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Stanley Foundation Bipolar Network
An NIMH-NAMI Research Institute Program

Bipolar Network News

Clinical Trial Update

Robert M. Post, M.D.

Welcome to the SFBN and to the New Year. During a very productive 1995, the Network recruited 148 patients into the naturalistic phase studies at the Los Angeles, Dallas, Cincinnati, Bethesda, and Utrecht sites. Dr. Joseph Westermeyer from the Minneapolis VA in Minnesota has also joined forces with the Network and will be participating in the naturalistic studies and in the first randomized double-blind protocol comparing bupropion (Wellbutrin®), sertraline (Zoloft®) and venlafaxine (Effexor®) in bipolar patients on mood stabilizers who have break-through depressions during their ongoing long-term maintenance treatment. The sites are ready to begin these studies in an open phase with a transition to the double-blind phase later this Spring when the blinded preparations and the slow release formulation of bupropion become available from the respective drug companies.

In the meantime, we thank each patient and clinician for their contribution to the Network in helping to extend the knowledge base in bipolar illness. From the data already collected, nine studies have been outlined to be written up this year. While major strides have been made to advance studies in bipolar illness through various aspects of Stanley Foundation-supported and other research funding efforts, the relative neglect over the past decade of research in bipolar illness compared with the other major psychiatric disorders has not, as yet, been adequately corrected. For example, at the recent major psychopharmacology meeting, the American College of Neuropsychopharmacology (ACNP) in December 1995, there were 14 half-day scientific panels on topics related to schizophrenia, and none specifically on bipolar illness (although three did pertain to various aspects of the depressive disorders).

The initiatives which the Stanley Foundation has helped to support in the area of bipolar illness have already begun to rectify this deficient funding of bipolar research. There has never been a more exciting time for new developments, drug discovery, and approaches to recurrent affective disorders than at the present, and there are a panoply of studies in the bipolar disorders that beg only for adequate funding.

At our January meeting in Washington, D.C. the SFBN decided, among other things, to pursue a randomized comparison of the prophylactic effects of high- versus low-dose valproate (Depakote®) and, possibly, carbamazepine (Tegretol®). Patients will be able to participate in this randomized trial in order to discover whether, as postulated, higher doses of these anticonvulsants achieve better long-term prophylactic effects and are tolerated almost as well as lower doses. Patients will be able to enter this randomized prophylactic trial as well as those evaluating the relative efficacy of the antidepressants, should they have need for such treatment because of a depressive breakthrough during their prophylactic treatment.

The Network is also discussing a clinical trial of gabapentin (Neurontin®) versus placebo for patients with refractory manias or cycling despite treatment with regular mood stabilizers. These types of add-on trials should provide important new information about alternative approaches using drugs with different mechanisms of action that may be helpful in bipolar illness, as initial case reports and uncontrolled studies suggest. Another promising drug that may play a role as a mood stabilizing anticonvulsant with antidepressant properties is lamotrigine (Lamictal®) (See page 4 of this issue).

During a very productive 1995, the Network recruited 148 patients into the naturalistic phase studies...

As we begin 1996, the Network is interested in hearing from patients who have been well on long-term treatment with lithium. We are studying the characteristics of patients with treatment-responsive illness compared to those groups of patients, studied at the NIMH and other sites, who are not as responsive to lithium and require a variety of alternative treatments.

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The SFBN is now in the process of recruiting bipolar patients who have been well stabilized on lithium for at least five years.

If readers of the BNN, their relatives, or friends know of such individuals who have had excellent and long-term sustained responses to prophylactic treatment with lithium, and who would be willing to respond to a confidential questionnaire outlining the characteristics of their illness, we would appreciate hearing from them. Please call 1-800-518-SFBN(7326) or write to the SFBN 6001 Montrose Road, Suite 809, Rockville MD 20852 to gain further information about participation in this study and to receive a questionnaire.

LIFE CHART - HIGHLIGHT

Response to the Lithium-Carbamazepine Combination and the Problem of Episode Reemergence.

Gabriele S. Leverich, M.S.W.

