

Bipolar Network News

Organization and Clinical Trials

Robert M. Post, M.D.

The Stanley Foundation Bipolar Network's (SFBN) five academic field centers (Los Angeles, Dallas, Cincinnati, Bethesda, and Utrecht) have admitted over 85 patients into the naturalistic follow-up study (NFS). Most patients and clinicians are finding the longitudinal approach to life charting mood, sleep, and functional and social impairment on a daily basis easy to accomplish and helpful to overall clinical evaluation and management.

Institutional approval for the Network's Level I double-blind randomized study of treatments for patients on mood stabilizer therapy experiencing break through depression has been received at one site and is expected soon at all of the other sites. With institutional approval, acquisition of data about bupropion's (Wellbutrin®), sertraline's (Zoloft®) and venlafaxine's (Effexor®) acute antidepressant effects and long-term efficacy in preventing depressive recurrences can begin.

In addition to the initial five formal academic field centers, a number of other affiliated sites are being brought into the Network including: the Minneapolis VA Medical Center's Department of Psychiatry headed by Dr. Joseph Westermeyer; McLean Hospital in Boston headed by Dr. Mauricio Tohen; Stanford University Department of Psychiatry headed by Dr. Terence Ketter; and a site in Italy headed by Dr. Julia Perini.

We will continue to reach out to investigators, clinicians, and their patients at other academic institutions to further the common use of as many core measurement instruments of the Network as possible so that standard assessments will allow maximal interchange of information among

a variety of clinical and research settings. Each of the five academic field centers is also establishing a community outreach program so that larger number of patients can be studied in randomized, but open, clinical trials in parallel to the small but more intensive double-blind studies at each academic field center.

The contributions of the Theodore and Vada Stanley Foundation which established this Network, in conjunction with the NIMH, have allowed us to move toward fulfilling many of the recommendations of the 1989 and 1994 NIMH-NIH-sponsored conferences on bipolar disorder to increase acute- and long-term study of this illness. We have also obtained commitments from several pharmaceutical companies to provide free medicines for some of the clinical trials involved in the Network studies. We hope this consortium of patients, clinicians, academic field centers, patient advocacy groups, and pharmaceutical firms will bring to fruition the Network's goals of rapid acquisition and promulgation of new knowledge on bipolar illness.

We will continue to reach out to other investigators, clinicians and their patients at academic institutions to further the common use of as many core measurement instruments of the Network as possible...

Patients with Refractory Affective Illness: The Need for Complex Combination Therapies

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Tracking of the longitudinal course of affective illness through the NIMH life chart method has been implemented at all participating Network field centers as an easy and effective way to monitor mood and resultant functional impairment on a daily basis. Additionally, the construction and review of each patient's retrospective life chart continues to be one of the important clinical and research goals of the Network. This ensures that crucial clinical information is collected and available when important treatment decisions are made for the individual patient and that the Network is able to learn as much as possible about all aspects of this difficult and recurrent illness.

A continuing part of the BNN has been the presentation of a patient's life chart with a discussion of some of the salient points arising from it. In this issue we discuss the case history of a patient whose illness progressed quite rapidly and proved to be unresponsive to a variety of psychopharmacological agents for six years prior to her entry into the NIMH treatment and research protocols. Her depressions were marked by severe cognitive impairment, marked sleep disturbance, significant psychomotor slowing, and suicidal preoccupation. When hypomanic she would be hyper-energetic, at times intrusive and irritable while at other times gregarious, very social, with some excessive spending and impaired judgment. Highly functional and successful at work prior to the onset of her illness, she was now unable to hold her job and had spent much time at home struggling with her illness. As indicated on her life chart, she responded inadequately to lithium alone or in combination with a variety of typical and atypical antidepressants. She did have transient degrees of improvement with the addition of the mood stabilizer carbamazepine (Tegretol®) in 1986 and again in 1988 but lost the partial response both times after about 6-8 months.

At NIMH she did not respond to the calcium channel blocker nimodipine which has shown promise in some treatment-refractory patients. She demonstrated a good antimanic but inadequate initial antidepressant response to valproate (Depakote®) in combination with T₃ (Cytomel®) and T₄ (Synthroid®).

