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Bipolar Network News

Clinical Trial Update

The first large-scale randomized comparison of different antidepressants in the treatment of bipolar depression has been initiated with the first patients at the Bethesda site being randomized in a blind fashion and patients in Utrecht being randomized in an open fashion. Approved protocols at the other field centers are ready for initiation in this study.

At the January 1996 Network investigators' meeting held in Bethesda, MD, nine different papers were outlined to be written this year based on data already collected from the naturalistic phase of the Network. This now includes more than 175 patients entered into long-term follow up. The papers range from those addressing the basic methodology of the Network to those addressing the reliability of specially designed scales such as the Clinical Global Impression (CGI) scale, which has been specifically modified for use in bipolar illness. Other papers will look at ways of validating several of the other instruments used in the long-term studies, such as the life-chart methodology (LCM). The LCM has been preliminarily validated against a number of different measures in the studies of Denicoff and associates.

The specially designed instruments for longitudinal assessment of patients with bipolar illness will help to accomplish the first phase of Network activities, which was to design a package of instruments that would be readily adapted by any investigator or clinician in the field for acute and long-term assessment of bipolar illness. Up to this time, a lack of consensus about methodology had been a major stumbling block in initiating NIMH-funded grant proposals in bipolar illness.

Additionally, Dr. John Rush will formally publish his set of recommendations presented at the 1994 NIMH-sponsored meeting on bipolar illness in Rockville, MD. At this meeting, he enunciated a series of principles which, when utilized, will facilitate the recruitment of patients into studies and will provide a wider acceptance of more flexible entry criteria and design characteristics so that studies in bipolar illness can receive higher priority scores for funding. These principles, nicknamed "Rush's Rules", include:

1. Inclusion of comorbidities (i.e., patients with co-morbid alcohol and substance abuse, comprising almost half of the patients with bipolar illness, should not be excluded from study).

2. Development of a semi-standardized rating package.

3. Development of a systematic longitudinal approach (to track the subtleties of mood fluctuations in both a retrospective and prospective fashion).

4. Broadening of the inclusion criteria (to accept patients with rapid cycling disorders and other illness variants).

5. Adoption of more liberal criteria for entry from acute treatment into prophylactic studies of the illness.

6. Inclusion of bipolar I, bipolar II, and bipolar NOS subjects in studies.

7. Broadening of acceptable clinical designs.

At the February 1996 meeting of the Psychiatric Research Society, Dr. Robert Post presented a review of clinical designs and statistical methods most likely to be effective in studies of bipolar patients. He highlighted an additional difficulty in the design and funding of studies in bipolar illness. The traditionally-used randomized parallel group design method that is optimal for most psychiatric illnesses, is poorly matched to the heterogeneous presentations and extreme individual variability of illness course in patients with bipolar disorders. Dr. Post suggested a variety of other options including B-A-B-A trials and crossover designs and outlined some of the methodological and statistical approaches to analyzing these alternatives. A major thrust of the presentation was the discussion of current statistical techniques that can be used to estimate the necessary trial duration for each individual that would be required to show a given degree of improvement at a given level of statistical significance. In this way, clinical trials could be designed to fit

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Managing Editor:
Robin M. Sadja

Contributors:
Robert M. Post
Gabriele S. Leverich

For communication or to be placed on the mailing list, please write or fax to:

Bipolar Network News
c/o Stanley Foundation
Bipolar Network
5430 Grosvenor Ln
Suite 200
Bethesda, MD 20814

Phone:
1-800-518-SFBN (7326)

Fax:
(301) 571-0768

Internet address:
stanley@sparky.nimh.nih.gov

Stanley HomePage:
chief@sparky.nimh.nih.gov

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the patient and his/her individual illness characteristics rather than forcing patients with diverse illness presentations into a single trial duration. A preprint of this paper will soon be available upon request.

