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A Quarterly Publication of the Bipolar Network

March 2000

Bipolar Network News

BNN 2000 Update

Several important changes have occurred in the funding and production of the Bipolar Network News newsletter in the last few months. Because of these changes, there were only two issues printed for 1999. We apologize for any misunderstandings concerning our publication schedule. Both this issue and the last issue are longer than usual to fill in any information gaps we may have missed. We will resume publishing four issues per year; this issue is the first issue of 2000.

Funding Support

We are most appreciative for the contribution of an unrestricted grant by Janssen Pharmaceuticals, a subsidiary of the Johnson & Johnson company, to continue to publish the *BNN*. This unrestricted grant for the *BNN* is directed at better informing patients, their families, physicians, researchers, and all others interested in bipolar illness of the latest developments in the field. We value this generous support and its unrestricted nature.

BNN Content

As in previous editions of the *BNN*, we will try to provide detailed updates on the most current findings in bipolar illness, with a particular focus on activities in the Stanley Foundation Bipolar Network and the Intramural Program of the National Institute of Mental Health from which most of the active work of the editors emanates. In addition, we will try to note new developments in the illness as revealed by the Systematic Treatment Enhancement Program (STEP) and other NIMH, Stanley, and National Alliance for Research on Schizophrenia and Depression (NARSAD) initiatives that are focused on acquiring new data on the neurobiological mechanisms involved in bipolar illness, and the development of more effective treatments.

Also as in previous editions of the *BNN*, we will include case reports using the NIMH-Life Chart Method (NIMH-LCM™) of a patient's course of illness and response to treatment illustrating an important characteristic or treatment principle about the illness. We will also continue to review selected highlights from national and international meetings to preview some of the new developments and emerging trends in the field around the world.

Disclaimer

It is important to emphasize that in many instances, the findings noted in the *BNN* are highly preliminary and/or based on prepublication presentations and abstracts. Although we have and will continue to try to accurately report preliminary findings, we cannot be responsible for errors of fact or interpretation in this preliminary communication format. Thus, patients and physicians should not act clinically on the basis of information provided in the *BNN* without further materials from formal, peer-reviewed publications in the scientific literature. In particular, patients should always consult with their treating physicians about any potential alterations in their therapeutic approach raised by information in the *BNN* or other preliminary material.

The views expressed in the *BNN* are solely those of the editors and individual contributors, and do not represent the views of the NIMH, the Stanley Foundation, any scientific or academic society, or any pharmaceutical firm. We are proud of our close alliance with treatment advocacy groups including the National Depressive and Manic-Depressive Association (NDMDA) and the National Alliance for the Mentally Ill (NAMI), but the scientific reporting and commentary in the *BNN* also do not reflect the policies of these organizations.

We will continue to print a short disclaimer warning in each subsequent issue, but patients should be aware that any potential ideas (either good ones or

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In This Issue:

BNN 2000 Update

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treatment misconceptions) generated from reading the *BNN* need to be carefully reviewed with their treating physician; only he or she can assume medical responsibility for treatment decisions so made.

The articles and information printed in the *BNN* are not copyrighted and may be reproduced without permission. We welcome comments about the content of the *BNN* and the expression of alternative points of view on any of the clinical or scientific material noted or referred to. ■

Bipolar Network News

Editors-in-Chief:
Robert M. Post, MD
Gabriele S. Leverich, MSW

The *BNN* is published four times a year by an international group of investigators working with patients with bipolar disorder to better understand the long-term course and treatment of the illness. The goal of the Network is to help develop new and more effective treatments for bipolar disorder.

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

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New Research

Gabapentin (Neurontin®) in the acute treatment of refractory bipolar disorder

Lori Altshuler, Paul Keck Jr., Susan McElroy, Trisha Suppes, E Sherwood Brown, Kirk Denicoff, Mark Frye, Michael Gitlin, Sun Hwang, Robyn Goodman, Gabriele Leverich, Willem Nolen, Ralph Kupka, and Robert Post

Full Article Appeared in the Journal: *Bipolar Disorders* 1: 61–65, 1999

BACKGROUND: Gabapentin, a new anti-epileptic agent, has been anecdotally reported to be effective as an adjunctive treatment in bipolar illness. We systematically assessed the response rate in bipolar patients being treated with open adjunctive gabapentin for manic and depressive symptoms or rapid cycling not responsive to standard treatments.