With the ongoing expansion of the SFBN, the construction of a retrospective life chart (**LCM**-R) and daily prospective life charting continue to be important clinical tools for all participating patients. Monitoring and recording of current mood and associated functional impairment on the prospective (**L**ife **C**hart **M**ethod-**P**rospective) **LCM-P** rating form takes only about two or three minutes at the end of the day and enhances patient participation in the management of their own illness.

Retrospective life charting continues to teach us much about the course of bipolar illness and the details of prior treatment response in bipolar illness. As part of our ongoing emphasis on the usefulness of mood charts we would like to present another life chart which reveals many of the fundamental aspects of bipolar illness that were initially described at the turn of the century by the German psychiatrist Emil Kraepelin in the untreated patient and which we can still observe in patients initially unresponsive to treatment.

This patient's life chart (see page 3) illustrates the general tendency for the untreated or inadequately treated illness to progress. While the patient's initial course of illness was characterized by longer well intervals, the patient began to cycle more rapidly and regularly in a relatively continuous pattern following antidepressant treatment despite co-treatment with lithium.

After two years of continuous cycling and a more prolonged depression, the patient entered a new phase with episodes lasting less than a week (in a pattern that we call ultra-rapid cycling), with further progression to an even more accelerated phase of documented mood switches occurring within a single day, (called ultra-ultra rapid or "ultradian" cycling). We very carefully monitored and recorded her cycling pattern when she was at the NIMH by mood ratings performed by nurses and the patient every two hours. We described this phenomenon of ultradian cycling as an aspect of bipolar illness heretofore not well documented in the literature (Kramlinger & Post,1996; George et al, 1996; Pazzaglia et al, 1993). The prospective life chart (the LCM-P) is constructed to help track ultradian cycling by providing a space in which to indicate the number of mood fluctuations that occur over a 24-hour period.

The patient showed an initial incomplete response when started on carbamazepine (Tegretol®) on a double-blind basis at NIMH. The addition of lithium, which had previously been ineffective alone or in combination with antidepressants, produced a period of remission that lasted approximately four years, during which the patient returned to a high-stress job able to function well.

Minor episodic depressive breakthroughs, however, occurred occasionally during remission, and continued to emerge with gradually increasing severity and rapidity. Adjunctive antidepressant interventions with a variety of agents were not effective in preventing further breakthrough depressions. A switch from carbamazepine (Tegretol®) to valproate (Depakote®) did not produce the hoped-for response in this patient. The addition of desipramine (Norpramin®) to lithium eventually brought a year-and-a-half period of renewed good functioning, but significant depressive break-

