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Bipolar Network News

Clinical Trials Update

At the October Stanley Foundation Bipolar Network meeting in Dallas, Dr. Kowatch (of the Dallas Network Site) reported an update of his randomized trial comparing lithium, valproate, and carbamazepine in mania for pre-pubertal and adolescent children. In 38 children, valproate has been the most effective medication (60% response rate), followed by lithium (40%) and carbamazepine (27%). Dr. Kowatch reports that monotherapy is usually inadequate for achieving remission. A combination of mood stabilizers, in conjunction with small doses of a psychomotor stimulant (to treat residual symptoms of attention deficit hyperactivity disorder in children who carry this additional diagnosis), is often necessary. Dr. Findling (Case Western Reserve Network Center) has also found very good responses to the combination of lithium and valproate in early onset mania, and he is conducting a randomized clinical trial to see which drug in monotherapy is more effective in long-term prophylaxis.

The details of the omega-3 fatty acids protocol were finalized at the Dallas meeting, with a consensus that 6 grams of the purified eicosapentaenoic acid (EPA) preparation would be used as an adjunctive therapy in comparison to placebo for patients with inadequate response to previous mood stabilizers. This double-blind, randomized phase of the trial would last 4 months in order to be able to detect sustained acute response and prophylaxis in patients with ultra-rapid cycling presentations. After the 4-month blind phase, all patients will be offered an 8-month open treatment phase with omega-3 fatty acids so that even those randomized to placebo in the first phase will have a substantial amount of time to evaluate the efficacy of this agent for their mood disorder. Based on the earlier work of Stoll and associates (in press, 1999), no side effects of this treatment are anticipated with the exception of mild gastrointestinal distress.

Two papers describing the methods and early results of the Bipolar Network are now in press: (1) "The Stanley Foundation Bipolar Treatment Outcome Network: I. Longitudinal Methodology," by Leverich et al., and (2) "The Stanley Foundation Bipolar Treatment Outcome Network: II. Demographics and Illness Characteristics of the First 261 Patients," by Suppes et al., both to appear in the *Journal of Affective Disorders*. This latter paper reveals a disturbing 10-year lag between the first symptoms of bipolar disorder meeting diagnostic thresholds and first treatment, and the considerable illness-related morbidity that persists despite current treatments in the community. The latter paper also reveals two important components of the way bipolar illness develops longitudinally—genetic background and early psychosocial stresses. Patients with early onset bipolar disorder (i.e., on or before age 17) had both of these vulnerability characteristics as well as a higher incidence of learning disabilities, a history of more than 20 episodes of mania or depression, a history of worsening course of illness, and a pattern of rapid cycling (particularly ultradian cycling). These and other data, again, strongly emphasize the importance of early and sustained intervention and pharmacoprophylaxis in this illness. Early onset bipolar illness should not be viewed as a benign illness responsive to watchful waiting, but one that requires much more active intervention.

Divalproex Trial in Children at High Risk

The early intervention protocol of the Network has been finalized and is now ready to submit for approval at the respective investigational review boards (IRBs) of the Network Sites and Centers. We will be recruiting children from families whose parents both have a history of affective disorders (at least one bipolar), which places the children at high risk for the development of an affective disorder themselves. The protocol design is an intended 5-year comparison of divalproex (Depakote®) versus watchful waiting with careful monitoring to determine whether divalproex would be effective in treating acute symptoms that are subthreshold for an affective disorder diagnosis, and help prevent the development of full-blown affective illness. For those patients experiencing continued or breakthrough symptoms, lithium or

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Clinical Trials Update

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gabapentin (Neurontin®) could then be added in a randomized open fashion.

Families who wish to consider entering their children into this protocol should contact the Sites and Centers nearest them (see right) or write to Emily Fergus, 5430 Grosvenor Lane, Suite 200, Bethesda, Maryland 20814; phone: (301) 496-4805; fax: (301) 402-0052; e-mail: emily.fergus@nih.gov).

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Survey: Early Symptoms Preceding A Diagnosis Of Childhood Affective Illness

Parents whose children ages 4–16 have been diagnosed with (1) **bipolar disorder**, (2) **unipolar depression**, or (3) **no psychiatric diagnosis** (children doing well in school, social, and family environments) are encouraged to participate in a retrospective survey to better define the earliest symptoms of these affective illnesses (1 and 2) compared with non-ill controls (3). This survey, which would be mailed to you, will take approximately an hour or more to complete—depending on your child's age and symptoms experienced—and will provide the Network with very important preliminary data about the early presentation of childhood affective disorders, which can then be further validated and pursued in more detail in prospective studies.

We thank all those who have already contributed to this study, the results of which will be reported. However, it now appears that we will need a substantially larger number of parents who have children with major depression in order to draw more definitive conclusions about what early behaviors are most typical of childhood onset bipolar versus unipolar illness. We hope you can contribute to this effort. Please contact Emily Fergus at the following address or phone number to participate: 5430 Grosvenor Lane, Suite 200, Bethesda, Maryland 20814 (phone: (301) 496-4805; fax: (301) 402-0052; e-mail: emily.fergus@nih.gov).

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 together with patients with bipolar disorder who participate in research studies investigating 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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Meeting Highlight

Society of Biological Psychiatry Annual Meeting
American Psychiatric Association Annual Meeting
May 27–June 4, 1998, Toronto, Canada

New data on lamotrigine and gabapentin, topiramate, nefazodone, omega-3 fatty acids, and rTMS.

A number of important findings relevant to the work of the Stanley Foundation Bipolar Network were reported at the 1998 Biological Psychiatry and American Psychiatric Association meetings held this year in Toronto, Canada. Highlights included the following:

Lithium-Valproate Combination

Dr. J. Calabrese reported on preliminary data from his randomized study comparing lithium versus valproate in long-term prophylactic treatment, after patients were stabilized on both drugs in combination and then randomized to monotherapy. Few patients entered the stabilization phase on the combination, because many dropped out for administrative or noncompliance reasons. Thus, only a small percentage of the original group was able to be entered into the clinical trial, highlighting the difficulty in studying bipolar illness.