Bupropion (Wellbutrin®) added to valproate and T₃ and T₄ appeared to shorten depressive periods but still left the patient with a significant degree of functional impairment. Finally, with the addition of the fifth drug, lithium carbonate, which had previously been ineffective in association with a variety of other drugs, the patient stopped cycling and entered a period of virtually complete remission. She suffered minimal side effects, such as a mild tremor and some transient hair loss, and was able to return home without being plagued by incapacitating depressions or disruptive hypomanias for the first time in seven years.

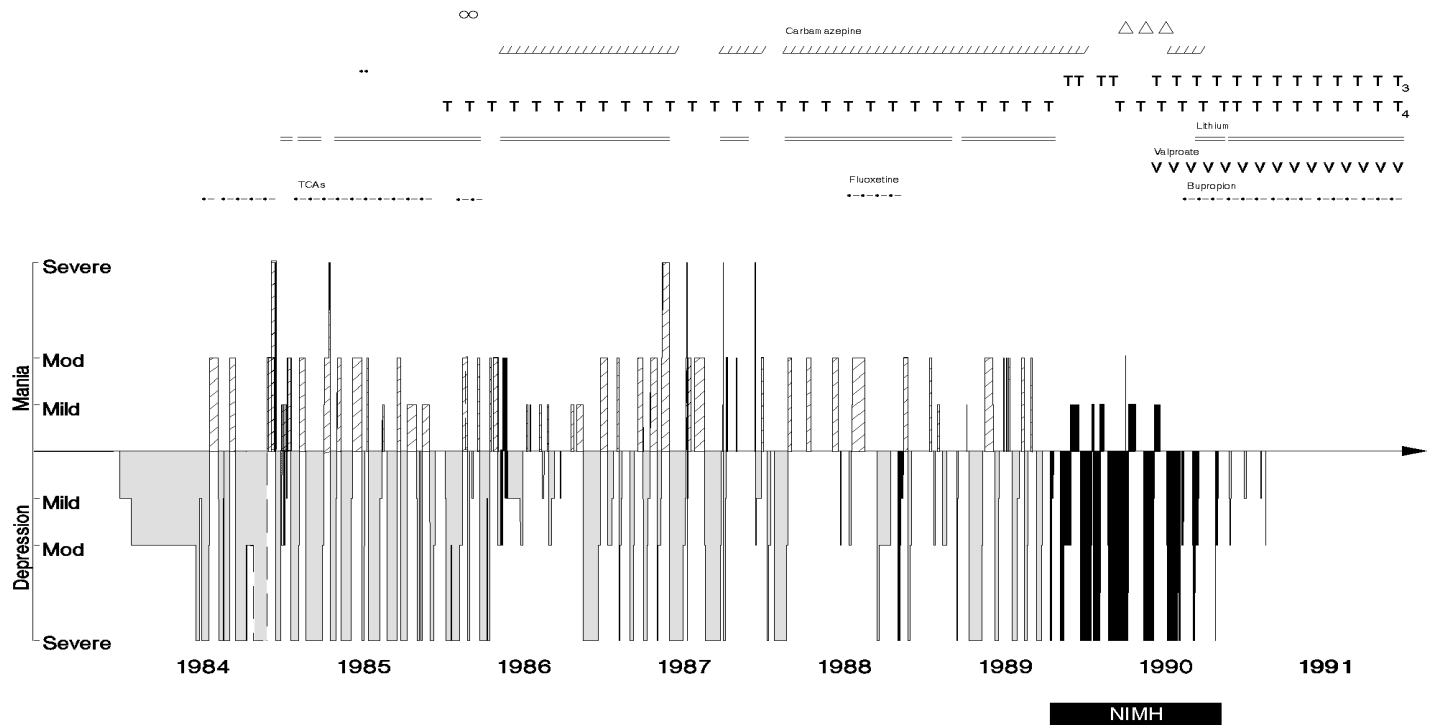
The patient was able to reintegrate into a full and active life, and the adoption of a child brought additional richness and happiness to her and her husband. She eventually resumed part-time work in her earlier field of study and has been engaged in a productive and rewarding life to this day. Based on the patient's previous treatment refractoriness prior to NIMH, the success of the complex polypharmacy, the general good tolerability, and the concern about the possibility of intractable symptom reemergence, this regimen of five different agents was not submitted for further "academic" testing to assess whether all of these drugs in combination were absolutely necessary for the patient's improvement. Neither the patient nor her physicians have been willing to risk a potential relapse and the added possibility of repeated refractoriness.