LIFE CHART

Long-term Response to Carbamazepine Maintained with Careful Titration and Augmentation Strategies

We have chosen this patient's life chart to: 1) illustrate that remissions can be achieved when a new mood stabilizing drug is introduced; and 2) show that careful management of prophylactic treatment with the use of adjunctive medications can help maintain a good long-term response even in someone with a very severe pattern of recurrent illness.

This patient was admitted to the NIMH in 1980 with a 25-year history of multiple hospitalizations for recurrent psychotic depressions, accompanied by confusion, agitation, and mood lability. As illustrated in the life chart included in this article (page 3), she received multiple successful courses of ECT, in each instance rapidly terminating her psychotic depression. However, even with lithium, neuroleptic and tricyclic prophylaxis, she continued to cycle into profound depressions with increasingly shorter well-intervals between relapses, illustrating the phenomenon of illness acceleration previously discussed in the BNN (Vol 2, Is 1, 1996), and was hospitalized 11 times in the three years prior to her NIMH admission.

At the NIMH, the onset of new episodes of depressive psychosis were again observed. Following the institution of carbamazepine (Tegretol®) on a double-blind basis, a considerable degree of improvement was achieved. Lithium, which had previously been ineffective, was used adjunctively upon discharge and the combination of lithium and carbamazepine brought the patient the first lengthy remission after several years of incapacitating illness. Drug reduction and discontinuation in 1981-82, due to inadvertent medication alterations by the patient in the process of transition to outpatient care in her local community, resulted in rehospitalizations, further suggesting the efficacy and need for full dose treatment with this new combination therapy. Careful adjustment of lithium and carbamazepine for alleviation of side effects and the addition of thioridazine (Mellaril®, 50-100 mg) at bedtime restored the patient to a level of functioning she had not experienced in many years.

Her clinical course continued to be mapped with monthly phone calls and completion of the prospective NIMH Life Chart Method (LCM). A hospitalization for a serious medical illness (not charted) and the death of her husband, with whom she had been extremely close, did not bring relapses during treatment with the carbamazepine/lithium combination. As part of the attempt to optimize her illness, a tricyclic antidepressant was added prior to the first Christmas without her husband and the anniversaries of his death, in order to help prevent potential exacerbation of her illness. She was treated adjunctively with benzodiazepine augmentation on other stressful occasions to help with sleep and to alleviate anxiety, especially around Christmas (described by the patient as her "holiday blues"), and during intermittent difficulties with her son. Careful titration of her medications to maximize clinical effect and minimize side effects was closely maintained by her treating outpatient psychiatrist. Not only did she weather a variety of major psychosocial stressors in her life, but she has continued to remain well (with only one very brief hospitalization at her own request for some mild confusion) on this carbamazepine/lithium regimen for the last 14 years without the need for further courses of ECT.

Thus, in spite of the patient's extremely severe prior course of illness, requiring multiple pharmacotherapies and over 18 separate courses of ECT between 1956-1980 (which previously was the only treatment to bring her out of her profound psychotic depressions), the addition of a new mood stabilizer made a dramatic difference. The combination of carbamazepine and lithium yielded sustained improvement when the dose was closely