Although the results of Dr. Calabrese's trial are still blind, a number of patients were observed to relapse in the monotherapy phase after the randomization, suggesting that for many patients, ongoing treatment with the combination may be necessary. ***Ed. Note:*** These data are similar to those of Denicoff et al. (1997, *J Clin Psychiatry* 58: 470–478) at the NIMH, indicating a low monotherapy response to either lithium or carbamazepine, but a 53% response to the combination.

Lamotrigine and Depression

Drs. Calabrese and Bowden presented preliminary data from 192 outpatients recruited from 21 sites in the U.S. and Europe, comparing 50 vs. 200 mg/day of lamotrigine (Lamictal®) to placebo for 7 weeks in patients with bipolar depression. Both 50 and 200 mg/day of lamotrigine were significantly more effective than placebo.

These data were highly convergent with those presented at the same meeting by Dr. M. Frye of the NIMH, indicating that lamotrigine monotherapy was superior to gabapentin (Neurontin®) and placebo in a 6-week, randomized, double crossover study in treatment-refractory affectively ill patients. Each patient received all 3 drugs. ***Ed. Note:*** Although this unique design (double crossover) has some liabilities such as carryover effects from the previous phase, it has many advantages over a parallel group design, particularly for patients with bipolar illness studied in a clinical research setting, such as: (1) each patient is able to be assessed for his or her potential response to both lamotrigine and gabapentin and thus has an opportunity to be exposed to two potentially clinically useful agents (see "Life Chart Highlight"); (2) the ability to include all research subjects in neurobiological measures or positron emission tomography (PET) scans versus subjects in a randomized, parallel group design, in which only one-half or one-third of the patients would be exposed to a given treatment and which would markedly increase the number of patients required to make these types of assessments; (3) greater likelihood of being able to assess whether individual patients are responsive to a given treatment phase: clinical improvement could be observed on active drug, potentially loss of response in the next phase (placebo), and then re-acquisition of improvement when the drug was reinstituted in the "response confirmation" phase; and (4) fewer patients are required to reach statistical significance compared with a randomized parallel group design.

In Frye et al.'s study, lamotrigine was found to be superior to both gabapentin and placebo ($p < 0.02$). Overall, 52% responded to lamotrigine, 27% to gabapentin, and 23% to placebo. If the first 6 week phase of the protocol was analyzed in isolation, the percentage of response would have been quite similar, but would not have reached statistical significance. ***Ed. Note:*** We continue to raise these methodological issues because arguments over optimal clinical research design are one of the reasons that bipolar illness funding for clinical trials has markedly declined at the NIMH over the past two decades. Little progress has been made in broadening patient entry criteria and accepting designs other than the parallel group vs. placebo design, which the Food and Drug Administration has traditionally required for drug approval. Given the extreme variability of clinical presentation types, as well as illness patterns and fluctuations in bipolar patients, the traditional parallel group design protocol is extremely difficult to achieve other than in a large, multi-center, expensive collaborative study such as that described by Calabrese. It is encouraging that similar quantitative and qualitative results were observed in the alternative trial design of Frye et al., with a much smaller and more intensively studied patient group.

Gabapentin and Bipolar Disorder

Dr. T. Young and colleagues reported that in an open study, adjunctive treatment with gabapentin in 30 patients with bipolar disorder was a highly effective mood stabilizer in the majority of patients. Eighty-two percent of patients during a manic phase and 55% during a depressed phase experienced improvement. Nonrapid cyclers tended to have a more robust and sustained response. ***Ed. Note:*** These findings are of particular interest because they mirror similar observations of gabapentin in open, adjunctive studies of our patients in the Stanley Foundation Bipolar Network (Suppes et al, *Journal of Affective Disorders,* in press) but not those of Frye et al. described above, using gabapentin monotherapy in a double-blind, placebo-controlled clinical trial. Further work is needed in order to reveal the utility and spectrum of action of gabapentin in bipolar illness. The initial data suggest that it is inadequate in monotherapy, but may have clinically relevant effects when used adjunctively.

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Meeting Highlight: APA

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Fluoxetine and Pregnancy

Data from an expanding case series was presented by Dr. L. Cohen and associates indicating that the serotonin-selective reuptake inhibitor (SSRI) fluoxetine (Prozac®) did not appear to be associated with any notable congenital malformations or birth defects in 31 newborns whose mothers used fluoxetine during pregnancy.

PET Imaging and Prediction of Response

Dr. T. Kimbrell et al. reported that initial PET scan data suggest a remarkable change in regional cerebral blood flow (rCBF) in responders versus nonresponders to lamotrigine, although not all of the data have been analyzed. Those patients who responded to lamotrigine started with reduced flow at baseline, that increased to above the range of a normal volunteer control group matched for age and gender. Conversely, in nonresponsive patients, baseline rCBF was within the normal range but significantly decreased during treatment with lamotrigine. ***Ed. Note:*** These initial findings are partially convergent with other studies indicating that baseline blood flow and metabolism on PET may help in predicting the degree of clinical response or choosing medication. We hope that this type of differential response can ultimately be used to help better match individual patients to optimal treatment.

rTMS Update

A symposium on repeated transcranial magnetic stimulation (rTMS) of the brain for the potential treatment of affective disorders was held at the Society for Biological Psychiatry meeting ("Antidepressant Effects of rTMS: Who, How, and Why"). New data were presented from several investigative groups indicating significant effects of active rTMS versus sham rTMS or other types of controls.

However, there continues to be considerable controversy over the magnitude and consistency of effects and, at the moment, few groups feel that the optimal parameters for rTMS have been established. Thus, it appears that further work is required to delineate the many different parameters of rTMS, including intensity, location, frequency, duration, pulse width, and interstimulus interval, as well as other more general parameters such as number of times per day or week, etc.