Highly functional and successful at work prior to the onset of her illness she was now unable to hold her job and had spent much time at home struggling with her illness.

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RESPONSE TO COMBINATION THERAPY IN A REFRACTORY BIPOLAR PATIENT

Pt 5444



This complex polypharmacy of two mood stabilizers (lithium and valproate), T₃ (Cytomel[®]) and T₄ (Synthroid[®]), and the antidepressant bupropion (Wellbutrin[®]) has been successfully maintained for the last 5 years. Neither the patient nor her physician have been willing to test whether all five drugs continue to be necessary for the patient's ongoing mood stability because of the risk of a potential relapse or possible repeated refractoriness.

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The discharge regimen of this patient is actually not atypical of the general trend that has occurred over successive five year intervals since the 1970s on our clinical research unit of the Biological Psychiatry Branch at the NIMH. From 1971 to 1975, three-quarters of the patients were discharged on monotherapy. In the latest five year epoch, 1990 to present, only one-quarter of the patients have been discharged on monotherapy while three-quarters of the patients have been treated with multiple drugs. Although the rate of marked improvement (relative absence of mood symptoms), to moderate improvement (substantial, clinically relevant improvement) has remained relatively constant, there is a clear-cut trend in the past 25 years for an increasing number of drugs required to achieve the same clinical outcome in NIMH treatment-refractory patients.

A variety of factors may contribute to this phenomenon: 1) In the early years patients were likely “prescreened” for lithium refractoriness only, so that NIMH-initiated treatment with novel agents in monotherapy (such as carbamazepine) made a substantial impact. Increasingly, patients are now exposed to a wide variety of treatments before being referred to the NIMH as “refractory.”

2) The “cohort” effect, in which successive generations after World War I have a higher incidence and earlier onset of both unipolar and bipolar disorders in the U.S. and many other countries, may produce patients with more difficult-to-treat-illnesses. 3) The experience of growing amounts of physical and substance abuse and psychosocial stress, as well as greater numbers of affective episodes through earlier illness onset, may have an increasing experiential impact on gene expression. This may contribute to a patient population more vulnerable on an experiential basis to affective recurrences.

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The phenomenon of more complex treatment regimens in late or difficult-to-treat phases of this illness is perhaps not dissimilar to other severe illnesses such as heart disease or cancer. While a single antidiuretic drug can often treat mild edema and a minor surgical procedure can be palliative or curative in the early stage of cancer, complex medication combinations and other interventions are often required for the patient with congestive heart failure or metastatic cancer.

While large-scale clinical trials have been conducted to evaluate the efficacy of multiple drug combinations in cancer, there is a relative lack of data not only in the evaluation of single agents in the different stages of bipolar illness, but also a virtual and alarming absence of studies on the efficacy and long-term outcome of combination therapies in affective illnesses.

The Stanley Foundation Bipolar Network hopes to address these deficiencies by collecting data in a large number of patients about the longitudinal course of bipolar illness and its response to treatments, either single agents or combination therapies, in different stages of the illness. Much information can be accumulated through the collaboration between patient and clinician in research and clinical practice settings. The life chart method of tracking the past and present course of bipolar illness is one of the important steps toward that goal.

The life chart in this article illustrates the need for combination therapy in a treatment-refractory patient and also conveys a very important perspective and hopeful message. Patients with difficult-to-treat mood disorders can take heart that complete remission is possible even after many years of total incapacitation. This may require many different and complex psychopharmacological trials, but, repeatedly, we have seen that success can be achieved in the majority of patients. Sometimes, as demonstrated in this life chart, it may require two or more mood stabilizers such as lithium, and valproate, as well as thyroid augmentation in combination with an antidepressant to achieve such a therapeutic

profile. The construction of one's own retrospective life chart, careful assessment of past treatment responses, and the monitoring of the present course of illness can make a significant contribution to the long-term management of the illness and may assist in the formulation of effective rational polypharmacy.