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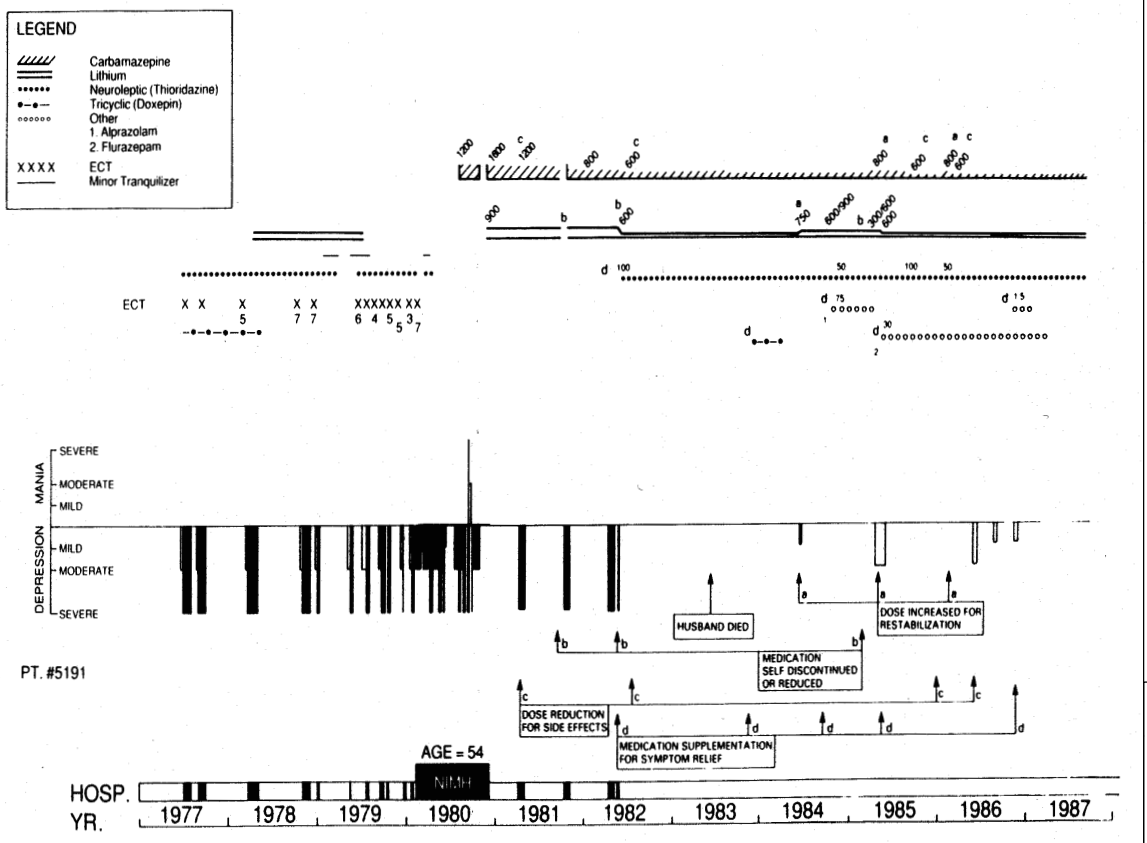
CARBAMAZEPINE PROPHYLAXIS MAINTAINED WITH OPTIMAL MANAGEMENT OF DOSE TITRATION



If you would like to construct your own retrospective life chart and track your present course of illness and response to treatment prospectively, a Life Chart Manual and retrospective and prospective LCM forms are available on request. Please call Gabriele S. Leverich at (301) 496-7180.

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titrated for efficacy and side effects, and medication augmentation was used in the face of psychosocial stress.

Her lifechart clearly reveals the importance of a detailed retrospective mapping of the course of illness and highlights the need for novel interventions in the not uncommon instances of patients' unresponsiveness to lithium and other treatment modalities. Carbamazepine, valproate (Depakote®), and other novel mood-stabilizing anticonvulsants can sometimes dramatically impact on illness course. Moreover, non-response to one mood-stabilizer does not predict non-response to another (Vol 1, Is 2, 1995). If a patient fails to improve on one type of medication, others should be systematically explored. Additionally, careful titration and augmentation of medications around periods of insomnia and increased stressors may be able to help avoid relapses. This patient is one of a series of patients who demonstrate that new prophylactic regimens can usually be found that can result in significant and sustained improvement even in the most severe forms of recurrent affective illness.

CLINICAL RESEARCH UPDATE: A Focus on Gabapentin

Gabapentin (Neurontin®) is a new FDA-approved anticonvulsant that is currently being studied for its potential role as a mood stabilizer. Gabapentin is an analog of the major inhibitory neurotransmitter in brain gamma-aminobutyric acid (GABA). Gabapentin does not appear to directly mimic GABA but is a potent inhibitor of the transporter for GABA and other amino acids. Its precise mechanism of action remains unknown but is approved for use as an adjunct in the treatment of resistant partial seizures that either have or have not become secondarily generalized to full-blown major motor seizures.