A partial consensus does appear to be emerging that suggests rather important lateralization effects of stimulation (see table below). Moderate to high frequency rTMS (10-20 Hz) appears to be more effective when administered to the left compared with right frontal cortex. These initial findings of Dr. Pascual-Leone et al. have now been replicated by him and another group. Moreover, in his most recent study, low frequency stimulation (1 Hz) appeared to be effective in depression when administered on the right but not the left side of the brain. Converse or reciprocal effects appear to occur in mania, wherein Belmaker et al. found therapeutic effects of 20 Hz rTMS over right, but not left frontal cortex. Initial data of Speer et al. from the NIMH suggest that low frequencies are also promising in mania when administered over left or mid frontal locations.

Dr. E. Klein et al. presented data suggesting 1 Hz rTMS over right frontal cortex was effective in patients with major depression (47% response) versus sham stimulation (17% response) in a double-blind, placebo (sham) controlled study.

Dr. L. Grunhaus described the results of his ongoing clinical trial comparing rTMS and electroconvulsive therapy (ECT). The rTMS parameters that he chose were similar to those of Dr. Pascual-Leone, utilizing 10 Hz stimulation at 90% of motor threshold over left frontal cortex.

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	Left Frontal	**Right Frontal**
High (20 Hz)	+ (20 Hz) vs sham *George et al., 1997* + (20 Hz) with baseline hypometabolism predicts response *Kimbrell et al., 1998* – (20 Hz) **not** effective for mania.....	+ (20 Hz) **antimanic** effect .....*Belmaker et al., 1998*
Medium (5-10 Hz)	+ (10 Hz) antidepressant *Pascual-Leone et al.,.....1996,1997* + (10 Hz) ≈ = ECT *Grunhaus et al., 1998* + (5 Hz) antidepressant *Nahas et al., 1998*	– (10 Hz) **not** effective .....
Low (1 Hz)	– (1 Hz) **not** effective ..... + (1 Hz) with baseline hyperactivity predicts response *Kimbrell et al., 1998*	+ (1 Hz) ↓ PTSD symptoms *McCann et al., 1997* + (1 Hz) antidepressant .....*Pascual-Leone et al., 1998* + (1 Hz) antidepressant vs. sham *Klein et al., 1998*

Response to repeated transcranial magnetic stimulation (rTMS) as a function of frequency (Hz) and hemisphere laterality (left vs. right frontal cortex) interaction.
+ = effective, – = not effective

Meeting Highlight

Collegium Internationale Neuro-Psychopharmacologicum (CINP) Congress
July 12–16, 1998, Glasgow, Scotland

The CINP, founded in 1957, is an international collegium of scientists dedicated to the study and advancement of neuro-psychopharmacology

A number of new and clinically relevant findings were presented at the 21st meeting of the CINP congress in Glasgow, Scotland:

Substance P

Dr. T. Hokfelt chaired a symposium on the neuropeptide substance P which, in the peripheral nervous system, is thought to be a critical neurotransmitter and neuromodulator of pain pathways entering the spinal cord. Dr. Hokfelt reviewed the remarkable previously published findings indicating that upon stimulation of this substance P pain pathway, the substance P receptors on the next neuron in the spinal cord undergo a dramatic transformation, whereas in the unstimulated resting condition, these receptors all remain adjacent to the outside cell membrane of the neuron. Upon painful stimulation and release of substance P, these receptors are all internalized and enter the cytoplasm throughout the cell in a highly diffuse punctate (spotted) pattern.

The consequences of this dramatic substance P receptor internalization for long-term pain responsivity are not known, but could account for some element of pain sensitization phenomena. Disappointingly, substance P antagonists that are now available in an oral form (and cross the blood-brain barrier) do not appear to be good anti-pain medications.

Nevertheless, an orally available substance P antagonist (MK-869) appears to have powerful antidepressant effects equivalent to that of the serotonin-selective antidepressant paroxetine, but with an even more benign side-effects profile. ***Ed. Note:*** Thus, one can be very optimistic that in the future, an antidepressant will become available that specifically targets a neuropeptide system rather than blocking reuptake or preventing neurotransmitter amine breakdown, the traditional mode of action of the antidepressants or monoamine oxidase inhibitors, respectively. No clinical trials of this compound have been conducted in bipolar patients to date.

Inositol

In a symposium on intracellular transduction mechanisms, Dr. S. Gershon presented data from an ongoing clinical trial of inositol in bipolar depression breaking through ongoing treatment with a mood stabilizer such as lithium, carbamazepine, or valproate. A higher percentage of patients responded to inositol than responded to placebo in the study. This finding was not statistically significant given the small sample size, but the findings are in the same direction as other clinical trials conducted by Belmaker and colleagues suggesting that high doses of inositol (12–16 gms/day) may have positive effects in depression, anxiety disorders, and obsessive-compulsive disorders, a spectrum also very responsive to SSRIs.

Dr. D. van Calker presented new data showing that all of the major mood stabilizers—lithium, carbamazepine, and valproate—downregulate the inositol transporter that carries inositol from the outside to the inside of the cell body. Thus, it is possible that actions at this site as well as the more traditional site in the membrane may be relevant to the potential effectiveness of inositol.

Tamoxifen

As reported in a previous issue of the BNN, Dr. H. Manji (see "Around the Network", p. 9) continues to observe positive effects in bipolar illness of the protein kinase C (PKC) inhibitor tamoxifen. This anti-estrogen drug, used widely in cancer chemotherapy and prophylaxis, has an even more potent effect as an inhibitor of PKC. Seven of the first 8 patients treated with tamoxifen have shown antimanic responses, usually with rapid onset. ***Ed. Note:*** This study represents one of the first potential new agents for the treatment of a component of bipolar illness (mania) to emerge from studies of the comparative actions of the mood stabilizers lithium and valproate.

Lithium and Valproate

Dr. H. Manji has further found that lithium and valproate both increase the cytoplasmic protein Bcl-2 in rat brain, which is of considerable interest because Bcl-2 prevents preprogrammed cell death (apoptosis) in response to a variety of biochemical or X-irradiation (X-ray) insults.