Update on Repeated Transcranial Magnetic Stimulation (rTMS) of the Brain: Recruitment of Patient Volunteers with Depression

Robert M. Post, M.D.

A preliminary report on the efficacy in two of the first six patients treated with rTMS in an open clinical trial has been published in the journal *NeuroReport* (George MS et al, *NeuroReport* 6(14): 1853-1856, 1995). A more controlled, double-blind randomized clinical trial is in progress and six patients have been randomized and treated with some showing excellent improvement. Repeated TMS involves placing a magnet over the frontal cortex (an area shown to be hypoactive in depression by PET scans) and then using a magnetic field to generate electrical activity perpendicular to it; i.e., directed into the frontal area of brain. When this kind of magnetic-induced selective stimulation is used over the motor cortex (located more towards the middle of the head), for example, it can generate muscle contractions in the appropriate limbs on the opposite side of the body. During rTMS for depression, the intensity of electrical current is placed at 80% of this motor threshold and stimulation occurs over the front part of the brain so that no motor events occur. The patient normally does not feel many sensations, except some mild contractions and tension in the scalp muscles. The sessions last approximately 20 minutes and are administered from 3-5 times per week. In contrast to electroconvulsive therapy (ECT), rTMS does not require anesthesia, seizures are not induced and there is no associated memory loss or post-seizure confusion after treatment.

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The randomized clinical trial involves ten days of active rTMS compared with ten days of sham rTMS with all patients getting both phases with only the order differing. If patients with a sustained period of depression of greater than one month's duration would like to volunteer to participate in this randomized clinical trial in order to help establish the efficacy of rTMS, they should contact Gabriele Leverich, LCSW, at 301-496-7180 or Dr. Tim Kimbrell at 301-402-2293. In order to qualify for the protocol they must be otherwise medically healthy and not taking other medications. However, bipolar patients in a depressive phase of illness despite ongoing maintenance medication might also be eligible for the clinical trial. Patients from outside the Bethesda-Washington, DC area could be studied either as inpatients at the NIH Clinical Center or stay in a local hotel facility and come to the NIMH for daily treatments. Those in the local area may be able to receive the treatment either on an outpatient basis or on an inpatient basis if the severity of depression warrants.

Another study of rTMS is also being initiated conjointly with Dr. Jan Fawcett and his colleagues at the Rush Presbyterian Hospital in Chicago. This study's objectives are to more definitively identify the optimal parameters for rTMS in terms of placement of the magnet, frequency, duration, and number of stimulations. Ultimately, a randomized trial will be conducted to compare rTMS with ECT. Eventually, it is hoped that rTMS will come to play a role in at least a percentage of patients who would otherwise need ECT. To the extent that a substantial group of patients will respond to rTMS in lieu of ECT, the treatment could have a dramatic impact on broadening the range of options for the treatment of depression, making it more readily acceptable and cost-effective, and thus helping to destigmatize the treatment of affective illness. Participation in this clinical trial could be of potential benefit not only in the possibility of achieving an acute antidepressant response for the individual participant, but in helping to broaden the knowledge base for the treatment of the illness.

Around the Network

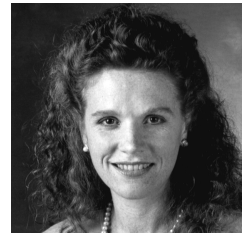
An Introduction to the Cincinnati Investigators Susan McElroy, M.D. and Paul Keck, M.D.

The Network is fortunate to have two of the most superb clinical research investigators in bipolar illness at the Network's Cincinnati field center. Recognizing each other's mutual scientific excellence, commitment, and enthusiastic pursuit of new knowledge, they changed their residency plans and joined forces (in marriage) and in training at Boston's McLean Hospital to serve the understudied and underserved populations with major and difficult-to-treat psychiatric disorders with a special focus on bipolar affective illness.