METHOD: Twenty-eight bipolar patients experiencing manic (n = 18), depressive (n = 5), or rapid-cycling (n = 5) symptoms inadequately responsive to at least one mood stabilizer were treated in an open fashion with adjunctive gabapentin at one of four sites. Illness response was assessed every two weeks using the Clinical Global Impressions Scale modified for Bipolar Disorder (CGI-BP). A 'positive response' was operationalized as a CGI response of much or very much improved.

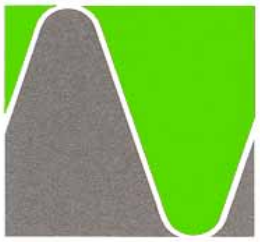
RESULTS: Of the 28 patients treated with open adjunctive gabapentin, an overall positive response was seen in 20 patients (72%). Fourteen (78%) of the 18 patients treated for hypomania (n = 6) or mania (n = 12) had a positive response to a dosage range of 600–3600 mg/day. Patients with hypomania responded fastest, with a positive response achieved in 12.7 ± 7.2 days. Patients with classic mania had a mean time to positive response of 25 ± 12 days, and in patients with mixed mania it was 31.8 ± 20.9 days. The five patients treated for depression had a positive response within 21 ± 13.9 days. Only one of five patients with rapid cycling had a positive response, however. Gabapentin was generally well tolerated, with the most common side effect being sedation (n = 5; 18%).

CONCLUSIONS: Gabapentin appears to have positive effects when used as an open adjunctive treatment for residual manic and depressive symptoms, but not rapid cycling. Prospective double-blind studies are needed to further delineate its acute and prophylactic efficacy in conjunction with other mood stabilizers.

Note: Two double-blind trials of gabapentin were negative—response rates did not exceed those of placebo. These studies included: 1) the NIMH study of Frye et al. (2000; *J Clin Psychopharmacol*, in press) where lamotrigine (Lamictal®) was superior to both gabapentin and placebo in a six-week monotherapy trial for refractory patients; and 2) the failure of gabapentin to exceed placebo in an outpatient study of acute mania (Pande et al., 1999; see p. 4). In the study of Frye et al., better gabapentin response was associated with younger age, shorter duration of illness, and lower initial body weight (Obrocea et al., unpublished data). Clearer definitions of the utility of gabapentin in bipolar disorder requires much further systematic investigation. ■

Meeting Highlights

Third International Conference on Bipolar Disorder Pittsburgh, Pennsylvania, June 17th–19th, 1999



The Third International Conference on Bipolar Disorder, like the previous two conferences in 1994 and 1997, produced a wide variety of interesting and exciting new findings in the treatment of bipolar disorder. Among the many excellent presentations were the following highlights:

Lithium Update

DRS. R. BALDESSARINI, L. TONDO, AND J. HENNEN of Harvard Medical School reviewed the literature on patients who continued long-term treatment with lithium versus those who discontinued. Suicidal acts rose 22-fold, and fatalities increased 14-fold, within the first year after discontinuing lithium. They concluded from their data that there are "…powerful, long-sustained protective effects of lithium against suicidal behavior.…" A slow taper of lithium during discontinuation is somewhat helpful in decreasing the rate of suicide, but the risk is still 11-fold higher than for those who continue on lithium.

Note: These data continue to indicate the great importance of lithium in treatment regimens for bipolar patients, even though lithium, in monotherapy, is not completely effective for mood regulation in some patients. Despite the growing availability of other putative mood stabilizers, a continued role for lithium as adjunctive therapy, if not monotherapy, remains high on the list of treatment approaches.

DRS. BALDESSARINI AND TONDO also reported data contrary to numerous previous studies in the literature, that neither a long latency until institution of prophylactic lithium therapy (i.e., after many episodes have been experienced) nor rapid cycling conferred a negative prognosis for ultimate lithium response.