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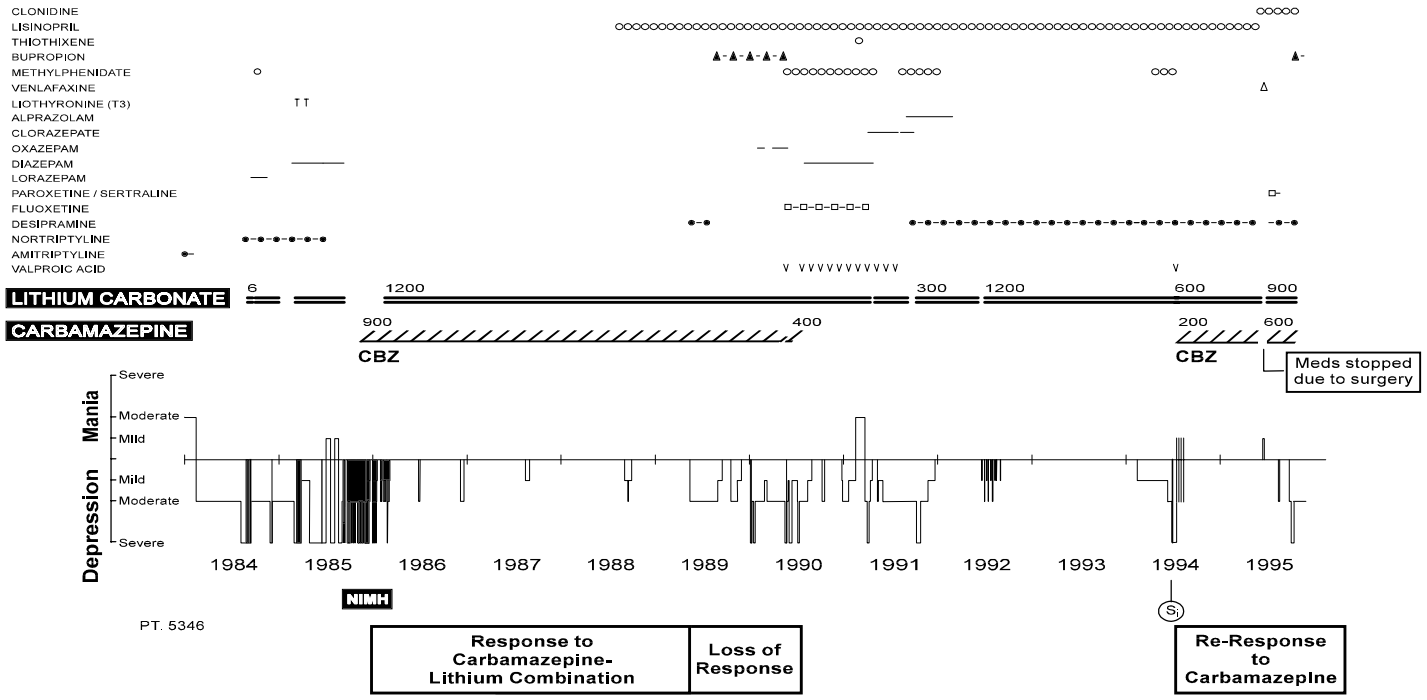
LOSS OF RESPONSIVENESS TO CARBAMAZEPINE-LITHIUM COMBINATION: RE-RESPONSE TO CARBAMAZEPINE AFTER PERIOD OFF DRUG



This patient's rapid cycling is not atypical and is representative of a group of patients who appear to do better on the combination of lithium and carbamazepine (Tegretol®) than on either medication alone.

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throughs started to recur with a progression to ultra-rapid and ultradian cycling. The subsequent re-institution of carbamazepine again produced a good initial response, as it had in 1985, and a year of good functioning.

This patient's rapid cycling is not atypical and is representative of a group of patients who appear to do better on the combination of lithium and carbamazepine (Tegretol®) than on either medication alone. These data are convergent with those of Okuma in Japan and Denicoff in our group which show an approximate 50% response rate of rapid cycling patients to the drug combination, with only an approximate 25% response rate to monotherapy with either lithium or carbamazepine alone. This suggests that rapid cycling patients may do better on aggressive combined treatment from the onset rather than monotherapy with lithium or carbamazepine alone. Valproate (Depakote®) is another option for the rapid cycling patient as discussed in the July 1995 issue of the BNN (1995, Vol.1, Issue 2).

The problem of episode reemergence following a period of stabilization on a treatment regime, illustrated in this patient's life chart, is a problem that can occur in a small subgroup of patients after an initial good response. This loss of efficacy appears to represent a type of treatment resistance or tolerance development that may have a different underlying biochemistry from the type of treatment resistance where a patient fails to respond to a drug regimen in the first place. The Network will be pursuing studies to develop the best treatment algorithms (sequential treatment approaches) to address this problem of loss of drug responsiveness.

In the initial issue of the BNN (1995, Volume 1, Issue 1), we discussed another patient who discontinued her medication after a long period of wellness and upon relapse failed to re-respond to the reinstitution of the same drug at the previously effective or even higher dose. We re-emphasized the importance of remaining on long-term effective prophylactic

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treatment when patients are doing well, since bipolar patients are at very high risk for relapse following maintenance treatment discontinuation (e.g. 50% relapse within the first five months of lithium discontinuation, and 90% relapse in the first 18 months off medication).