Gabapentin (Neurontin®) has a variety of attributes that make it particularly promising for an adjunctive agent in affective illness.

Thus, as a potentially unique anticonvulsant with actions above and beyond those of more traditional agents in the refractory epilepsies, gabapentin has begun to be studied for its putative mood stabilizing effects in patients with affective disorders. This is based on the indirect evidence of a variety of other anticonvulsant compounds, particularly carbamazepine and valproate, being effective in affective illness even in the absence of seizure disorder. A considerable literature also exists implicating alterations in GABA function in the potential pathophysiology of the affective disorders.

Gabapentin has a variety of attributes that make it particularly promising for an adjunctive agent. It is not bound to plasma protein and is not metabolized in humans. Absorbed gabapentin is excreted unchanged directly in urine and does not induce hepatic microsomal enzymes. Therefore, the drug is highly compatible with most other agents used in psychopharmacology and no problematic interactions have been noted with a variety of other anticonvulsant agents.

Gabapentin has a relatively short half-life of 5 to 9 hours, and the time to steady state is one to two days. There is some evidence that very high doses of the drug inhibit its own transport into the brain, making it potentially even safer than expected in situations of overdose. Gabapentin comes in pills of 200, 300, and 400 mg which are best initiated with a night-time dosage, as transient drowsiness often accompanies initial doses. Because of the relatively short half-life and potential effects on transport as dosages are increased, b.i.d. and q.i.d. doses are recommended. Doses of 1200 to 1800 mg/day resulted in a 57% decrease in seizures in one study and a reduction of seizure frequency by one half in some 31% of patients in another study. Extensions of these studies have reported doses up to 3600 and 4800 mg/day with good toleration even at these large doses.

The most frequent side effects reported are somnolence (15%), fatigue (13%), dizziness (7%) and weight gain (5%). No systematic studies of the efficacy of gabapentin have been reported in affectively ill patients to date. However, gabapentin is currently being studied in several open clinical trials and one placebo-controlled, randomized, parallel group design study at the NIMH. Network investigators Drs. McElroy, Keck, and Suppes have reported promising effects of gabapentin in several patients as a potential mood stabilizer alone or in augmentation with other anticonvulsants such as valproate. Two of the first nine NIMH patients treated with gabapentin monotherapy in a double-blind randomized trial have shown evidence of a good response to this agent when they had been refractory to many other treatment modalities (Frye et al, 1996).

The field eagerly awaits more systematic data on the potential efficacy of gabapentin in the treatment of bipolar illness and a delineation of its ultimate role in the treatment algorithm for patients unresponsive to more conventional approaches. It is hoped that the Stanley Foundation Bipolar Network, in conjunction with NIMH-sponsored trials and industry-sponsored controlled investigations, will rapidly provide answers to the question of the possible role of gabapentin in the treatment of affective illness.

CLINICAL HIGHLIGHT

Barrickman et al reported that bupropion (Wellbutrin®) was equal in efficacy to methylphenidate (Ritalin®) in the treatment of attention-deficit hyperactivity disorder (ADHD) in the *Journal of the American Academy of Child and Adolescent Psychiatry*, 34:649-657, 1995. These findings are of potentially great importance for children of bipolar parents who present with ADHD, which is often difficult to distinguish from mood lability and other aspects of the early presentation of bipolar illness.

To the extent that bupropion is a widely accepted antidepressant for adults in the treatment of depression in general, and bipolar depression in particular, and has been used in conjunction with lithium in some cycling and rapid cycling patients with a considerable degree of success, one could consider the first use of bupropion in children with ADHD-like symptoms from families with histories of bipolar illness. Thus, regardless of whether the behavior was a manifestation of affective illness or ADHD, bupropion might be able to treat it.

In contrast, methylphenidate is only effective in ADHD and there is some concern about its inability to be an optimal treatment in bipolar patients. While this possibility remains to be directly tested, it should be recognized that for children of bipolar parents who present with ADHD-like problems, treatment options other than the psychomotor stimulants (amphetamine, methylphenidate, or pemoline) are available for consideration.