Sue McElroy began her luminous clinical research career at McLean, where she rapidly became recognized as an expert diagnostician and psychopharmacological pioneer. Following careful chart reviews and clinical studies suggesting the acute and long-term efficacy of the mood-stabilizing anticonvulsant valproate (Depakote®), she and her colleagues initiated and completed the first double-blind comparison of valproate versus placebo in the United States. This was the forerunner and part of the database of the major collaborative study that supported Abbott Pharmaceutical's successful application for FDA approval for Depakote® as a first-line treatment of acute mania.

The data from that first small but carefully controlled study previewed essentially all of the findings in the subsequent larger, multi-center collaborative study, and has led to the widespread use of valproate. This resulted in a dramatic improvement in the lives of many patients who had been refractory to lithium and/or carbamazepine (see BNN Vol. 1 Is. 2) and led to the now widespread recognition of valproate as a major mood stabilizer.

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Susan McElroy, M.D.



Paul Keck, M.D.

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Paul Keck's career has been equally illustrious. He is widely recognized as one of the world authorities in the development and use of novel treatments not only for the affective disorders but also for the anxiety disorders and other difficult-to-treat major psychiatric illnesses. He has studied the pharmacokinetics of some of the major psychotropic interventions and has also reported the efficacy of using carbamazepine and valproate in combination in patients who were refractory to either agent alone.

Dr. Keck was instrumental in the rigorous methodological design of the first blind, randomized study in the United States indicating the efficacy of valproate in acute mania, and is a consultant to or on the advisory board of numerous pharmaceutical firms which seek his methodological and clinical expertise.

Drs. McElroy and Keck are now taking a leading role in the study of the new anticonvulsant gabapentin (Neurontin®) and lamotrigine (Lamictal®) for the treatment of lithium-nonresponsive bipolar patients. Together they have also pioneered the initiation of valproate dosing with 20 mg/kg/day from the outset in order to achieve a rapid response. They found that the drug administered in this fashion was well tolerated.

When the formal extramural funding sources of the NIMH did not include many studies in bipolar illness over the past decade, the McElroy-Keck team was not deterred, performing outstanding and state-of-the-art novel intervention studies with shoestring budgets and alternative sources of funding. It is a great honor to have two such skilled and charismatic clinical research investigators as leaders of the Cincinnati field center of the Stanley Foundation Bipolar Network.

**Consortium of Investigators
of the Biochemistry
of Manic-Depressive Illness Bethesda,
Maryland March 1995**

Robert M. Post, M.D.

This consortium was organized by Drs. William Z. Potter and Hussein K. Manji of the National Institute of Mental Health (NIMH) to further concerted efforts in the study and treatment of bipolar illness.

Dr. Bob Prien (NIMH) reported on research funding. While the good news is that a few bipolar grants have been funded, the bad news is that the level of support is nowhere near that for research in schizophrenia, unipolar depression, or anxiety disorders despite the often repeated demonstration of a great need for new work in the bipolar area. Of the millions of dollars available for services research, only one of 178 projects funded related to bipolar illness. It is clear that more funding should be allocated to bipolar illness research, especially in light of the long-term morbidity, suffering, and financial and social impact of inadequately treated bipolar illness in this country.

Dr. Alan Swann (University of Texas at Houston) reviewed the biogenic amine studies of bipolar illness. He noted the consistent evidence for increased cerebral spinal fluid (CSF) norepinephrine in mania and the hypercortisolemia observed in dysphoric mania, which is similar to that in depression, but not in euphoric mania.

Dr. Ghanshyam Pandey (University of Illinois at Chicago) reviewed evidence that 5-HT₂ (serotonin) receptors are elevated on both blood elements and in autopsy specimens of patients who make serious suicide attempts or commit suicide. The relationship of alterations in this serotonin receptor subtype to depression and suicide remains a highly provocative area for further investigation and study especially in light of the antidepressant effects of the selective serotonin reuptake inhibitors (SSRIs).