DR. A. VIGUERA et al. of Harvard Medical School reported similar rates of relapse in 42 pregnant (52%) and 59 non-pregnant (58%) women who discontinued their lithium for 40 weeks. However, in the post-partum period (i.e., weeks 41–64 after lithium discontinuation) relapses were 3.3 times more frequent in the pregnant versus non-pregnant women (80% vs. 24%, respectively).

DR. M. BAUER and colleagues at the University of Berlin reported an increased prevalence of goiter in 100 lithium-treated patients that was related to duration and dose of lithium treatment and was prevented by thyroxine (T_4, Synthroid®) treatment.

Note: These data, together with those of Frye et al. (1999; Am J Psychiatry 156:1909–1914) reporting that lithium-treated patients with low free T_4 had more depression and cycling, continue to suggest several positives (in efficacy and side effects) for considering thyroid augmentation strategies.

DR. S. GHAEMI et al. of Massachusetts General Hospital reported data from a 1.7 year open-label comparative trial of divalproex (Depakote®) vs. lithium in the treatment of bipolar disorder. They found both to be equally effective in 43 patients; lithium nonresponders responded well to divalproex, and vice versa. Divalproex monotherapy was notably effective in treating depressive symptoms.

Antidepressants

DR. C. GUILLE et al. of Massachusetts General Hospital reported on a continuing study of bupropion (Wellbutrin®) vs. desipramine (Norpramin®) in bipolar depression (Sachs et al., 1994; J Clin Psychiatry 55:391–393), and found that over the one-year follow-up, the rate of switching into hypomania and mania was still significantly greater in the desipramine group (37%) compared with the bupropion group (13%, $p<0.05$).

DR. R. JOFFE et al. of McMaster University, Canada, reported that for 25 patients in a randomized, controlled six-week trial, adjunctive treatment with the antidepressant paroxetine (Paxil®) was equally effective for depression breaking through ongoing mood stabilizer treatment as the addition of a second mood stabilizer, typically valproate to lithium or vice versa.

Note: Although rapid cyclers were not included, this is a highly important study and should help refocus attention on the relative safety and efficacy of the newer antidepressants for bipolar depression.

DR. L. ALTSHULER and colleagues at the UCLA Neuropsychiatric Institute found that the risk of depressive relapse for 27 bipolar patients after antidepressant discontinuation was 67% versus 39% in the 18 patients who remained on antidepressants.

Note: Although this was a retrospective chart review and not a randomized study, it suggests that the previous recommendation—discontinuing antidepressants as soon as possible in patients with episodes of depression breaking through mood stabilizers—should continue to be reevaluated as new data become available. *(Continued on page 4)*

Meeting Highlights: 3rd Intl. Bipolar Conf.

(Continued from page 3)

New Treatments

DR. A. PANDE of Parke-Davis Pharmaceutical Research presented data indicating that gabapentin (Neurontin®) was not an effective treatment for acute mania. In a 10-week, double-blind, placebo-controlled trial of adjunctive gabapentin, flexibly dosed between 900 and 3600 mg/day, gabapentin was not superior to placebo as an adjunctive treatment for bipolar I symptoms of hypomania, mania, or mixed states. These data are convergent with the data from the NIMH double-blind study (Frye et al., 2000; *J Clin Psychopharmacol*, in press) indicating that lamotrigine (Lamictal®) was more effective in a group of patients with a variety of refractory affective disorders than either gabapentin or placebo (neither of which differed statistically from each other).

In contrast to Dr. Pande, DR. M. HARDOY et al. of the University of Florence, Italy, reported a 60% moderate to marked response rate for open-label, adjunctive gabapentin in the treatment of bipolar and schizoaffective disorders, a response rate similar to the results from open-label, adjunctive studies in the literature. Gabapentin has also been shown to be effective in some anxiety disorders including social phobia, and is widely used for adjunctive treatment in pain syndromes. Thus, its spectrum of therapeutic efficacy in adjunctive treatment for anxiety and depression associated with bipolar disorder remains to be further delineated.

DR. S. HOOPES, (private practice, Boise, Idaho) in a study of lamotrigine in the treatment of bipolar depression and other affective disorders in 218 patients, found that lamotrigine combined well with antidepressants, neuroleptics, lithium, and other anticonvulsants, and produced high rates of response in combination (69%) and in monotherapy (42%). These data parallel the open and double-blind data of Calabrese et al. (1999; J Clin Psychiatry 60:79–88).