Dr. D. Chuang in the Biological Psychiatry Branch, NIMH, reported that lithium has neuroprotective effects for several types of cells grown in culture, and also is neuroprotective against the size of a stroke and the associated degree of neurological deficit in rodents whose middle cerebral artery is ligated. Whether the neuroprotective effects of lithium emanate from actions on Bcl-2, its ability to increase another neurotrophic factor (brain-derived neurotrophic factor, or BDNF), or an entirely different mechanism, remains to be seen. ***Ed. Note:*** The potential efficacy of many drugs acting on membrane and intracellular messengers (including tamoxifen, inositol, choline, and omega-3 fatty acids) suggests that second-messenger signaling systems may become new targets of therapeutics in the future in addition to the more traditional drug targets on the neurotransmitter amines and their reuptake mechanisms. Based on Dr. Chuang's data, clinical studies of lithium's potential neuroprotective effects should be conducted.

Donepezil

Dr. F. Jacobsen reported that the drug donepezil (Aricept®)—approved for use in Alzheimer's disease—helps reverse some of the cognitive deficits (memory loss),

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Life Chart Highlight

A double-blind, randomized, crossover design: lamotrigine vs. gabapentin vs. placebo

Bioethical and clinical implications

The informed consent process in psychiatric research involving double-blind designs and placebo

The patient depicted in this issue's Life Chart Highlight is a 28-year old male bipolar patient with a 14-year history of incapacitating psychosis, mania, and depression. Prior to his NIMH admission, he had failed to respond adequately to multiple clinical trials of a variety of psychotherapeutic agents, and remained substantially impaired by his affective illness. Previous treatment included: the mood stabilizers lithium, valproate, and carbamazepine; the antidepressants amitriptyline, imipramine, phenelzine, bupropion, fluoxetine, venlafaxine, and nortriptyline; and the antipsychotic agents thiothixine, thioridazine, trifluoperizine, haloperidol, risperidone, and olanzapine (Figure 1).

Upon admission to the NIMH, his depressive episodes were manifested by hypersomnia, anergia (lack of energy), negative ruminations, guilty religious preoccupation, anhedonia (absence of pleasure), and self-deprecatory hallucinations. With a switch into full-blown psychotic mania, his symptoms were characterized by grandiose ideation, hyper-religiosity, referential thinking, dysphoria, agitation, and persecutional delusions.

Informed Consent During NIMH Treatment

Both prior to and throughout his NIMH hospitalization, the patient was made aware of the research context of his hospitalization and repeatedly stated his willingness to undergo double-blind clinical trials with medications that might or might not be of therapeutic value to him. The patient signed a detailed NIMH informed consent statement after a thorough explanation of the potential benefits and risks involved—including the potential for developing a severe, life-threatening rash from one of the compounds that he would receive in randomized, double-blind order for 6 weeks. These double-blind, randomized protocols would involve an initial phase of medication-free evaluation, if possible; a period of up to 6 weeks on placebo or lamotrigine or gabapentin; and the randomized crossover phases to the other two agents. His family was aware of his decision and the risks involved, and supported his entry into the study.

Details of the NIMH hospitalization and course of illness are illustrated (Figure 2). Each week the patient's willingness to remain in this clinical trial was reassessed by physicians, nurses, and social workers (who were blind to medications) during weekly clinical rounds. The patient, because of clinical deterioration, was advanced early from phase I (which turned out to be placebo) to phase II and he remained in phases II and III for the full 6-week period.

Following completion of all three phases of the study, the patient was offered the option of returning to the previous phase when he had felt best (phase II), in order to reconfirm response to that medication on a continued double-blind basis. The medication at that time was still unknown to both the patient and all staff members with the exception of the collaborating pharmacist, who was not involved in any of the rating assessments or clinical care decisions. The patient again showed a partial but clinically relevant degree of improvement in this "response confirmation" mode but, because of remaining symptoms, his treatment regimen was supplemented with lorazepam (Ativan®) and then topiramate (Topamax®) (which were not helpful) before beginning an augmentation trial with olanzapine (Zyprexa®) (see BNN Vol. 4, Issue 2). Olanzapine and several other atypical neuroleptics appear to have a better side-effects profile and range of efficacy than the typical neuroleptics in treating the negative symptoms and depressive components of schizophrenia (see Table 1A, BNN Vol. 4, Issue 2).

Despite the addition of olanzapine and its supplementation with valproate, the psychotic components of the illness remained severe; thus, the patient was switched to the atypical neuroleptic clozapine (Clozaril®) with some initial success. Even with the continued presence of his father on the Unit for support, the patient wanted to return to his hometown of New York City and left the NIMH. During a month and a half of further hospitalization at an academic center in New York, the dose of clozapine was increased to 300 mg/day, lamotrigine was titrated to 400 mg/day, clonazepam (Klonopin®) was used for anxiety as needed, venlafaxine was briefly added for residual depression, and synthyroid was used for potentiating venlafaxine.

Thus, the combination of an approved agent (clozapine) for schizophrenia (requiring weekly blood monitoring), an experimental mood stabilizer (lamotrigine) found to be clearly but only partially helpful in NIMH double-blind clinical trials, a high potency benzodiazepine (clonazepam) approved for use in anxiety disorders, and venlafaxine (approved for use in unipolar depression) were used to achieve, for the first time in many years, almost complete clinical remission.

