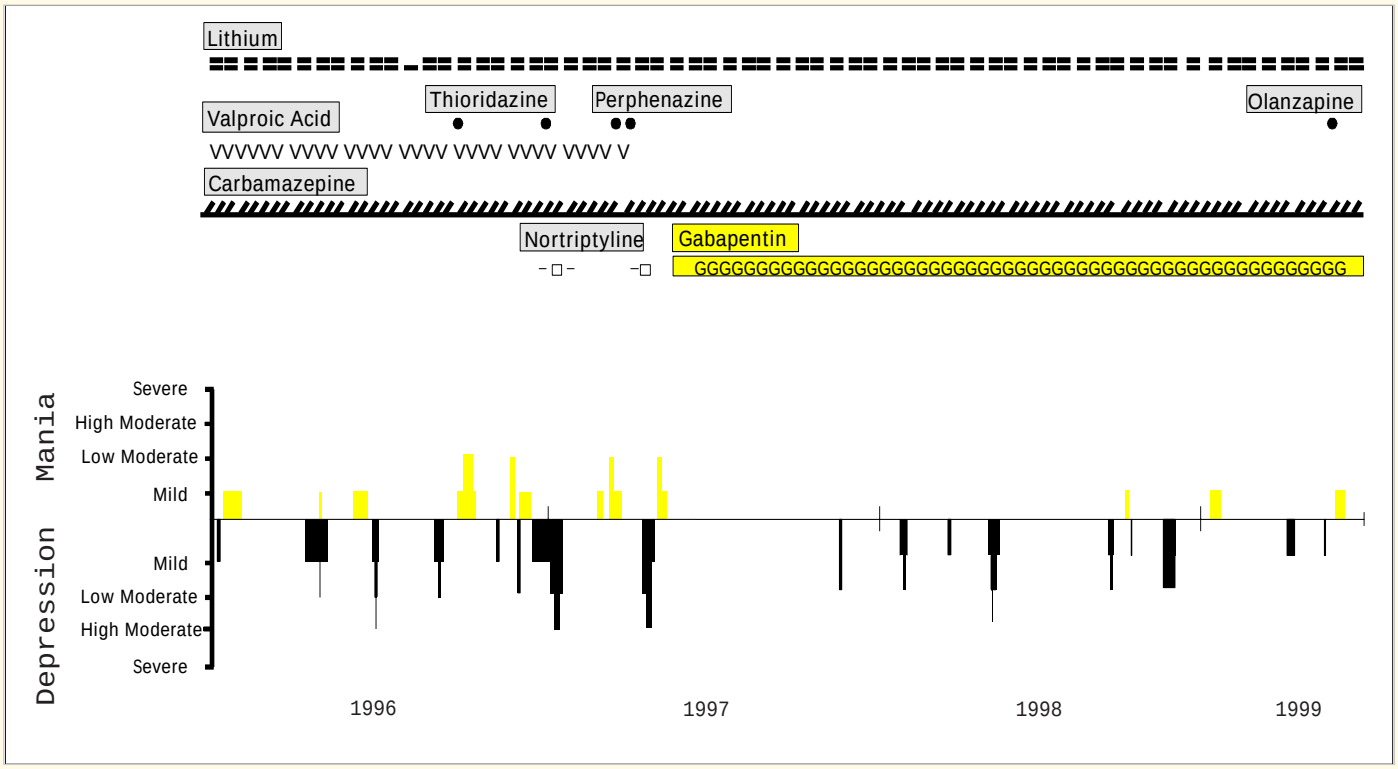

Figure 1: Gabapentin augmentation of lithium and carbamazepine was associated with the absence of hypomanic and depressive episodes for approximately 10 months. The effect on hypomania was sustained, but depressive episodes of increasing duration began to re-emerge, suggesting a partial loss of efficacy likely related to a tolerance mechanism.

Clinical Trials Update

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though both agents are currently being widely used by clinicians for bipolar illness.

Topiramate will be compared with gabapentin (Neurontin®) in a randomized, open, adjunctive trial for patients with inadequately stabilized bipolar illness. These two agents have very different mechanisms of action—topiramate decreases glutamate release and blocks glutamate AMPA receptors, gabapentin increases brain GABA levels—and have not been systematically compared for efficacy and side effects. Given the initial open Network data that both of these agents produce 50% improvement rates, we wish to directly compare them in a randomized study and potentially identify clinical and biological markers of response.