DR. A. LAURENZA and colleagues at GlaxoWellcome Research performed a double-blind, placebo-controlled study in 437 outpatients that supported the efficacy of lamotrigine in unipolar depression, finding it equal to desipramine and superior to placebo.

DR. T. SANGER et al. of Eli Lilly and Company reported data from a study using olanzapine (Zyprexa®) in the treatment of rapid cycling bipolar I patients. Twenty-five rapid cycling patients were randomized to placebo and 19 to olanzapine; olanzapine (which has now been FDA-approved for the treatment of mania) was statistically significantly superior to placebo in mean reductions on the Young Mania Rating Scale.

DR. R. CHENGAPPA et al. from Western Psychiatric Institute in Pittsburgh reported data on topiramate (Topamax®) as an adjunctive treatment for bipolar disorder, finding a 56% much or very much improved response rate in 16 patients after six weeks; four of the 16 patients had transient parasthesias (i.e., an unpleasant sense of touch) and two had word-finding difficulties. All patients lost weight (average of 10 lbs). These findings are very similar to those in the Stanley Foundation Bipolar Network as reported by Dr. S. McElroy et al. (2000; *Biol Psychiatry*, in press) in 56 patients.

DR. V. KUSUMAKAR and colleagues at Dalhousie University, Canada, also found positive results of open-label topiramate augmentation in female patients with refractory rapid cycling bipolar disorder. Eight of 15 patients who completed the 16-week study achieved euthymia, and almost half the patients lost 1–5% weight.

DRS. A. SCHAFFER AND A. LEVITT (University of Toronto), and DR. R. JOFFE (McMaster University) reported on mexiletine (Mexitil®) in treatment-resistant bipolar disorder. This agent, which has anticonvulsant, antiarrhythmic, and analgesic properties, was examined in an initial open-label study of 13 rapid cycling patients at doses ranging between 200–1200 mg/day. A full response was observed in 46% of subjects.

Note: This promising study of mexiletine in rapid cycling patients maintained on other mood stabilizers deserves further follow-up.

DR. L. SHAFFER et al. of Sutter Community Hospital reported data from the use of primidone (Mysoline®) in the treatment of refractory bipolar disorder. They reported a modicum of success, i.e., eight (31%) of 26 patients treated with adjunctive primidone experienced a persistent positive therapeutic effect.

Note: These data parallel the previous data of Hayes (1993; Ann Clin Psychiatry 5:35–44) showing a 33% response to primidone.

DR. U. YAROSLAVSKY et al. of Ben-Gurion University, Israel, conducted a double-blind controlled trial of phenytoin (Dilantin®) vs. placebo in mania for five weeks and found that there was significant therapeutic benefit for phenytoin, beginning on week three. They concluded that "the results suggest that antimanic properties may be true for all anticonvulsants."

Psychotherapy

DR. D. HIRSHFELD-BECKER et al. at Massachusetts General Hospital, in a study of short-term adjunctive cognitive-behavioral therapy for bipolar disorder, found significant decreases in the rate of relapse in those so treated. These data parallel those of DR. E. FRANK at the University of

(Continued on page 5)

Meeting Highlights: 3rd Intl. Bipolar Conf.

(Continued from page 4)

Pittsburgh, presented in the opening session of the conference, showing decreased depressive symptomatology in response to interpersonal and social rhythm therapy.

DR. H. LAM DOMINIC et al. from the Institute of Psychiatry, London, also presented data on cognitive therapy for bipolar illness. In a pilot study of relapse prevention with six-month post-therapy follow-up data, they found there were fewer bipolar episodes, higher social functioning, and better coping strategies for bipolar prodromes in the cognitive therapy group compared with the control group that received treatment as usual. There was no evidence that improvement in the therapy group was due to more medication being prescribed.

DR. R. MORRISS of Royal Preston Hospital, UK, conducted a randomized controlled trial of teaching bipolar disorder patients to identify early symptoms of relapse and obtain early treatment. This method was highly effective in reducing the number of days in relapse with mania at 6 months (93%, p=0.007) and at 18 months (58%, p=0.02).