After the completion of his hospitalization in New York, the patient returned to the NIMH for his blind breaking (revealing to the patient when he had been on a particular medication). This "opening of the blind" had been deferred by him and his family until he was more stable and better able to absorb the implications for his long-term treatment. The patient's father was present during much of the discharge phase of the NIMH, as noted above, but both he and the patient wanted to await the occurrence of a more com-

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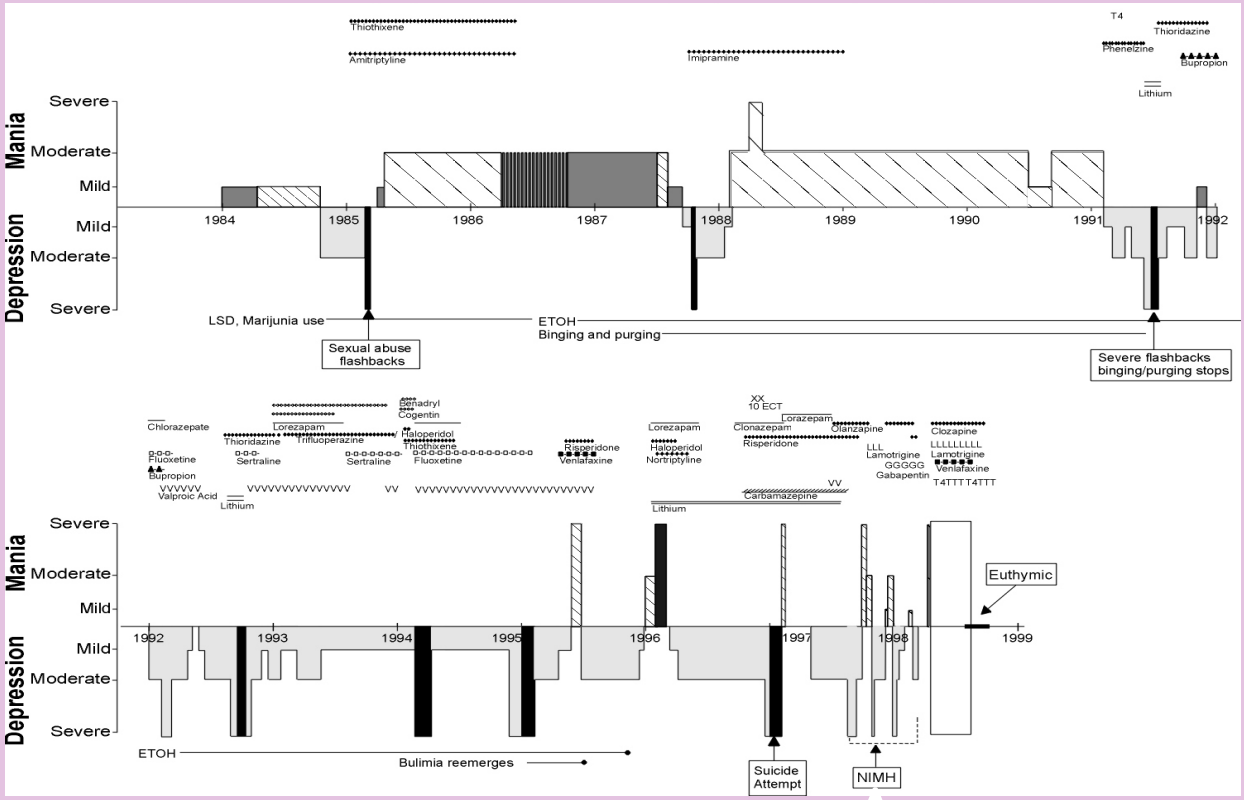

Figure 1: Fourteen years of nearly continuous BPI incapacitation and refractoriness to 20 treatments; partial response to lamotrigine; complete response with adjunctive clozapine, venlafaxine, and synthroid.

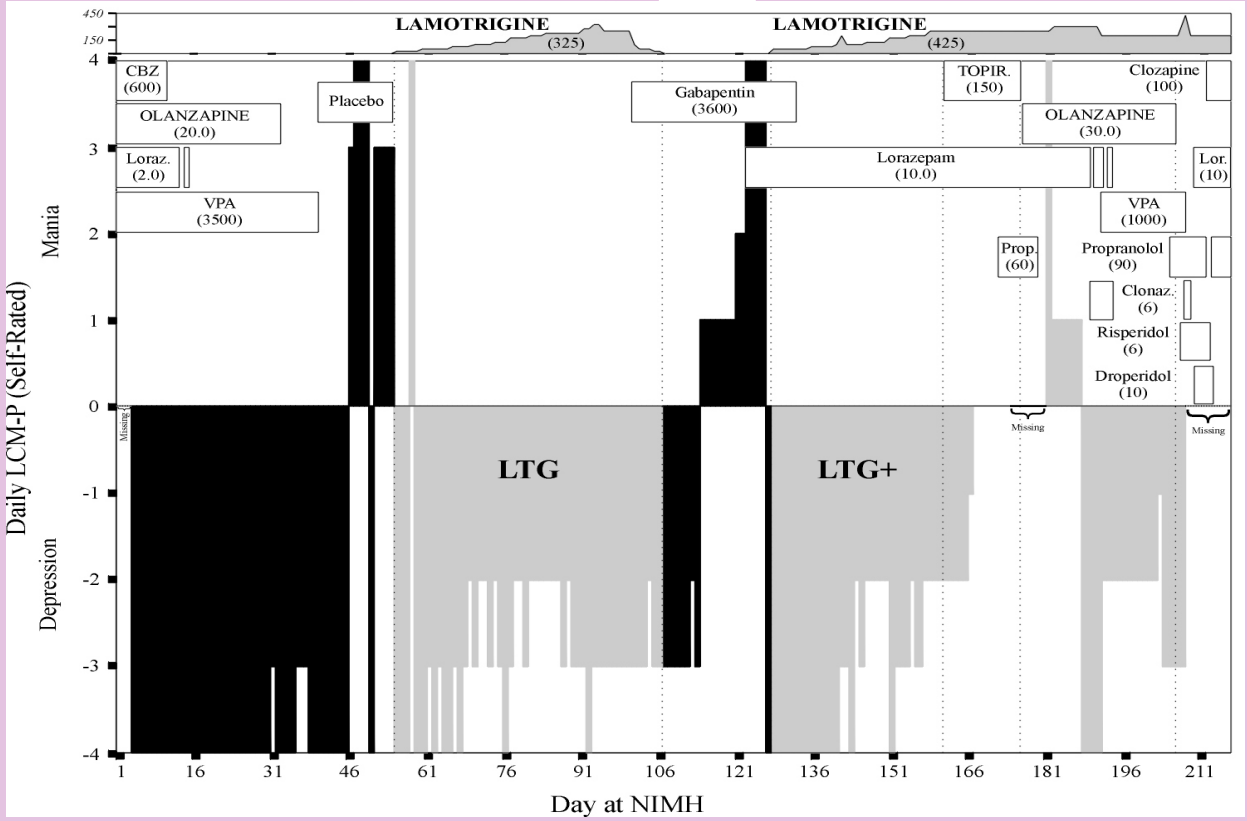

Figure 2: Confirmed partial response to lamotrigine in a double blind, off-on-off-on trial; daily dose in mg in parentheses.