In contrast, in the face of loss of efficacy via the gradual development of treatment resistance (tolerance), as illustrated in the current patient, the utility of switching to drugs with different mechanisms of action should be considered. A new trial of the drug the patient had initially responded to, after a period of time off from the drug, may also be tried in an effort to recapture a treatment response. Constructing a retrospective life chart and continuing daily prospective life chart ratings will help insure that the best possible information is available when making critical decisions with regard to the next treatment step. Additionally, many patients with bipolar illness, as illustrated in this life chart, require treatment with several agents in order to bring on remission. The importance of an ongoing mood chart for the development of an optimal treatment program is again highlighted.

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CLINICAL RESEARCH UPDATE

Lamotrigine as a Potential Approach to Bipolar Illness

Given the mood stabilizing effects of carbamazepine and valproate in bipolar illness, the potential utility of other anticonvulsants is continuing to be explored. Lamotrigine (Lamictal®) is a newly-approved anticonvulsant that is effective as an add-on therapy in patients with temporal lobe epilepsy who do not respond well to other agents. It is well tolerated in epilepsy as an add-on medication with substantial improvement in one-quarter to one-third of the patients.

We re-emphasized the importance of remaining on long-term effective prophylactic treatment when patients are doing well...

Lamotrigine's desirable pharmacologic properties include: low protein binding (55%); an absence of enzyme induction; and linear pharmacokinetics. A significant adverse effect is rash, leading to withdrawal from clinical trials in 2% of patients. The rash appears to be, at least in part, based on blood levels and is more prominent with faster rates of dose increases and in patients treated with valproate, because valproate inhibits lamotrigine metabolism, which results in higher blood levels. The studies in epilepsy are reviewed by Messenheimer (*Epilepsy*, 36[suppl 2]:S87-S94, 1995). Lamotrigine has begun to be explored in the treatment of bipolar patients in light of its desirable effects and its potential novel mechanism of action in inhibiting the release of the excitatory amino acids glutamate and aspartate (probably via blockade of voltage-sensitive sodium channels).

Weisler and associates (APA abstracts, 1994) reported successful treatment with lamotrigine in two patients who had failed to respond to lithium, antidepressants, antianxiolytics, other anticonvulsants, and other agents. Marked improvement in depression was also noted by Calabrese and associates (including Susan McElroy and Paul Keck of the SFBN Cincinnati field site), who reported effects of an open treatment trial with lamotrigine in 67 refractory bipolar patients at the Second International Conference on Affective Disorders in Jerusalem (September 4-8, 1995). Fifty patients, the majority of whom were in the depressive phase of their illness, received lamotrigine as an add-on to other psychotropics, while 17 received lamotrigine alone. Lamotrigine was added to an average of 2.2 drugs (with a range of 1-5 that included an augmentation of lithium in 18 patients, carbamazepine in 6, valproate in 18, antidepressant medications in 18, and antipsychotic agents in 22). The average dose of lamotrigine was 140 mg/day in those on non-mood-stabilizing anticonvulsants, while it was 170 mg/day on carbamazepine and 80 mg/day on valproate.

Lamotrigine appeared to have substantial antidepressant effects, with 46% of the 39 patients treated for depression showing marked improvement and an additional 23% showing moderate improvement. Of the 25 patients who were in hypomanic or mixed states, 60% showed marked improvement and an additional 16% showed moderate improvement. In terms of side effects, 19% of patients reported headache, 16% sedation, 16%

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rash, 15% nausea, 15% dizziness, and 13% tremor. The drug was discontinued in six patients due to rash and in one patient due to nausea. More rashes occurred during valproate treatment despite very slow titration with 25 mg every other day for the first two weeks and then 25 mg/day for the second two weeks.

These promising results deserve much further systematic study, but preliminarily suggest that the drug may be useful in some bipolar patients who are inadequately responsive to more traditional treatment approaches with the accepted mood stabilizers lithium, carbamazepine, and valproate. Overall, moderate to marked antidepressant responses to lamotrigine were seen in 69% of patients and antimanic responses in 76% of patients, including many with rapid cycling presentations.

AROUND THE NETWORK

Introduction to the Dallas Investigators: John Rush, M.D. and Trisha Suppes, M.D., Ph.D.

The Stanley Foundation Bipolar Network is particularly honored to have Drs. John Rush and Trisha Suppes as co-principal investigators at the Dallas, Texas SFBN field center.