Finally, topiramate and sibutramine (Meridia®) will be directly compared for their ability to reverse psychotropic drug-induced weight gain while not destabilizing mood. Sibutramine is a recently approved agent for weight loss for patients who wish to counter their psychotropic drug-related weight gain. The relative efficacy of these two agents in aiding both weight loss and bipolar illness (without exacerbating the illness) represents important information for Network patients and the field in general.

Network Rating Instruments

The clinicians and clinical raters at each of the Stanley sites have evaluated and rated tapes of clinical patient interviews using the Structured Clinical Interview for DSM-IV (SCID)—the major diagnostic instrument for the Network—to confirm a diagnosis of bipolar disorder and to clarify any other concomitant psychiatric diagnoses. All raters (22 clinicians and clinical research assistants) have demonstrated excellent reliability in the Network (intraclass correlation r=0.93). This task had been previously successfully completed for the other rating instruments used by the Network, including the Clinical Global Impression (CGI) severity measures, the Inventory of Depressive Symptomatology (IDS), the Young Mania Rating Scale, and the NIMH-Life Chart Methodology-prospective (NIMH-LCM™-p).

Data on the ratings from the prospective form of the LCM show high correlations with the appropriate manic and depressive ratings from accepted scales such as the IDS (r=0.78) and Young Mania (r=0.66); thus the LCM now represents the most detailed and best validated longitudinal assessment instrument for bipolar disorder. We encourage all patients with bipolar illness to complete the self-rated form of the LCM because we and most of our patients have consistently found it to be an asset in the evaluation and better treatment of their illness.

Patients should not forget or underestimate the implicit message in each of the BNN life chart case presentations, i.e., the importance of consistent mood charting for optimizing therapeutics. Given the increase in the number of medications that have potential mood stabilizing effects, as well as another large group of drugs with specific antidepressant or antimanic effects, the importance of accurately assessing these drugs (used alone and in combination) with a systematic technique such as the NIMH-LCM™ becomes even more important. Moreover, if patients experience difficulties in controlling their illness, such a systematic record of previous drug response will greatly enhance the likelihood of receiving an excellent reevaluation or consultation about other approaches most likely to be effective. ■

Personal Calendar

A six-month diary

For patients who are not directly involved with the Stanley Foundation Bipolar Network, we are pleased to note that an identical version of the pocket NIMH-LCM calendar is available free of charge by contacting:

National Depressive and Manic-Depressive Association (NDMDA)
730 N. Franklin Street, Suite 501
Chicago, IL 60610-3526
Phone: (800) 826-3632
Fax: (312) 642-7243
Web site: www.ndmda.org

Network Publication Update:

Lamotrigine for the treatment of bipolar disorder: a clinical case series

Trisha Suppes[a], E. Sherwood Brown[a], Susan L. McElroy[b], Paul E. Keck Jr.[b], Willem Nolen[c], Ralph Kupka[c], Mark Frye[d], Kirk D. Denicoff[e], Lori Altshuler[d], Gabriele S. Leverich[e], Robert M. Post[e]

Journal of Affective Disorders 53: 95-98, 1999

Introduction: Early reports in epilepsy studies suggested mood improvement associated with lamotrigine treatment. More recently, published reports suggest that lamotrigine may have antidepressant and mood-stabilizing properties in patients with treatment-resistant bipolar disorder, including rapid cycling and bipolar depression. When using lamotrigine with a slow initial dose titration, there is a 3 to 8% risk of a benign rash usually requiring medication discontinuation, and a 0.1 to 0.3% risk in adults and children, respectively, of severe dermatologic reactions often requiring hospitalization.

Methods: Seventeen patients meeting DSM-IV criteria for bipolar I (n=9) or bipolar II (n=8) disorder displaying affective symptoms and a past history of inadequate response or tolerability to at least two standard mood stabilizing agents were recruited through the Stanley Foundation Bipolar Network (SFBN) and treated with lamotrigine. The SFBN consists of five sites, four within the United States and one in the Netherlands. Principal investigators are studying patients with bipolar disorder in long-term follow-up to find ways of improving treatment and management of this illness. A retrospective chart review used the Clinical Global Impression scale modified for bipolar disorder (CGI-BP) rating change in manic and depressive symptoms targeted, and overall improvement in those exposed to lamotrigine. Treatment responders were defined as much or very much improved by CGI-BP change scores for the lamotrigine targeted symptoms. Inclusion criteria required at least 2 weeks of treatment with lamotrigine and at least 50 mg/day of lamotrigine exposure (25 mg if receiving divalproex). In most cases, lamotrigine was added to stable medication regimens which were only partially effective in ameliorating symptoms.