MEETING HIGHLIGHTS

CINP Satellite Meeting - February, 1996
La Jolla, California

This meeting, jointly sponsored by Lewis Judd, M.D., President of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) and the Chair of the Department of Psychiatry, University of California at San Diego (UCSD), and the National Depressive and Manic-Depressive Association (NDMDA), focused on the long-term course of recurrent unipolar depressive illness. A series of potential advances in the treatment of refractory depression and the variable course and incomplete response that patients often obtain with traditional acute therapeutic approaches was highlighted at this meeting. Long-term and prophylactic treatment approaches to the illness were emphasized throughout. The first day's session stressed that virtually all known active antidepressants interact directly or indirectly with serotonergic systems, including those that are relatively selective for noradrenergic mechanisms, such as desmethyl imipramine (DMI), desipramine (Norpramin®), or maprotiline (Ludiomil®) which indirectly affect serotonergic tone.

Dr. Claude de Montigny (the 1995 Selo Prize awardee for his work with lithium augmentation and understanding its potential mechanisms in augmenting serotonin responsivity of the antidepressants), and Dr. Steve Stahl presented some of the basic data on the different mechanisms exerted by the serotonin-active antidepressants. In addition to reuptake blockade making more serotonin available at the synapse achieved by the standard Serotonin Selective Reuptake Inhibitors (SSRIs) Prozac®, Zoloft®, and Paxil®, a new drug nefazodone (Serzone®) also blocks 5HT2 receptors (which tend to be increased in depressive illness). Buspirone (Buspar®) acts directly at 5HT1A autoreceptors and thus is often a useful augmenting strategy, and in some instances investigators believe that it helps treat the gradual development of loss of efficacy to the SSRIs. Lithium augmentation increases both

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the uptake of tryptophan (a precursor of serotonin biosynthesis) and increases release and sensitizes some types of serotonin receptors. This increased pre- and post-synaptic effect of lithium is thought to relate to its ability to potentiate a variety of antidepressant modalities. Inhibiting serotonin synthesis with a tryptophan-depleting diet transiently reverses the antidepressant effects of serotonin-active antidepressants, which further strongly implicates serotonin mechanisms in the antidepressant effects of these drugs. However, this manipulation causes no exacerbation of depressed mood in those responsive to DMI or other norepinephrine-active drugs, suggesting that different drugs can act through very different pathways.

A new drug, mirtazapine, with a new mechanism of action as an alpha-2 blocking agent was described that increases serotonin impulse flow by acting upon the noradrenergic alpha-2 autoreceptors on the cell bodies of serotonin neurons. This new drug with a new mechanism of action should be available soon.

A new Reversible Inhibitor of Monoamine oxidase type-A (RIMA), befloxatone, was also discussed. Befloxatone is more potent than moclobemide and appears to be devoid of the problems of other nonselective MAOIs for increasing vulnerability to high blood pressure with dietary tyramine. This is one of the chief reasons that the MAOIs tranylcypromine (Parnate®) and phenelzine (Nardil®) are less widely used, even though they have the highest percentage response rate of any of the drugs used for patients who initially fail the first or second antidepressant treatment trial. It is hoped that befloxatone will eventually be an important addition to the therapeutic armamentarium for depressed patients, allowing patients to have a safe, novel antidepressant modality without having to fear that minor dietary indiscretions will precipitate a hypertensive crisis. However, approval by the FDA may be one to two years away.

[Editor's note: If one is on a nonselective MAOI, such as Parnate or Nardil one should carry a 10 mg capsule of the calcium channel blocker nifedipine so that if a severe headache (perhaps suggestive of a high blood pressure reaction) were precipitated, one could take this drug (which has a relatively quick onset of action in lowering blood pressure and treating the associated headache) on the way to a doctor's office or an Emergency Room for appropriate blood pressure monitoring.] The MAOIs potentiate serotonin, dopamine, and norepinephrine by virtue of their inhibition of the breakdown of each of these substances. Thus, they may provide a broader spectrum antidepressant, not only potentiating serotonergic mechanisms, but also the other neurotransmitter systems implicated in depression (dopamine and norepinephrine).