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Dr. Manji (NIMH) summarized data that are highly supportive of the possibility that G-protein abnormalities can be involved in many major medical illnesses. Three studies suggest a G-protein abnormality in bipolar illness and this appears to be a target for the actions of not only lithium but perhaps carbamazepine and valproate, as well. Dr. Jerry Warsh (Clark Institute, Toronto, Canada) also reviewed G-protein abnormalities in post-mortem brain studies. He hopes this research will lead to identification of other neurobiological abnormalities underlying bipolar illness.

Dr. Robert Belmaker (Ben Gurion University, Israel) reviewed work suggesting that lithium inhibits the phosphoinositol pathway and that inositol might be depleted in affective illness. Based on this notion he has treated patients with 12 grams of inositol with success in an initial double-blind, placebo-controlled trial. Patients with panic disorder have also shown response to inositol, providing new starting points for the therapeutics of several major psychiatric illnesses.

Evidence for increased intracellular calcium in the blood elements of patients with bipolar affective disorders was discussed by Dr. Charlie Bowden (University of Texas at San Antonio). This finding is interesting in that the mood stabilizers lithium, carbamazepine, and valproate target different aspects of calcium metabolism, and that the dihydropyridine L-type calcium channel blockers, nimodipine and isradipine, appear to be effective in a subgroup of bipolar patients.

Dr. Terence Ketter (Stanford University/NIMH) surveyed the new brain imaging studies from his group and other researchers indicating consistent evidence of frontal cortical and limbic system defects in the recurrent affective disorders. With a limbic-selective probe using procaine, Dr. Ketter's data suggests a dysfunction in the neural substrate of the deep midline structures that have long been postulated to be involved in pathological affective regulation. Dr. Ketter has preliminary evidence that different patterns of cerebral metabolism in depression may be associated with selective antidepressant responses to carbamazepine versus nimodipine.

A focus of the consortium was to find ways to foster further research and collaborative efforts among different research groups. Consensus on several areas of exploration included: 1) to make available a cell bank of immortalized fibroblast cells of patients with bipolar illness and their affected and unaffected relatives, so that studies can be done to determine whether or not the intracellular calcium defect (observed in a variety of blood elements) is shared by these cells and among family members; 2) Drs. Fuller Torrey and Joel Kleinman have organized a major national consortium for the collection of autopsy of specimens from patients with bipolar illness so that neurobiology of the illness can be better understood and treated; and 3) the Stanley Foundation Bipolar Network (SFBN) has offered to make its longitudinal assessment and rating instruments available for all investigators in the consortium. The SFBN will also provide, in the future, information on how patients and their families might be able to donate blood, CSF, or microscopic samples from the skin for fibroblast cell lines.

Typical and Atypical Neuroleptics in the Treatment of Bipolar Illness

Mark Frye, M.D.

Limitations of the Typical Neuroleptics (Major Tranquilizers)

A dramatic evolution in the treatment of full-blown mania has occurred over the last several decades. The antipsychotic medications which block dopamine receptors were widely used with lithium in the treatment of acute mania and as an adjunct in patients whose mania broke through lithium prophylaxis. These antipsychotic agents include the typical phenothiazine medications chlorpromazine (Thorazine®), thioridazine (Mellaril®), trifluoperazine hydrochloride (Stelazine®), and perphenazine (Trilafon®), the butyrophenones such as haloperidol (Haldol®) and the thiothixenes (Navane®). These agents are effective in some three-quarters of patients with mania, reducing manic agitation, insomnia, aggressiveness, and psychosis. However, they can have troublesome side effects.