Life Chart Highlight

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plete remission for more detailed aspects of the unblinding of the different medication phases.

This case report represents to us an ideal union of (1) acquiring new knowledge from a double-blind, controlled clinical trial series, and (2) markedly advancing the patient's clinical therapeutics based partially on information obtained in the double-blind clinical trial. The patient and his family, both before and after the blind breaking, appreciated the opportunity to help assess the effects of potential new therapies. Despite being markedly disabled and at times delusional, the patient was able to give informed consent about his wish to participate in the clinical trials and undergo complex research procedures, including positron emission tomography (PET) scans and regional cerebral blood flow (rCBF) with 0^{15} water requiring arterial cannulization. The patient gave ongoing verbal consent, and with acute procedures, frequently renewed his written consent. When members of the clinical research team, particularly at the beginning of the hospitalization and at mid points during his clinical trials, had questions about his ability to be managed in the clinical trials or give adequate informed consent, the patient was able to clearly indicate his wish to continue in each phase. His ability to consent was also affirmed by his father who spent significant amounts of time with his son on the Unit.

At the same time, because of his clinical research participation, we were able to obtain reconfirmed evidence of a partial response to lamotrigine, as indicated by: (1) improvement upon active treatment; (2) deterioration in mood and behavior following its discontinuation to begin another phase; and (3) re-response once the phase II agent (lamotrigine) was reintroduced on a double-blind basis in the "response confirmation" phase of the protocol (Figure 2). This evidence enabled us to use the degree of clinical improvement as a new baseline from which to attempt further treatment with other agents. As noted above, this was, in fact, accomplished, and the patient for the first time in almost two decades felt that he did not have to struggle with either a full-blown psychotic mania or moderate to severe depression. The concurrence of the patient's family with these clinical research decisions also was of considerable assistance in both supporting the patient and the staff and in enabling the full research phases of the NIMH hospitalization to be completed.

New OPRR Proposed Rules For Informed Consent

The Government Office of Protection of Patients' Research Risk (OPRR) is considering a series of new regulations that would make this type of patient-initiated clinical research participation difficult, or potentially impossible in the future. Psychiatric patients, among all of the patients with various brain diseases, would be singled out as not being able to give informed consent and would require a surrogate or ombudsman to enter into negotiations between the patient and the clinical research team concerning even initial participation in protocols.

Moreover, these proposed OPRR regulations would mandate that patients in a given psychiatric diagnostic category—such as all those with a diagnosis of depression—would not be allowed to enter into protocols in which there was more than minimal risk or in which there was no potential for individual clinical gain. Thus, if a patient with depression wished to participate in a clinical investigation of the impact of depression on coronary artery disease, he or she would be precluded from entering such a trial without an intermediary. Similarly, a patient with depression would be prohibited from volunteering as a control subject for a PET scan study examining whether particular abnormalities were specific to schizophrenia.

The problem of these new proposed regulations is not that they attempt to further enhance and assure the informed consent process, but that they stigmatize psychiatric patients as a group, treating all as a general class who have to be specially regulated. This proposed selective removal of an individual's opportunity to give consent on the basis of a psychiatric diagnosis was discussed at length at a recent National Alliance for Research in Schizophrenia and Depression (NARSAD) meeting and was vigorously attacked as a further stigmatization of psychiatric patients compared to those with other brain disorders. The American Psychiatric Association joined with other consumer groups in opposing these proposed regulations. Lana Skirboll of the Office of the Director, NIH, also formally noted the problems inherent in these proposed regulations.

Individuals wishing to obtain a copy of the proposed regulations can request them directly from OPRR (website address: http://grants.nih.gov/grants/oprr/oprr.htm). Those wishing to express opinions about these proposed regulations had been invited by the OPRR to comment. Although the initial deadline for commentary on the draft regulations was this summer, there may still be an opportunity (for those who wish to do so) to comment before the new regulations are finalized. ■

Research Update: Clozapine

In this Life Chart Highlight, we observed a patient who failed to respond adequately to the atypical neuroleptic olanzapine, but did respond to clozapine (Clozaril®). Several investigators with the Stanley Foundation Bipolar Network have published important findings involving clozapine. Clozapine has been found to be particularly promising in patients with dysphoric mania characterized by psychotic features and chronic disability (Suppes et al., 1992, *Biol Psychiatry* 32: 270–280). Clozapine has also been shown to be effective in patients with rapid cycling bipolar disorder without psychosis (Suppes et al., 1994, *Biol Psychiatry* 36: 338–340).

Dr. Frye et al.'s review "Clozapine in Bipolar Disorder: Treatment Implications For Other Atypical Antipsychotics" (1998, *J Affect Disord* 48: 91–104) indicated an equal or higher response rate to clozapine in bipolar patients compared with schizophrenic patients. As noted in the last issue of the BNN, clozapine has a variety of undesirable side effects, including the requirement of weekly blood

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Around the Network

Dr. Husseini Manji

Director, Neuropsychiatric Research Unit
Wayne State University, Detroit, Michigan

Dr. Husseini Manji of the new Stanley Center at Wayne State University in Detroit, Michigan, is one of the few individuals able to work with a high degree of excellence in the realms of both molecular biology and clinical therapeutics, and has proven his unique and creative abilities in this regard.