Note: The above four studies clearly support the beneficial effects of focused psychotherapies as an important adjunctive treatment approach for bipolar illness.

Other New Research

DR. L. ALLOY et al. of Temple University reported data on lifetime comorbidity in 17–24 year olds with bipolar spectrum disorders. They reported higher lifetime rates of anxiety, substance abuse, Attention Deficit-Hyperactivity Disorder (ADHD), and eating disorders in bipolar than in unipolar depressed participants. Women with bipolar disorder had higher rates of anxiety (85% vs. 41%), ADHD (18% vs. 5%), and eating disorders (15% vs. 0%) than men with bipolar disorder, but not substance abuse disorders (41% vs. 32%). These data continue to point out the high rate of comorbidity of anxiety and substance abuse disorders in individuals of all ages with bipolar illness.

Note: This high rate of comorbidity should lead to a comprehensive, prospective treatment approach to these conditions as well as considering bipolar illness as a specific risk factor for substance abuse disorders in adolescents.

DR. D. AXELSON et al. of the University of Pittsburgh gave a clinical presentation of pediatric bipolar disorder, based on Kiddie Schedule for Affective Disorders (KSADS) interviews from 142 patients with a lifetime diagnosis of bipolar disorder from 1986 to 1995. They reported that the median episode duration of manic symptoms was one to two days in 117 patients who met criteria for mania or hypomania during the current mood episode. They concluded from the data that pediatric bipolar disorder in their outpatient, predominantly adolescent sample "…presented primarily with brief episodes and prominent depressive symptoms. Suicidality, psychosis, and comorbid disruptive behavior disorders were common features...The presence of mildly elated mood and increased energy may be important for distinguishing bipolar patients from other mood and anxiety disorder patients."

DR. L. GYULAI of the University of Pennsylvania reported that bone mineral density did not acutely decrease in pre- and postmenopausal women with refractory affective disorder treated with high-dose levothyroxine (T_4). ■

Complete abstracts of the Third International Conference on Bipolar Disorder were published in the journal *Bipolar Disorders*, an international journal of psychiatry and neurosciences (Vol. 1, Suppl. 1, 1999; www.munksgaard.dk).

//www: bipolar

The following internet websites might be helpful to all those interested in the research and treatment of bipolar illness:

www.nami.org

With more than 208,000 members, the **National Alliance for the Mentally Ill (NAMI)** is the nation's leading grassroots advocacy organization solely dedicated to improving the lives of persons with severe mental illnesses including schizophrenia, bipolar disorder (manic-depressive illness), major depression, obsessive-compulsive disorder, and severe anxiety disorders.

www.ndmda.org

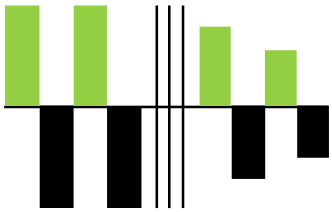
The **National Depressive and Manic-Depressive Association (NDMDA)** is the nation's largest patient-run, illness-specific organization. The mission of the National Depressive and Manic-Depressive Association is to educate patients, families, professionals, and the public concerning the nature of depressive and manic-depressive illnesses as treatable medical diseases; to foster self-help for patients and families; to eliminate discrimination and stigma; to improve access to care; and to advocate for research toward the elimination of these illnesses.

www.narsad.org

The **National Alliance for Research on Schizophrenia and Depression (NARSAD)** raises and distributes funds for scientific research into the causes, cures, treatments, and prevention of brain disorders, primarily the schizophrenias, depressions, and bipolar disorders. NARSAD has awarded $82.13 million to fund 2,130 grants to 1,048 scientists in 146 universities and medical research institutions.

Life Chart Highlight

Response to lamotrigine and gabapentin combination therapy?



As illustrated in the life chart (p. 7), this 44-year old male patient had recurrent and mild bouts of (winter) depression from 1960 until 1971, when they became disabling. The course of his illness changed in 1975 to more continuous hypomania, followed by severe depressions of many months' duration beginning in 1981. Treatment with antidepressants in 1983 (amitriptyline [Elavil®], and maprotiline [Ludiomil®) was associated with the induction of a more severe mania than had previously been observed, but no further manic episodes occurred despite a variety of subsequent antidepressant clinical trials.