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The mechanism of action of these agents likely resides in their ability to block dopamine receptors in the areas of the brain thought to be involved in manic mood behavior and psychosis, the mesocortical dopamine system. This system involves the nucleus accumbens (the reward area of brain); the amygdala and other limbic areas of brain (thought to be involved in the modulation of conditioned emotional responses); and the highly stress-responsive prefrontal cortical system (thought to be involved in thought disorder and psychosis). In addition to these desirable effects, however, these medications also block dopamine receptors in the areas of brain found to be depleted of dopamine in Parkinson's disease; the striatum (or caudate nucleus and putamen). In Parkinson's disease there is a loss of dopamine neurons. In drug-induced Parkinson's disease produced by the typical antipsychotic (neuroleptic) medications mentioned above, the dopamine system is intact, but dysfunctional, because of the blockade at the D2 receptors which mediate the effects of dopamine. These parkinsonian effects of typical antipsychotic medications result in patients often feeling stiff, having drug-induced tremor, masked facies, increased drooling, and other elements which, in high doses, inappropriately stigmatized all psychiatric medicines in general as "chemical strait-jackets". However, the antiparkinsonian medications diphenhydramine (Benadryl®), benztropine (Cogentin®) and trihexyphenidyl (Artane®) are highly effective in relieving these acute symptoms. Nevertheless, many patients find that taking neuroleptics produces some dysphoria and, in some instances, akathisia or severe motor restlessness (restless legs) which can be very difficult to tolerate.

While most of these parkinsonian side effects can be dealt with through dose adjustments and adjunctive medications, the more problematic side effects of long-term tardive dyskinesia are a real problem for patients with bipolar illness. Chronic treatment or even repeated intermittent treatment with these medications can produce this neurological syndrome characterized by extraneous involuntary movements of the mouth and tongue, other parts of the body including the hands, and in the worst cases, the trunk and the respiratory system. Sometimes

the syndrome is reversible over the long term but, at other times, it appears relatively irreversible and therefore is highly desirable to avoid.

Recent studies have indicated that when patients are acutely exposed to neuroleptics they tend to be maintained on them for relatively long periods of time (Semyak, et al 1994), which can increase the likelihood of tardive dyskinesia. Current data also indicate that patients with bipolar illness are as likely or more likely than patients with schizophrenia to develop tardive dyskinesia, and with age and long-term use there is a highly substantial incidence of 15%-40% of patients who show this neurological disability. Therefore, instead of first use of neuroleptics, we suggest instead first use of the anticonvulsant mood stabilizers (carbamazepine and valproate) and adjunctive use of high potency benzodiazepines.

Benzodiazepine Alternatives

Benzodiazepines, such as clonazepam (Klonopin®) and lorazepam (Ativan®) active at central-type benzodiazepine receptors, are also reported to have some antimanic efficacy when used alone, and clearly help with manic agitation, anxiety, aggressiveness, and insomnia when used in combination with other mood stabilizing agents (i.e., lithium, carbamazepine, or valproate). While their acute efficacy alone has not been proven, there is a very substantial clinical database indicating that the use of the high potency benzodiazepines in lieu of neuroleptics may be successful in the majority of patients. These high potency benzodiazepine medications are extremely well tolerated, do not cause acute neurological or tardive dyskinesia side effects, are not associated with akathisia, and have a useful profile of clinical efficacy, including helping the patient to sleep (because of their sedative side effects), and exerting anti-anxiety or anti-panic effects when these symptoms accompany the manic syndrome as they often can in dysphoric mania.

The Emergence of Atypical Neuroleptics

With the introduction of atypical neuroleptics there is now an additional treatment option. Clozapine (Clozaril®) is the prototypic atypical neuroleptic drug. Clozapine more selectively blocks dopamine receptors in the areas of the brain thought to be involved in

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psychoses (D4 receptors in the frontal cortex), and significantly reduces blockage of dopamine D2 receptors in the striatal areas thought to be attributable to parkinsonian problems. Convergent with this perspective are the clinical data that patients treated with clozapine do not develop parkinsonian side effects, other “extrapyramidal” side effects, or tardive dyskinesia. Clozapine has a number of problems associated with it, including a several percent incidence of potentially fatal loss of white cells (agranulocytosis) necessitating weekly monitoring with its use. In addition, it has potent biochemical effects on a variety of other neurochemical systems besides dopamine, and knowing which of these is attributable to its excellent profile in the treatment of schizophrenia, schizo-affective disorder, and affective illness remains to be fully elucidated. Nonetheless, the medication is highly effective in patients with treatment-refractory rapid cycling disorder and also in patients with difficult-to-treat dysphoric-mania. In fact, response rates in affective and schizo-affective syndromes are even higher than those in the schizophrenias for which the drug is currently FDA-approved and shows a response rate substantially greater than the typical drug such as haloperidol. In addition to agranulocytosis, clozapine’s other side effects that can be problematic include sedation, lowering of blood pressure, weight gain, increased night-time drooling, and seizures.