Dr. Manji completed both his Bachelor's of Science and Doctor of Medicine degrees at the University of British Columbia in Vancouver, British Columbia. His residency training in psychiatry was completed in 1988 at the University of Manitoba; he then came to the National Institute of Mental Health (NIMH) for fellowship training in psychiatry and psychopharmacology (1988–1990) and training in molecular and cellular biology (1992–1994). Dr. Manji has been the Director of the Neuropsychiatric Research Unit and the Laboratory of Molecular Pathophysiology since 1995 at Wayne State University in Detroit. His numerous research awards include the American College of Neuropsychopharmacology (ACNP) Mead Johnson Award in 1992, the A.E. Bennett Award for Neuropsychiatric Research in 1992, and a NARSAD Independent Investigator Award in 1998. He serves on the editorial boards of the journals *Neuropsychopharmacology* and the *International Journal of Neuropsychopharmacology,* and has published over 100 journal articles and book chapters.

Dr. Manji has spent a decade exploring intracellular signaling and transduction mechanisms to arrive at a potentially new treatment for acute mania with the PKC inhibitor tamoxifen. He has found that chronic treatment with both lithium and valproate exert common effects on two specific subtypes of the PKC enzyme and reasoned that this could relate to their actions as mood stabilizers. In order to more specifically test this hypothesis, he used the potent PKC inhibitor tamoxifen and found good response in 7 of the first 8 acutely manic patients studied (in press, *Arch Gen Psychiatry*). He is now designing a trial of a more specific PKC inhibitor without the anti-estrogenic effects of tamoxifen in order to further clarify this potential mechanism of action.

In addition, he has adopted an entirely new paradigm for attempting to identify targets for mood stabilizing agents, based on the assumption that the effects of lithium and valproate that emerge on chronic administration in animals, if they occur convergently, might provide new information. To this end, he has treated animals chronically with lithium and valproate and then subjected the brain tissue to differential display–polymerase chain reaction (DD-PCR) and defined 12 compounds that were increased and nine that were decreased for both agents. He purified one of the compounds that increases and identified it as the antiapoptotic compound Bcl-2 that could, in part, account for some of the recent observations of lithium's neurotrophic and antiapoptotic effects. In addition, he has found that both lithium and valproate increase activator protein-1 (AP-1) binding and this new DD-PCR promises to further identify the downstream effects of such transcriptional activation at the AP-1 binding site.

Dr. Manji's presentations at the Second International Conference on Bipolar Disorder (1997) and the 1998 CINP meeting (see "Meeting Highlights", p. 5) were among the most exciting talks at both meetings. His presentations of extremely complex neurobiological material are full of new data, yet are clearly delineated and understandable, even to a lay audience. His work, accordingly, is fundamentally important for understanding the mechanisms of action of the treatment of bipolar illness, and he has shown that such an understanding provides potential new targets of treatment.

The Stanley Center on Bipolar Illness at Wayne State University is directed by Husseini Manji, M.D., in the Psychiatric Department (Thomas Uhde, Chair). The Center's primary research objectives are understanding the molecular mechanisms underlying bipolar illness and its current treatments so that new therapeutic approaches with fewer side effects can be developed.

We are most grateful that his contributions have been facilitated by his Stanley Foundation Center grant, and look forward to his continued research successes in the future. ■

Research Update: Clozapine

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monitoring because of a small incidence of agranulocytosis (loss of white blood cells that are needed to fight infection).

Nonetheless, in patients with inadequate response to other treatment modalities including mood stabilizers and other atypical neuroleptics, a clinical trial of clozapine, on some occasions, can yield dramatic degrees of clinical improvement. Even though olanzapine is only one chloride molecule different from clozapine and has a very similar biochemical profile, it would appear that for some individuals, as illustrated in this Life Chart Highlight, clozapine may be more effective than olanzapine.

These data, again, stress the differences in clinical responsivity even within the same class of drugs, with some patients responsive to some types of mood stabilizers and not to others. The same differences are now apparent for antidepressants and even atypical neuroleptics. Thus, if a patient continues to respond inadequately to even complex pharmacological regimens involving several of these different classes of agents, continued exploration of treatment alternatives within each class would appear highly warranted. ■

Network News Briefs

Patients sought for studies at various Network Sites and Centers

Study volunteers sought for new study with omega-3 fatty acids, and continuing NIMH studies with rTMS and with lamotrigine vs. gabapentin

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. We continue to observe differential effects on mood and brain activity with low versus high frequencies of rTMS (see table, p. 4), and are attempting to ascertain which patients respond best to which frequencies. A new study at a higher intensity of stimulation 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 Dr. Robert Dunn at (301) 402-2293 or Gabriele Leverich, MSW, at (301) 496-7180.

Omega-3 Fatty Acid Protocol

The final details of a protocol comparing the efficacy of 6 grams of omega-3 fatty acids compared with an identical-looking placebo were completed at the Dallas Network meeting in October. This study will start with a 4-month randomized, blind phase in which omega-3 fatty acid or placebo capsules would be added to existing ineffective regimens for patients with persistent depression or cycling. After this 4-month randomization, an 8-month open extension phase with omega-3 fatty acid will be available, so all patients can be reassured that they will receive a substantial exposure to the active compound.

We are very excited about this first placebo-controlled clinical trial to be organized in the Network. All of the other Network trials have been comparisons of one drug to another. It is necessary to include a placebo in this trial in order to definitively demonstrate effectiveness of omega-3 fatty acids in bipolar illness, and in bipolar illness prophylaxis. Stoll et al. (1998) reported that omega-3 fatty acids, but not an olive oil control, were effective in preventing recurrent episodes in a small group of otherwise nonresponsive bipolar patients, in a 4-month, prospective, double-blind, placebo-controlled study (see BNN Vol. 4, Issue 1). This compound was particularly effective in the depressive component of the illness and produced few side effects. We are thus looking for patients who wish to participate in this double-blind, randomized study at the Network Sites (see box, right). These studies will be conducted as outpatient clinical trials with detailed daily longitudinal life chart methodology (LCM) ratings as well as cross-sectional measures.