Dr. Rush holds the Betty Jo Hay Distinguished Chair in Mental Health at the Department of Psychiatry and serves as Vice-Chairman for Research at the University of Texas Southwestern Medical Center in Dallas. Throughout his 20-plus year career, Dr. Rush has conducted clinical research that has spanned biological and psychosocial issues in mood disorders in adults, children, and adolescents and has promoted the application of clinical research findings to improve the diagnosis and treatment of these patients. He is widely acknowledged as one of the top leaders in psychiatry in the U.S. today. His credentials include expertise in cognitive-behavioral therapy of depression and in diverse investigations in biological psychiatry with particular focus on sleep EEG and brain imaging in the affective disorders.

Recently, Dr. Rush chaired the Panel on Practice Guidelines for Depression in Primary Care for the Agency for Health Care Policy and Research. This panel reviewed the efficacy of all of the antidepressants studied in double-blind, randomized trials. His definitive summary led to a series of recommendations for treatment of depression in clinical practice settings. His most scholarly review also formed part of the evidentiary database for the American Psychiatric Association guidelines in the treatment of de-

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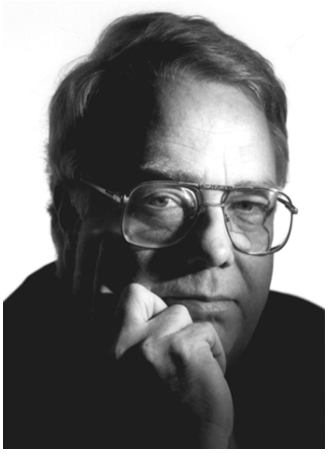

John Rush, M.D.

Trisha Suppes, M.D., Ph.D.

Dr. Rush holds the Betty Jo Hay Distinguished Chair in Mental Health at the Department of Psychiatry and serves as Vice-Chairman for Research...

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pression. Dr. Rush has won numerous awards recognizing his lifetime contributions to research, teaching and clinical work.

Dr. Rush has played a critical role in attempting to move the NIMH forward in identifying a series of methodological recommendations that should facilitate the funding of studies in bipolar illness. These have been informally labeled "Rush's Rules" and suggest the importance of studying a broader segment of patients with bipolar illness and not just those with non-rapid cycling patterns or without comorbid psychiatric illness and drug abuse, which eliminates a very large group of patients. Dr. Rush's "can do" attitude, indefatigable energy, sense of humor, and scholarly excellence are warmly welcomed and appreciated by the Network.

Dr. Trisha Suppes, an Associate Professor in the Department of Psychiatry at the University of Texas Southwestern Medical Center...

Dr. Trisha Suppes, an Associate Professor in the Department of Psychiatry at the University of Texas Southwestern Medical Center, joined Dr. Rush from Boston's McLean Hospital where she distinguished herself as an outstanding young clinical investigator. Armed with both M.D. and Ph.D. degrees, Dr. Suppes completed the definitive meta-analysis on the outcome of treatment-discontinuation in bipolar illness. In her 1991 classic paper published in the *Archives of General Psychiatry*, she noted that 50% of bipolar patients relapsed within the first five months of discontinuing lithium and 85-90% relapsed within the first 18 months of discontinuing their medication. These data, more than any in the field to date, crystallized the high recurrence rate of patients with bipolar illness and the need for ongoing prophylactic treatment, even after many years of wellness on medication.

With colleague Giovanni Faedda, she additionally elucidated that patients who abruptly stopped their lithium were at even higher risk for relapse than those who underwent a very slow taper. These data are invaluable in helping to convey the importance of sustained treatment with lithium and other agents in this recurrent illness.

Dr. Suppes has also completed studies indicating the efficacy of clozapine (Clozaril) in patients with rapid cycling and treatment-refractory bipolar illness, and has thus contributed greatly to the acquisition of new knowledge about treatment approaches to the affective disorders. Her scholarship, knowledge, methodological rigor, and pursuit of new treatment options for bipolar patients will be invaluable in the Network.