The antidepressants amitriptyline and nortriptyline (Pamelor®) were inadequate for preventing depressions in 1987 and 1989, the latter of which did not remit until the combination of desipramine (Norpramin®) and fluoxetine (Prozac®) was instituted. With the onset of another depression in 1991, the monoamine oxidase inhibitor (MAOI) phenelzine (Nardil®) in combination with lithium was instituted without success, and only a partial response to electroconvulsive therapy (ECT) was observed in 1994. The serious depression of 1996 did not respond to treatment with two mood stabilizers (lithium and valproic acid [Depakote®]), the addition of the antidepressant amoxapine (Asendin®), augmentation with the psychomotor stimulant methylphenidate (Ritalin®), and thyroid hormone (T_4, Synthroid®).

NIMH Double-Blind Trial

The patient was admitted to the National Institute of Mental Health (NIMH) (p. 7, bottom) and gave written informed consent for participation in a double-blind randomized clinical trial comparing placebo, lamotrigine (Lamictal®), and gabapentin (Neurontin®) (see *BNN* Vol. 4, Iss. 4). As illustrated, the patient showed no response in Phase I during placebo administration, but in Phase II had a substantial, but partial, response to lamotrigine (i.e., a 'B' for "much improved" on the Clinical Global Impressions [CGI] Scale). Then, in Phase III, he showed some loss of response during gabapentin administration (resulting in a CGI rating of 'C' or "minimally improved"). In Phase IV for response confirmation, the Phase II drug was reinitiated on a double-blind basis (later revealed to be lamotrigine), although in this instance the response was not as robust as previously observed (receiving a 'C' on the CGI). At this juncture, gabapentin was added to lamotrigine, which resulted in rapid, substantial improvement to a virtual symptom-free baseline (i.e., an 'A' or rating of "very much improved" on the CGI).

Although we highlight this case as a potential clinical response to lamotrigine and gabapentin in the presence of only partial responses to monotherapy, the data conveyed and inferences that can be drawn from this life chart are not unambiguous. On first view, it appears that a partial response to lamotrigine was converted to a more complete one with the addition of gabapentin. However, it is also possible that this improvement resulted from a natural "cycling out" of a depressive episode, as might be expected on the basis of prior durations of depression (p. 7, middle line). It is noteworthy that the time frame on the time line or date line is changed on the bottom line row, so that months rather than years are illustrated (i.e., 5/97 – 12/97).

The patient continued in remission from November 1997 to July 1998, but a moderate depressive episode ensued despite ongoing continuation prophylaxis with both lamotrigine and gabapentin at the same doses previously utilized (not shown). Although the depression was less severe than observed in previous episodes, the failure of lamotrigine and gabapentin to prevent the onset of the next episode further supports the possibility that the presumptive response to the addition of gabapentin to lamotrigine was related to the natural course of illness.

Discussion

Despite this ambiguity, we present this case for discussion for a number of reasons. Several other partial responders to lamotrigine appeared to benefit from the addition of gabapentin at the NIMH. The two drugs have very different mechanisms of action which could result in additive effects. That is, gabapentin increases the levels of the major inhibitory neurotransmitter in brain, gamma-aminobutyric acid (GABA), whereas lamotrigine is thought to act in part by decreasing the release of the excitatory amino acid glutamate in the brain. In addition, the two drugs have very different mechanisms of anticonvulsant effects on amygdala-