Results: Of the 17 bipolar I and II patients who received open-label add-on treatment with lamotrigine, 11 (65%) of 17 were rated as much or very much improved on the CGI-BP for overall global improvement and for target symptoms at entry, including 6 (67%) of 9 rapid cycling patients. The mean dose of lamotrigine was 187 ± 157 mg/day (range 50–600 mg/day) for a mean duration of 159 ± 109 days (range 14–455). In the majority of patients (n=11) lamotrigine was initiated for depressive symptoms. Seven patients reported side effects, but no patients discontinued the drug due to intolerance or rash.

Discussion: These findings are consistent with other preliminary reports suggesting that lamotrigine may have antidepressant and possibly mood-stabilizing properties in patients with bipolar disorder. As with all open case series, results are hypothesis generating. Clinical data collected retrospectively in an unblinded fashion potentially bias observation toward favorable results. Also, given the recurrent nature of bipolar disorder, spontaneous improvement and remission symptoms cannot be excluded. However, these patients were relatively treatment-resistant with limited treatment response to many past medication regimens. Since lamotrigine was predominantly administered as add-on therapy, it is not possible to evaluate its independent action. However, these data are consistent with the NIMH double-blind monotherapy study (Frye et al., 1999) and the study of Calabrese et al. (1999; *J Clin Psychiatry* 60: 79–88) in bipolar depression, and suggest a future role of this agent in bipolar illness, and in bipolar depression in particular. Additional controlled studies are needed to more precisely define the efficacy of lamotrigine in mood disorders and identify clinical and biological markers of response.

[a] Dallas Network Site, [b] Cincinnati Network Site, [c] Utrecht, Netherlands Network Site
[d] Los Angeles Network Site, [e] Bethesda Network Site

Meeting Highlights: Stanley Symposium

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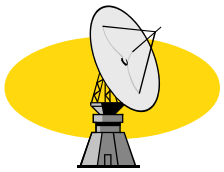

Dr. Peter B. Jones, of the University of Nottingham, spoke on the **"specificity of developmental precursors to schizophrenia and affective disorders,"** highlighting the case-controlled study of Cannon et al. (1997; *Am J Psychiatry* 154: 1544–1550) that indicated that low birth weight, poor premorbid adjustment in childhood and adolescence, and deficits in social and school adjustment were associated with the later development of schizophrenia, whereas bipolar illness was associated with less severe indices of social maladjustment later in adolescence, and no association with low birth weight. Surprisingly, there was a positive association of bipolar illness with higher socio-economic status. A review of cohort studies indicated a strong association between late onset of schizophrenia and slower onset of developmental milestones, poor motor coordination, early educational deficits, and perinatal brain damage. Strikingly, the month when a child was able to walk on his or her own without support represented a highly significant linear association with the risk of schizophrenia—later walking was associated with increased risk and earlier walking with decreased risk. The occurrence of perinatal brain damage and the occurrence of later motor milestones was even more highly associated with the later development of schizophrenia.

Dr. R. Yolken, Chief of the Stanley Foundation Neurovirology Laboratory at Johns Hopkins University, presented new evidence on **"the role of retroviruses in etiopathogenesis of schizophrenia and bipolar disorder."** Dr. Yolken found strong evidence of an endogenous retrovirus (ERV, X54—related to the Rous sarcoma virus) elevated in the brains of bipolar patients compared with all other groups, including those with schizophrenia, depression, Huntington's chorea, and controls. He also examined cerebrospinal fluid (CSF), finding evidence of ERV infection and MSRV (multiple sclerosis retrovirus, the agent etiologically involved in multiple sclerosis) infection in 35 recent-onset schizophrenics, compared with moderate levels in those with relapsing schizophrenia and no levels in 18 unaffected individuals.