The A-selective MAOIs such as clorgyline (not available), moclobemide (available by mail from Canada), and the potential new drug befloxatone, inhibit MAOI type-A which is localized in areas of brain containing norepinephrine cell bodies (the locus coeruleus), serotonin cell bodies (the raphe nucleus), and in limbic areas of brain (the hippocampus, nucleus accumbens, cingulate gyrus, and prefrontal cortex), each of which has been implicated in depression. Thus, it is hoped that these A-selective drugs will be as effective as the older nonselective MAOIs that block both types of MAOIs, and will be much safer because of the lack of a tyramine effect on blood pressure.

Dr. Hagop Akiskal reviewed the other antidepressants and some of their unique properties in clinical practice. He highlighted the utility of venlafaxine (Effexor®) as another treatment for refractory depression because of its ability to block the reuptake of both norepinephrine and serotonin. Venlafaxine often has substantial problems with side effects in the first several weeks of treatment, may be slightly activating and anxiogenic in the initial phases, but with slow upward titration, appears to be highly effective in many patients not responsive to other first line treatments. Bupropion (Wellbutrin®), which has dopaminergic properties, appears to have fewer problems with weight gain, sexual dysfunction, and (possibly) switching into mania than some of the other antidepressants, although this remains

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Recruitment of volunteers who have responded well to lithium for at least five years

We are seeking to identify characteristics of bipolar illness associated with a good response to lithium. If you have been taking lithium and have been well for more than 5 years, please call Nancy Palmer at: 301 496-6827 or write for a questionnaire survey to:

NIMH/BPB
10/3N212
10 Center Dr
MSC1272
Bethesda, MD
20892-1272.

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to be more definitively demonstrated, and will be one of the focuses of the first SFBN antidepressant trial comparing bupropion with the SSRI sertraline (Zoloft®) and SNRI venlafaxine (Effexor®). Nefazodone (Serzone®) also appears to cause less sexual dysfunction than the SSRIs, perhaps because of its blockade of 5HT2 receptors. This mechanism of action is also thought to account for why the drugs relatively selectively increase the deeper phases of slow wave sleep (SWS), which are often remarkably suppressed in depressed patients. This loss of SWS often occurs in association with a decreased time to enter the REM (rapid eye-movement) phase of sleep associated with dreaming; i.e., the classic and well-replicated finding of a short REM latency in seriously depressed patients. Trazodone (Desyrel®) also appears to block 5HT2 receptors and this may be the reason that it has been associated with priapism on very rare occasions, although this has not been reported for nefazodone (Serzone®).

Dr. Jules Angst highlighted the variable long-term course of depressive illness in a remarkable community sample of 20-year-old men and women in Switzerland followed for an additional 15 years. The high prevalence of depression in the general population was documented with an approximate double incidence of major depression in women compared with men (12% lifetime incidence in men and 24% in women) and of recurrent brief depression (RBD) (with another 8-12% of the total population who have RBD). Both are associated with considerable disability.

Dr. Angst additionally emphasized that patients can present with recurrent brief depression and minor types of depression that proceed on to more major depression. Major depression can change its form to a more recurrent brief pattern; e.g., multiple short brief episodes typically lasting one to three days and occurring several times per month (not associated with the menstrual cycle in women). This recurrent form of depression is said to be poorly responsive to traditional antidepressant modalities and preliminary, but placebo-controlled data from several patients studied on our unit indicate that the calcium channel blockers may help some patients with recurrent brief depression (Pazzaglia et al, *Psych Res,* 49:257-272, 1993). The incidence and magnitude of responsivity to this class of agents remains for further study in larger numbers of subjects.