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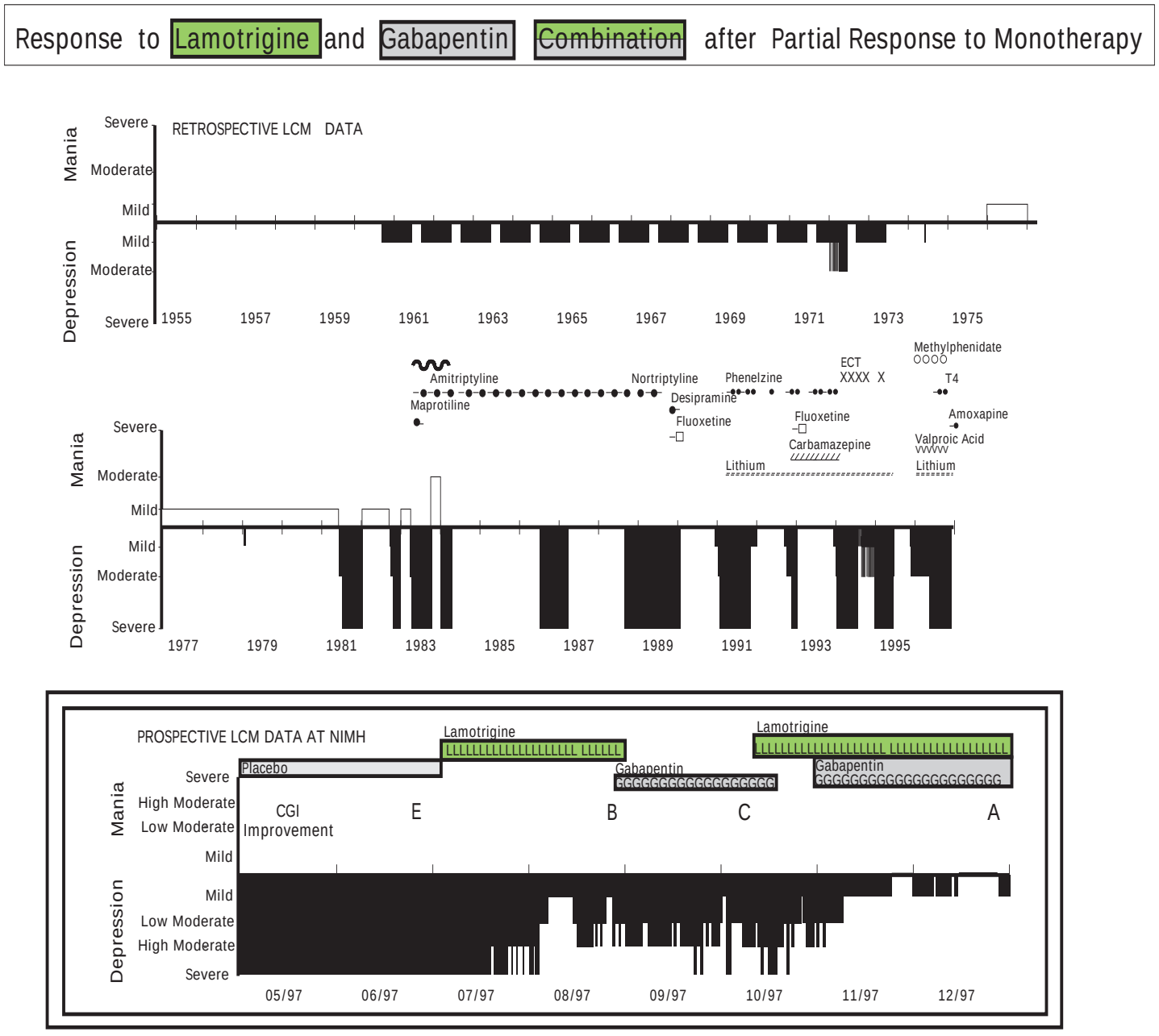

Figure 1: Multiple antidepressants, mood stabilizers, and ECT failed to adequately block severe depressive recurrences from 1983 to 1996 in this patient with bipolar II illness. At the NIMH (bottom row), daily prospective LCM ratings during the double-blind randomized protocol of Frye et al. (2000; *J Clin Psychopharmacol*, in press) revealed: no response to placebo (CGI - "minimally worse" = 'E'); moderate response to lamotrigine (CGI - "much improved" = 'B'); slight deterioration while on gabapentin, but still slightly improved from earlier "worst phase" (i.e., CGI - "minimally improved" = 'C'); beginning of a re-response in phase IV response confirmation mode when the phase II medication (lamotrigine) was blindly added again; and then a complete response to the lamotrigine+gabapentin combination (CGI - "very much improved" = 'A').