Stanley Foundation Bipolar Network Site Addresses:

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B116AA, Bldg 158, Room 104
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Mood Disorders Research Program
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Los Angeles, CA 90095-7057

Cincinnati
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College of Medicine
Biological Psychiatry Program
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Bethesda
NIMH
Biological Psychiatry Branch
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Bethesda, MD 20892

Dallas
UT Southwestern Medical Center
Bipolar Disorder Clinic
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Dallas, TX 75247

Utrecht
HC Rümke Groep
Willem Arntsz Huis
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Netherlands

Meeting Highlight: APA

(Continued from page 4)

Remarkably, he continues to find effects of equal magnitude and incidence compared to ECT in his subgroup of nonpsychotically depressed patients. However, in the psychotic subgroup of patients, ECT was clearly superior to rTMS. Moreover, in all patients thought to be candidates for a therapeutic trial of ECT, a considerable percentage of those initially randomized to rTMS did not require ECT. In the majority of patients failing rTMS, particularly in this psychotic subgroup, most then went on to respond to ECT, again indicating a superiority of ECT over rTMS. ***Ed. Note:*** Given the finding that ECT has proven to be more effective than most of the traditional tricyclic antidepressants in comparative clinical trials, the ability of rTMS to be as equally effective as ECT in a nonpsychotic subgroup remains impressive and of considerable interest, particularly given the very marked differences between rTMS and ECT in cost, convenience, lack of requirement of general anesthesia, and lack of a seizure (producing a more benign side-effects profile on learning and memory).

Dr. J. Little and associates at the NIMH found no evidence of impaired learning and memory on a variety of neuropsychological and cognitive tests prior to, during, and after 2 weeks of rTMS at 80% of motor threshold at either 1 Hz or 20 Hz over left frontal cortex. In contrast, ECT at times can have notable effects on learning and memory, producing an acute confusional reaction in the immediate post-seizure period, and typically, some minimal degree of retrograde amnesia. ***Ed. Note:*** Although this amnesia typically includes only the loss of ability to recall events during the period of time of ECT or just prior to its onset, we are aware of a small numbers of patients who have had much more profound degrees of retrograde memory loss. Conversely, we are also aware of several small case series wherein ongoing prophylactic electroconvulsive therapy for patients with recurrent unipolar or bipolar depression is apparently the only treatment that is effective, with a minimum of cognitive impairment.

Dr. T. Kimbrell also reported preliminary evidence that patients with hypermetabolism at baseline were more likely to respond to low frequency (1 Hz) rTMS, whereas those with hypometabolism at baseline appeared more likely to respond to high frequency (20 Hz) rTMS. Dr. A. Speer reported that rCBF changes with these two frequencies were in the expected direction, with 1 Hz decreasing blood flow in many regions of the brain, including the frontal cortex, and 20 Hz, in contrast, increasing blood flow. ***Ed. Note:*** Previously, Dr. T. Ketter found that patients with baseline hypermetabolism were more likely to respond to carbamazepine with a normalization of this hyperactivity, particularly in the left insula, whereas those who were hypometabolic at baseline were more likely to respond to the dihydropyridine L-type calcium channel blocker nimodipine. ■

Meeting Highlight: CINP

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constipation, and dry mouth of antidepressants and perhaps lithium. He also observed several cases of new induction of mania, although changing the time of administration resolved the mania. These findings are of considerable interest because Burt et al. reported at the APA meeting that donepezil had antimanic properties in a small open study series.

Topiramate

Dr. S. McElroy presented the Stanley Foundation Bipolar Network data on 31 patients who took topiramate (Topamax®) adjunctively suggesting positive effects on mood stabilization, but with more definitive evidence of the positive side effect of weight loss, as had previously been reported in patients with epilepsy. Dr. J. Calabrese also reported on a positive open case series in 11 patients with mania treated with topiramate monotherapy, although the degree of efficacy was unclear. ***Ed. Note:*** Nevertheless, this agent appears potentially promising for adjunctive treatment of some elements of bipolar illness, with the potential utility of sustained dose-related weight loss as a positive side effect in psychiatric patients. Topiramate has a unique mechanism of action in its ability to block glutamate AMPA-type receptors, as well as a variety of other effects such as blocking sodium influx and excitatory amino acid release, increasing gamma-aminobutyric acid (GABA) effectiveness, and blocking carbonic anhydrase (the presumptive reason for a 1% incidence of kidney stones with topiramate, almost exclusively in males).

Nefazodone

Data were reported from a clinical trial of nefazodone (Serzone®) in post-traumatic stress disorder (PTSD) with positive effects not only on mood but also on sleep disturbance. Similar data have recently been published by Davidson et al. (1998, *Int Clin Psychopharmacol* 13: 111–113). ***Ed. Note:*** These data, in conjunction with the recent clinical trial of Rush and associates comparing the sleep profile of fluoxetine and nefazodone and finding nefazodone more beneficial to sleep, suggest that nefazodone may be the preferred serotonin-related agent for the treatment of PTSD. Certainly nefazodone, in conjunction with other putative mood stabilizing anticonvulsants such as carbamazepine, valproate, lamotrigine, or gabapentin, deserves further study in PTSD.

Omega-3 Fatty Acids

Dr. D. Horrobin, one of the leading pioneers in the study of the potential therapeutic effects of membrane lipids such as omega-3 fatty acids, indicated that his group had found that the eicosapentaenoic acid (EPA) type of omega-3 fatty acids is the type that is effective in depression. He will be providing a pure preparation of this compound in active and placebo matching pills so the Network can proceed with a double-blind, randomized comparison of omega-3 fatty acids as an adjunct in treatment-refractory bipolar patients (see p. 10). ■

Bipolar Network News
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