For the first time, Dr. Yolken found evidence of viral replication using the electron microscope when CSF from individuals with schizophrenia was injected into new world monkey cells (which do not express the MSRV normally, but did so after CSF inoculation). When he examined c-DNA in the frontal cortex, he found evidence of some specificity with the ERV increased in the brains of patients with bipolar illness, and the MSRV, which is similar to the Mason-Pfizer monkey virus (MPMV), increased in the brains of schizophrenic patients. In addition, there was a 44% incidence of antibodies to this particular retrovirus, further supporting the likelihood that these individuals were, in fact, infected. These data raise the plausible argument that the seasonal increase in births of people who later develop schizophrenia and bipolar illness (see Dr. Torrey, above) could be related to the seasonal increase in viral infections, whereby any infection could reactivate viral processes leading to cytokine induction, whether or not there was reactivation of the retrovirus itself. Should these data be replicated, they would have profound implications for treatment of a subgroup of individuals with schizophrenia and manic-depressive psychosis.

Dr. T. Goldberg, of the National Institute of Mental Health, gave a presentation on **"neuropsychological distinctions between schizophrenia and bipolar disorder."** He reviewed the literature suggesting that many more famous individuals and those thought to have achieved expert performance in a given field, had manic-depressive illness rather than schizophrenia by a 7 to 1 ratio, even though the two occur with approximately the same incidence in the general population. He suggested that the greater severity of cognitive deficits measured in schizophrenia compared with manic-depressive illness might account for this disparity, and that deficits in working memory might particularly be implicated.

Dr. G. Pearlson, of Johns Hopkins University, discussed **"structural and functional brain changes in bipolar disorder,"** emphasizing comparisons with findings in schizophrenia. He noted that there is strong evidence for increased size of the ventricles in patients with bipolar illness in addition to those with schizophrenia, and new evidence for increases in the ventricle size of unaffected relatives of bipolar patients, a finding similar to that observed in schizophrenia. In contrast to schizophrenia, there is substantial evidence for increased white matter hyperintensities (unidentified bright objects, or UBOs) on the magnetic resonance imaging scans of patients with bipolar illness.

Ed. Note: Drs. Young and Ferrier, of Newcastle-upon-Tyne, found that these white matter hyperintensities (UBOs) were associated with winter births, again raising the possibility of an infection-related process.

Dr. Pearlson noted that the deficits in the volume of heteromodal association areas such as the dorsolateral prefrontal cortex, superior temporal gyrus, and inferior parietal lobule, which are observed in schizophrenia, are not present in bipolar patients.

Ed. Note: However, some data using magnetic resonance spectroscopy (MRS) suggest frontal and hippocampal deficits in both major psychoses.

Dr. Pearlson presented new and dramatic pictures of the brain utilizing diffusion tensor imaging which provides for

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Meeting Highlights: Stanley Symposium

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the possibility of two- and three-dimensional demonstration of the fibre bundles, as described in the work of Mori et al. (1999; *Ann Neurol* 45: 265–269). Using this new technique, one should be able to provide definitive evidence of alterations in fibre tracts should they exist in the major psychoses. Dr. Pearlson also reviewed evidence of amygdala activation with emotion induction paradigms using functional brain imaging, and presented a representative case wherein a bipolar patient showed left amygdala activation in response to negative affect emotion while euthymic, similar to that reported previously by Drs. Rauch and Pearlson for controls. However, when the same individual was depressed, the right rather than left amygdala was activated and wider areas of cortex were included as well. Surprisingly, when the patient was studied during hypomania, there was no activation in either the left or the right amygdala or in any other areas of the brain, suggesting the possibility of a ceiling effect in an already activated amygdala or a decreased reactivity on some other basis during this mood state.

Ed. Note: These data mirror those of Dr. Gyulai at the University of Pennsylvania (Gyulai et al., 1997; *Biol Psychiatry* 41: 152–161) suggesting opposite laterality of medial temporal lobe hyperactivity with single-photon computed emission tomography (SPECT) as a function of mood state.

Dr. Pearlson also indicated that in a group of unselected bipolar patients compared with controls, he was unable to replicate the exciting findings of Drevets et al. (1998; *Mol Psychiatry* 3: 220–226) indicating decreased function and substance in the subgenual part of the anterior cingulate gyrus.

Ed. Note: Drevets had observed these distinctions in those selected for pure *familial* unipolar and bipolar illness, and not in unselected populations.

Dr. B. Bogerts, of the University of Magdeburg, spoke on the **"pathomorphology of schizophrenia and mood disorders,"** and reported decreased size of the right putamen, right and left external pallidum, and left nucleus accumbens in a small group of brains from depressed patients compared with controls.

Ed. Note: These areas represent regions of decreased metabolism measured by positron emission tomography (PET), related to the cluster of depressive symptoms from the Beck Depression Inventory reflecting anhedonia and psychomotor slowing in the studies of Dunn and associates in our NIMH group.