These side effects can be minimized by conservative dosage strategies, particularly when the medication is used adjunctively with lithium or valproate. With high doses of over 450 mg of clozapine, many clinicians use an anticonvulsant in order to prevent seizures from occurring. Valproate is used in preference to carbamazepine because of the lack of confounding or double vulnerability to agranulocytosis and aplastic anemia with carbamazepine.

Risperidone (Risperidal®) is now a new atypical agent which works slightly differently from clozapine. Risperidone has some purported effects in blocking dopamine receptors in the striatum at high, but not low doses. Therefore, treatment with 2-6 mg/day appears to be a highly effective antipsychotic dosage regimen with minimal parkinsonian or extrapyramidal side effects and, presumptively, a minimal risk for long-term tardive dyskinesia. Preliminary data

indicate that risperidone has good mood stabilizing effects against both manic and depressive episodes, particularly in rapid cycling patients. However, observations by Drs. Paul Keck and Sue McElroy indicate that the drug might be associated with breakthrough manias in some cycling patients, and this issue of risperidone’s overall mood stabilizing effects remains to be further studied.

Other atypical agents are being avidly pursued by the pharmaceutical industry and a number are expected for approval within the next several years. Several companies are also working on a drug that selectively binds the dopamine D4 receptors which are thought to mediate much of clozapine’s favorable antipsychotic profile. The hope is that a drug with a selective set of actions at this receptor might be as equally clinically effective as clozapine but without its more problematic side-effects profile. With the eventual advent of a new range of safe atypical neuroleptic agents, the entire treatment algorithm of when to use neuroleptics in bipolar patients may change dramatically.

At the moment, the typical neuroleptic medications remain an important but adjunctive tool for patients not responding to other mood stabilizing modalities and combinations. The newly available atypical neuroleptics are playing an increasingly prominent role despite some of their remaining drawbacks. Even at their present state of early usage in the bipolar, schizo-affective, schizophrenic spectrum disorders, the atypical neuroleptics clozapine and risperidone appear to be a success in terms of their broader range of therapeutic efficacy and improved side-effects profiles compared to the typical neuroleptics, and directly speak to the success of a whole new range of treatments that have been derived directly from the recent advances in behavioral neuroscience research.

Future issues will report on an update of the new anticonvulsants gabapentin (Neurontin®), and lamotrigine (Lamictal®) as they are currently used in the treatment of neurological disorders and as preliminary open clinical trials suggest their potential efficacy in some patients with affective disorders.

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.

We receive many requests for information on bipolar disorder and the various anticonvulsant medications used to treat this illness. In our search for answers to these requests, we have found the Lithium Information Center in Madison, Wisconsin to be a wonderful resource. In this issue of Consumer Corner we wanted to share this resource with our readers.

The Lithium Information Center, founded in 1975, grew out of a collaboration between Dr. John H. Greist and Dr. James W. Jefferson, who were both interested in the use of lithium to treat bipolar disorder. Pooling their 500 lithium references the Lithium Information Center (LIC) was born. Today, the Lithium library, a computer database of 25,000+ references relating to lithium and alternative treatments for bipolar disorder, is available to psychiatrists, other medical and mental-health professionals, patients, and families who need reliable

information about lithium. Some of the subject areas that the LIC covers are:

- Lithium treatment for manic-depressive disorder and other psychiatric disorders
- All non-psychiatric medical uses of lithium
- Carbamazepine, valproate and other lithium alternatives
- History of lithium in medicine
- Environmental and industrial exposure to lithium
- Lithium in experimental psychology

LIC medical librarians answer information requests and maintain the computerized database. There are nominal fees charged for computer searches and the various booklets available from the LIC. To contact the LIC please write: Lithium Information Center, Dean Foundation for Health, Research and Education, 8000 Excelsior Drive, Suite 302, Madison Wisconsin 53717-1914 or phone, 608/836-8070, fax 608/836-8033.

Bipolar Network News

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