Meeting Highlights: Sixth Congress of the Interdisciplinary Society of Biological Psychiatry - Zeist, The Netherlands, October 12-13, 1995

A wealth of interesting data was presented at these proceedings. Dr. Julian Mendlewicz reviewed the data finding vulnerability factors to bipolar affective illness on chromosome 18. These findings, initially discovered by Dr. Wade Berrettini (Philadelphia) in collaboration with Dr. Elliot Gershon (Bethesda), have now been replicated by Dr. Raymond De Paulo's group at Johns Hopkins University (Baltimore). Interestingly, both groups find chromosome 18 vulnerability exclusively in families in which the genetic transmission is through the father and not the mother, which is typically the most common type of transmission. This unique finding suggests a novel mode of inheritance and also could account for some of the non-replications of the chromosome 18 finding reported in the literature. Both groups also found a markedly earlier onset of bipolar illness in the current generation (children of those with the illness) compared with the previous generation. Some groups have replicated Dr. Mendlewicz' findings of another vulnerability factor on the X chromosome, although these findings have not as yet been widely replicated by other researchers in the field. There are new hints by two groups of a vulnerability for bipolar illness on chromosomes 21 and 5. Together, however, these data suggest that multiple genes (that may differ across families) could be involved in vulnerability to the affective disorders.

Dr. Robert Post reviewed data exploring the environmental, psychosocial, and affective-episode-related variables (i.e., experience) that can alter gene expression. While inherited genes may provide vulnerability to affective disorders as noted above, environmental factors and life experiences can also change which genes are turned on and off, which in turn could affect the development and course of the recurrent affective disorders.

Dramatic new data was presented by Dr. B.A. Van der Kolk on brain imaging in post-traumatic stress disorder (PTSD). When patients are reading (and reliving) the scripts of their individual traumas, there is a marked increase in blood flow in the right frontal part of the brain, and the right amygdala, right insula, and right anterior cingulate gyrus. There is little activity on the other side of the brain and a marked decrement in the speech area in the left cortex. This suggests that patients with PTSD may have developed an autonomous affective memory system encoded in the right part of the brain that is very difficult to access with speech and verbal labels, which are mediated on the left side of the brain. It is interesting that these same areas of the brain are involved in the mood induction paradigms of Dr. Mark George and in the procaine activation studies of Dr. Terence Ketter in our group. However, in contrast to the PTSD findings, the induction of sadness increases activity predominantly on the left side of the brain and procaine activity is bilateral.

The neurobiology and treatment of bipolar disorder was reviewed by Dr. Willem Nolen, who emphasized the need for further clinical trials. He and his group are planning clinical trials for the SFBN involving the differential acute and maintenance antimanic response to low and high blood levels of the mood stabilizers during long-term prophylaxis.

Dr. Robert Belmaker reported that the drug inositol, given in the range of 12-16 grams per day, appears to be a highly effective treatment for patients with depression and panic/anxiety disorders, but not for patients with obsessive-compulsive illness. Inositol also decreased lithium-induced polyuria.

Dr. R.H. Van den Hoofdakker reviewed data on sleep and depression, indicating that one nights sleep deprivation is often able to induce a transient improvement in depressed mood. He found, however, that this is often not sustained unless the patient is on a concomitant treatment, such as lithium, or, as new data suggests, high intensity light; i.e., 2,800 to 10,000 lux (similar to that used in the treatment of seasonal affective disorder [SAD]). Dr. Hoofdakker also reported evidence in normal volunteers, studied in an environmentally controlled "cave" experience, that marked changes in mood can be associated with

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A wealth of interesting data was presented at the Sixth Congress of Interdisciplinary Society of Biological Psychiatry.

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nonsynchrony between the sleep/wake cycle and the circadian temperature rhythm.

Dr. B.E. Leonard reviewed recent pharmacological approaches to depression, including new findings that most antidepressants alter the glycine binding site of the NMDA receptor (findings pioneered by Dr. Phil Skolnick at the NIMH [Ed.]). These data are of interest from the perspective that lamotrigine (see pages 4-5 this issue) is an indirect glutamate antagonist because it decreases glutamate release.