In contrast to the brief and episodic patterns of RBD, new data on the robust response to antidepressants in patients with chronic low-level depression (i.e., dysthymia) was presented. These patients also show a high-incidence of relapse on treatment discontinuation. These and a host of other data suggest the continuity between minor and chronic and major and episodic depressive disorders, and the importance of treating each because of the involvement of considerable pain, disability, and potential for suicide. Whether early intervention in the treatment of the less severe forms of depression, particularly in those with a family history of mood disorders, would prevent the onset of more full-blown episodes, remains to be more fully studied but would appear to be a conservative approach to the illness.

Dr. Judd reviewed data that showed that major depression is associated with greater disability in social and employment functioning than many of the other major medical disorders, including heart disease, diabetes, and arthritis. Despite the tremendous psychological, social, and employment impairment associated with depressive illness, all of the presenters indicated vast undertreatment of this disorder in the general population, particularly in the U.S.

Data of Dr. Giovanni Fava indicated that once a patient has achieved a full remission on antidepressant medication, ten sessions of cognitive behavioral therapy (CBT) compared with no treatment may help forestall relapses which occur in 70% of unipolar patients receiving no medications and in 35% of those having received CBT. Whether these findings are generalizable to other populations of recurrent unipolar depression remains to be demonstrated. Currently, we strongly endorse the need for continuation of prophylaxis (which drops the relapse rate at one year of about 50% on placebo to under 25%

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Dr. DePaulo's group has evidence that paternal transmission of bipolar illness is on chromosome 18. This has been replicated by Gershon et al. DePaulo believes the risk for BPII illness is conveyed on chromosome 18.

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on maintenance antidepressant medications).

The focus of the meeting was unipolar illness, but Dr. John Kelso of UCSD mentioned that his group and several others have found evidence of another vulnerability marker for bipolar illness on chromosome 5, in addition to the now replicated findings on chromosomes 18 and 21 of the Berrettini/Gershon and DePaulo groups. What makes Dr. Kelso's findings so provocative is that, for the first time, a putative biochemical substrate of this genetic vulnerability has been identified, i.e., it is thought to involve the dopamine transporter or dopamine reuptake mechanisms. This is of considerable interest as a faulty or sluggish dopamine reuptake mechanism could lead to the relative excesses of dopamine postulated in mania and some of the alterations in dopamine and its metabolite HVA also reported in retarded depression. These findings would, as well, be convergent with some of the pharmacology of bipolar illness, wherein dopamine-active drugs such as bupropion (Wellbutrin®) and nomifensine (before it was withdrawn from the market) are highly effective antidepressants, and drugs that block dopamine receptors post-synaptically, such as the typical and atypical neuroleptics, are antimanic.

AROUND THE NETWORK

Dr. Lori Altshuler, M.D.

Dr. Lori Altshuler is the principal investigator at the Los Angeles field center of the Stanley Foundation Bipolar Network. She is the Director of Mood Disorders Research at the University of California - Los Angeles (UCLA) Neuropsychiatric Hospital and Chief of the Bipolar Disorders Outpatient Clinic at the West LA VA Hospital. She is renowned for her studies on the pathophysiology and treatment of bipolar illness.

After graduating from Cornell Medical School and attending UCLA-NPI for psychiatry residency training, Dr. Altshuler came to the NIMH for a clinical research fellowship from 1987 to 1989. During this time she distinguished herself as one of the most outstanding young investigators in the field. She emulated her renowned mother-in-law (Dr. Jan Stevens, who was a pioneer in the field of the pathophysiology of schizophrenia), and studied patterns of hippocampal neuronal orientation and volumetric MRI studies of limbic system areas (temporal lobe and hippocampus) in patients with schizophrenia, bipolar illness, and other psychiatric disorders compared with normal volunteer controls. Her recent meta-analysis documented increased numbers of periventricular densities on MRI scans, particularly in bipolar I patients compared with controls. These data stand with many other pieces of data indicating brain pathology in the bipolar affective disorders.