Dr. M. Knable, Medical Director of the Stanley Foundation Research Programs, presented the initial **"findings from studies of the Stanley Foundation brain collection."** (1) The Costa-Guidotti laboratory found that reelin, a crucial factor for CNS neural development and signal transduction, was significantly reduced in area 46 of the prefrontal cortex in both schizophrenia and bipolar illness compared with depressed patients and controls. This substance is found in the Martinotti and double bouquet interneurons containing gamma-aminobutyric acid (GABA). These findings are consistent with previous reports of GABA and glutamic acid decarboxylase (GAD) deficiencies in the cortex of schizophrenics by Benes et al. (1991; *Arch Gen Psychiatry* 48: 996–1001), Akbarian et al. (1995; *Arch Gen Psychiatry* 52: 258–266), and others. (2) Dr. J. Hurd has found that neuropeptide Y (NPY), as well as the mRNA for prodynorphin in prefrontal cortex, was selectively decreased in bipolar patients. (3) Dr. Schramm and associates found that the neurotrophic factor receptor Trk-C for neurotrophin-3 (NT-3) was decreased six-fold in the frontal cortex of schizophrenic patients compared with all the other groups. In contrast, the receptor for brain-derived neurotrophic factor (BDNF) (Trk-B) was decreased in depressed patients only in the cerebellum and was attributable to those patients who were on antidepressants at the time of death. (4) This finding is convergent with data of Dr. Young and associates showing increased cyclic AMP response element binding (CREB) protein in depressed patients on antidepressants (Dowlatshahi et al., 1998; *Lancet* 352: 1754–1755). Together, these data are consistent with the earlier preclinical studies of Dr. Smith et al. at the NIMH and Dr. Duman et al. at Yale, indicating that antidepressants increase BDNF (most likely through the cyclic AMP pathway) and that antidepressant drugs are, in part, able to counter the effects of stress on gene expression. (5) Dr. Drevets and colleagues (Ongur et al., 1998; *Proc. Natl Acad Sci USA* 95: 13290–13295) examined the number of glial cells in different autopsy specimens and found that only in the *familial* depressions and bipolar illness subgroups were there decreased numbers in the subgenual cingulate cortex of area 24, but when the entire group was taken together, there were no significant differences.

Ed. Note: These differences related to family history suggest the possibility of differential pathophysiological processes as a function of genetic as opposed to experiential illness vulnerability. Loss of glial cell number and density could have very substantial effects on CNS excitability and regulatory mechanisms, because glial cells not only provide an extraordinary buffering system for the signal transducing neuronal elements, but also are able to provide protective glutamate reuptake mechanisms to prevent cytotoxicity and apoptotic cell death

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Meeting Highlights: Stanley Symposium

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as well as produce a number of neurotrophic factors that sustain neuronal growth and development. Thus, glial alterations could prove to be a major factor in psychiatric illness wherein basic CNS processes (usually dysfunctional in those with neurological disease) remain intact, but modulatory processes appear to be abnormal, and much larger and more sustained deviations in mood and behavior are the pathognomonic signs of the major affective illnesses.

Dr. R. Post, Chief of the Biological Psychiatry Branch, NIMH, and Head of the Stanley Foundation Bipolar Treatment Outcome Network, compared the **"psychopharmacologies of bipolar illness and schizophrenia."** Dr. Post noted that the typical and atypical neuroleptics provide excellent convergence across acute manic and schizophrenic syndromes, thereby implicating dopaminergic mechanisms in both states. However, the major mood stabilizers for bipolar illness (lithium, carbamazepine, and valproate) appear much less effective in schizophrenia than in either acute mania or in prophylaxis of both manic and depressive episodes. These data suggest different signal transduction mechanisms in the two illnesses with those related to cyclicity and illness progression in bipolar illness different from those in schizophrenia. Both bipolar illness and schizophrenia appear to share sensitization mechanisms whereby stressors are involved in early episodes, but later are less necessary for the triggering of subsequent episodes. Moreover, increased numbers of episodes appear to convey increased vulnerability to relapse and decreased responsivity to either lithium in the bipolar illnesses or neuroleptics in the recurrent schizophrenic syndromes.