Various speakers presented findings in the area of schizophrenia. Dr. C.J. Slooff followed a group of patients with first-break schizophrenia for 15 years and found that 90% of them had recurrences, poor outcome, or chronicity. "Each relapse contributed to a higher risk of chronicity in terms of the persistence of negative-positive symptoms." (Slooff CJ, *Acta Neuropsychiatrica Scandinavica*, 1995, 7:3, FS 62). Dr. Slooff's data are very much consistent with that of the Hillside Hospital, indicating that each new episode of schizophrenic psychosis may be more difficult to treat than the previous one. This is similar to the sensitization concept in the affective disorders summarized by Dr. Post, and suggests that repeated episodes of schizophrenic psychosis may lead to relative treatment resistance or refractoriness. These data, along with the very substantial meta-analysis of Dr. John Davis that chronic, long-term maintenance therapy is highly effective in preventing schizophrenic relapses, should help to alter the treatment algorithm for patients with a first-break psychotic episode, so that the recurrences and the chronicity that may develop secondarily are prevented. Dr. Davis has also reviewed data that indicate that antidepressants prevent depressive recurrences at a level of statistical significance (i.e., $p < 10^{-34}$) in unipolar depression, further supporting the utility of long-term prophylaxis in this illness as well.

Several animal models for some of the cognitive dysfunctions found in schizophrenia were presented by Drs. B.A. Ellinbroek and A.R. Cools. These models included latent inhibition and pre-pulse inhibition. They were able to breed animals that showed increased tendencies for this abnormality (which is shared by schizophrenic patients), so that the neurobiological underpinnings can be more definitively explored. It is of considerable interest to assess which of these clinical tests is also abnormal in patients with bipolar illness.

Dr. Robin Murray reported new evidence for the neuro-developmental theory of schizophrenia with finding that there is a lack of development of normal cerebral lateralization in schizophrenic patients. Moreover, this finding has now been extended to family members of those with the illness and is observed in those at high risk for schizophrenia.

Dr. C.D. Frith reviewed evidence that auditory hallucinations could represent sub-vocalized speech that is abnormally perceived as coming from others rather than internally generated by the schizophrenic patients themselves. These auditory hallucinations could be induced in schizophrenic patients by changing the feedback of their own voice intonations. Moreover, Positron Emission Tomography (PET) scans revealed that there were abnormalities in areas of brain involved in speech perception when schizophrenic patients received this faulty voice feedback, compared with controls.

Finally, the conference ended with a scholarly review by Dr. G.E. Berrios of some of the conceptual problems in biological psychiatry research. In this review Dr. Berrios pleaded for a new emphasis on the descriptive aspects of the signs and symptoms of the major psychiatric illnesses and the need to relate these to the new regional neurobiology of the psychoses that is rapidly being discovered.

Consumer Corner*

*Note that while NAMI publications typically refer to afflicted individuals as consumers rather than patients, the Stanley Foundation Bipolar Network will continue to use the terms interchangeably. The SFBN will focus on "patients" in an effort to continue to medicalize and destigmatize bipolar illness.

Since one of the goals of the SFBN is to educate the public about mood disorders, we define some terms found in articles in this issue of the BNN:

Algorithm - a systematic method of solving a problem; i.e., the best sequence of treatments most likely to yield a positive response.

Chromosome - One of the 23 pairs of genetic material in each cell nucleus that carry the genes that convey hereditary characteristics.

Genes - specific sequences of DNA that encode the message for making a given protein.

Gabapentin - (Neurontin®) an amino acid antiepileptic drug was approved by the Food and Drug Administration (FDA) in December 1993 as an adjunctive agent for the treatment of complex partial seizures, with or without generalization, in patients over the age of 12.

Lamotrigine - (Lamictal®) a novel antiepileptic drug, was approved by the FDA in December 1994 for use as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

Psychopharmacology - the science of drug-behavior relationships. The use of drugs to influence affective and emotional states.

Tolerance - The gradual emergence of lack of effectiveness of a drug during long-term treatment.

Ultradian - relating to biologic variations or rhythms occurring in cycles more frequent than every 24 hours. Ultradian cycling refers to two or more mood switches occurring in a single day.

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