Dr. Altshuler has also completed an analysis of the role of antidepressant medication in precipitating manias and causing cycle acceleration, finding a likely role of antidepressants in causing the problems in 35% and 26% of treatment-resistant bipolar patients, respectively. Her analysis was unique in not counting the high incidence

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(82%) of manic switches observed during treatment with antidepressants, but only indicating where such a switch was unlikely to have occurred based on the natural course of illness, and thus be more likely attributable to the antidepressant intervention per se. Much controversy remains on the optimal treatment of depression occurring in bipolar patients and the Network looks forward to the strong methodological, statistical, pharmacological and neurobiological perspectives that she brings to the SFBN.

Dr. Altshuler has also taken a special interest in the impact of bipolar illness and its treatment on women, their reproductive system, and the potential liabilities for childbearing. This important issue is briefly reviewed in this edition of the BNN. (See **Consumer Corner**).

Dr. Altshuler's father is the Chairman of the Department of Psychiatry at Southwestern Medical School in Dallas, TX, thus attesting to the role of both heredity (Dr. Kenneth Altshuler) and environment (mother-in-law Jan Stevens) in the unfolding of a sterling academic career. Dr. Altshuler is no doubt supported and influenced by her husband Carl who specializes in emergency medicine and their two children Eric (age 7) and Daniel (age 4) who strongly encourage her academic interests.

CONSUMER CORNER

Use of Mood Stabilizing Drugs in Pregnancy: Teratogenic Effects

Cardiac and great vessel (Ebstein's) anomalies have been reported to occur with a higher frequency than expected in patients treated with lithium during pregnancy. However, recent retrospective and prospective studies have indicated that the risk may be only slightly greater than in control patients not exposed to lithium and in the normal population[A]. The risk is about 1/20,000 in normal controls and only about 10/20,000 in patients on lithium, i.e., 1/2000 which is small. In light of those data and the substantial risk of episode recurrence and its possible effects on the subsequent course of illness if lithium were stopped, the general practice of discontinuation of lithium in all patients wishing to become pregnant should be reevaluated.

Lithium may be safer than valproate or carbamazepine for the patient with prior frequent, severe, psychotic, or suicidal episodes that might render discontinuation inadvisable (Suppes et al, 1991; Faedda et al, 1993). However, if lithium is to be discontinued for a planned pregnancy, discontinuation should be accomplished extremely slowly, since a taper is less likely than rapid discontinuation to be associated with episode recurrence.

Recently, an increased risk of inducing minor congenital malformations has been reported for the anticonvulsants. Most disappear with time. A substantial and increased risk of spina bifida has been reported for valproate. The risk is only slightly lower with carbamazepine, and use of both of these mood-stabilizing agents should be avoided during the first trimester in pregnancy if possible[B].

Using the lowest effective doses and supplementing with folic acid should be considered in patients who need these agents during pregnancy. Consultation with a specialist for fetal monitoring and assessment of possible defects with ultrasound and other techniques is also recommended. Persisting biochemical alterations have been found in some animal studies of fetal exposure to antipsychotics, but have not been assessed systematically in follow-up studies in humans for their impact on mood, cognition, or behavior. Dubovsky argues that calcium channel blockers are particularly effective in those showing a positive response to lithium, and since they have not been associated with teratogenic effects, may be a very valuable lithium alternative during pregnancy. Use of the high potency benzodiazepines or the typical neuroleptics have likewise not reliably been associated with any specific fetal abnormality. ECT has been suggested to have the lowest risk to the fetus among the somatic treatments, but risks to the fetus from maternal seizures have not been adequately elucidated.

In summary, the revised view is as Jacobson states "... lithium is not a major teratogen. We

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believe that women with major affective disorder who wish to have children may continue lithium during pregnancy, and do not need to terminate pregnancy provided that level II ultrasound and fetal echocardiography are done" (*The Lancet*, 339, p. 533, 1992).

Further Reading

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Bipolar Network News

Stanley Foundation Bipolar Network
5430 Grosvenor Lane
Suite 200
Bethesda, Maryland 20814

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