Lithium can normalize the suicide rate in bipolar illness, as well as decrease excess medical mortality (in part caused by cardiovascular disease); recent data of Dr. Chuang at the NIMH indicate that lithium is also neuroprotective in animal models of stroke (Nonaka and Chuang, 1998; *NeuroReport* 9: 2081–2084). It might be useful to see if concomitant treatment with lithium (added to neuroleptics) might be more effective in long-term treatment of schizophrenic patients based on its neuroprotective and anti-suicide effects.

Drs. T. Kimbrell and A. Speer at the NIMH have found frequency-dependent effects of repeated transcranial magnetic stimulation (rTMS) of the brain in terms of differential effects on both mood and brain activity. Two weeks of 20 Hz rTMS significantly increased blood flow in frontal cortex (left greater than right), cingulate cortex (left much greater than right), and even in the left amygdala following stimulation of the left prefrontal cortex. Conversely, 1 Hz rTMS decreased blood flow in the same areas of brain, but to a lesser extent. These data raise the possibility of frequency-dependent modulation of areas of brain that are either hyper- or hypoactive at baseline with low and high frequency rTMS, respectively. Dr. R. Hoffman and collaborators at Yale (1999; *Biol Psychiatry* 46: 130–132) have reported that 1 Hz rTMS stimulation over the auditory cortex is helpful in reducing intensity and severity of auditory hallucinations in schizophrenic patients.

Ed. Note: These data also raise the possibility of using 1 Hz stimulation for suppressing some types of productive, positive symptoms, but also using higher frequencies (10-20 Hz) of rTMS over prefrontal cortex to reverse the hypometabolism associated with the negative symptoms of schizophrenia.

The symposium was well-received by its several hundred participants. The presenting investigators representing the constituent groups of their patients with manic-depressive illness or schizophrenia thanked Ted and Vada Stanley (who were in attendance) for their unparalleled contributions to advancing the understanding and therapeutics of these two serious psychiatric illnesses. ■

Life Chart Highlight

(Continued from page 4)

Even in the NIMH negative controlled study of gabapentin monotherapy, there appeared to be some potential markers or correlates of response to this agent, including patients who were: 1) younger at study entry, and 2) had shorter durations of illness. These relationships were not observed with lamotrigine or placebo, suggesting that younger patients early in their course of illness might be a particularly appropriate subgroup for further exploring the clinical utility of gabapentin. The major inhibitory neurotransmitter system in brain, involving GABA and its different $GABA_A$ and $GABA_B$ receptor systems, is constantly evolving. In an animal model, the $GABA_B$ agonist baclofen is very effective as an anticonvulsant in young animals, but completely without efficacy in older animals. Given its effects on GABA, there might be a similar proclivity in humans for gabapentin response in young age or early illness evolution that subsequently wanes when patients become considerably older and/or experience later, more refractory patterns of illness, as in the patient's course described here. ■

Network News Briefs

Repeated Transcranial Magnetic Stimulation (rTMS) and Patients with Depression

The NIMH Site continues to need volunteers (18 years or older) with a diagnosis of unipolar or bipolar depression who wish to participate in studies evaluating the comparative efficacy of high (20 Hz) and low (1 Hz) rTMS vs. sham rTMS (all patients will receive both active forms of rTMS [20HZ and 1 Hz] during the study). We continue to observe differential effects on mood and brain activity with low versus high frequencies of rTMS, and are attempting to ascertain which patients respond best to which frequencies. A future study at a higher intensity of stimulation (110% of motor threshold as compared to the current study set at 100%) will test 3 weeks of 1 Hz vs. 20 Hz rTMS vs. sham over the left frontal cortex. Each patient will have an opportunity for another 3 weeks of continued rTMS if they respond, or they can cross over to the other frequency should they fail to respond in the first phase. If you are interested in the rTMS study, please call Nadine Khoury or Dr. Andy Speer at (301) 402-2294.

Six-Week Comparison of Lamotrigine, Gabapentin and Placebo

The NIMH Site also continues to recruit bipolar patients with affective disorders who have not been treated with gabapentin or lamotrigine so that we can continue to examine the efficacy of these agents compared with placebo, and establish potential clinical and biological predictors and correlates of response. Currently, the data suggest that lamotrigine monotherapy is more effective than that of gabapentin or placebo. However, many of the add-on trials in bipolar illness with gabapentin show it to be effective, and the overall clinical utility of this agent remains to be further delineated. If you are interested in pharmacological intervention with lamotrigine and gabapentin, please call Gabriele Leverich, MSW, at (301) 496-7180.

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