Meeting Highlights

American College of Neuropsychopharmacology (ACNP) Acapulco, Mexico, December 12th–16th, 1999

The American College of Neuropsychopharmacology (ACNP), founded in 1961, is a professional organization of some 600 leading scientists. Members are selected primarily on the basis of their original research contributions to the field of neuropsychopharmacology, which involves the evaluation of the effects of natural and synthetic compounds upon the brain, mind, and human behavior. The official journal of the ACNP is *Neuropsychopharmacology*, published monthly by Elsevier Science, Inc. To learn more about the ACNP, visit their website at: www.acnp.org.

The 38th Annual Meeting of the ACNP took place from December 12–16, 1999, in Acapulco, Mexico. A variety of neuropsychopharmacological findings pertinent to bipolar disorder and the rest of the affective disorders were presented:

Drug Mechanisms

DR. H. MANJI et al. of Wayne State University updated their data concerning the possible neurotrophic effects of lithium and valproate (Depakote®). They previously reported findings that lithium increased brain levels of n-acetylaspartate (NAA), a putative marker of neuronal viability and function. At the meeting, they reported that valproate increased NAA as well, and robustly increased neurite outgrowth. This group also reported that lithium increased the number of new cells in the adult dentate gyrus.

Note: Lithium and valproate also increase brain-derived neurotrophic factor (BDNF) and Bcl2 (both cell survival factors) and decrease Bax and p53 (cell death factors).

DR. R. DUMAN of Yale University reported that chronic antidepressant treatment increases cyclic-AMP response element binding protein phosphorylation (CREB-P) and the expression of BDNF in hippocampus and cerebral cortex. Chronic administration of different classes of antidepressants, including norepinephrine and serotonin selective reuptake inhibitors, monoamine oxidase inhibitors, and electroconvulsive seizures, was found to increase the number of new cells in the subgranular zone of the hippocampus. The increased cell number was not observed after acute treatment, consistent with the therapeutic time course of antidepressants. In addition, this effect appeared to be pharmacologically specific to antidepressant treatment in that chronic administration of an antipsychotic (haloperidol) or an opiate (morphine) did not increase the number of new cells. These findings are consistent with the possibility that the action of antidepressant treatment is mediated, in part, by increased survival of neurons.

Note: These data suggest important roles for lithium, valproate, and antidepressants in a cascade of biochemical effects culminating in alterations in gene expression; some of these alterations may involve changes in the microstructure of the brain by increasing cell survival or even the development of new neurons in adulthood (neurogenesis).

DR. L. MARANGELL and colleagues at Baylor University reported on inhibitory effects of omega-3 fatty acids on protein kinase C (PKC) activity *in vitro*. Preliminary data suggest that omega-3 fatty acids may be effective mood stabilizers for patients with bipolar disorder (Stoll et al., 1999; Arch Gen Psychiatry 56:407–412). Both lithium and valproic acid are known to inhibit PKC activity after subchronic administration in cell culture and *in vivo*. The current study was undertaken to determine the effects of omega-3 fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—on PKC activity, *in vitro*. Dr. Marangell and colleagues found that both DHA and EPA, as well as the combination of DHA and EPA, inhibited PKC activity at concentrations as low as 4 mmoles/L. In contrast, lithium, valproic acid and arachidonic acid had no effect on the measure of PKC activity. They concluded that DHA and EPA significantly inhibit the activity of the catalytic domain of PKC beta in a manner distinct from lithium and valproic acid.

Stress and Trauma

DR. E. GOULD at Princeton University presented further evidence of neurogenesis in postnatal weeks of life in both the rodent and the marmoset. She found that in the rodent, the odor of a predator (fox odor, a potent rodent stressor) increased glucocorticoid receptors and decreased neurogenesis; social stress in the marmoset and the tree shrew also decreased neurogenesis. Dr. Gould stated that these findings, taken with those of Dr. Duman (above) that antide-

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Meeting Highlights: ACNP

(Continued from page 8)

pressants increase neurogenesis, suggest that not only do stress and antidepressants have opposite effects on a variety of neurotrophic factors such as BDNF, but they also have opposing effects on engendering new neurons.

A number of investigators spoke of the long-term effects of early trauma on behavior, neuroendocrinology, and brain function of the adult rodent. DRS. M. PLOTSKY AND C. NEMEROFF of Emory University gave a presentation on maternal separation as a vulnerability factor for disorders of emotional regulation. Disruption of maternal behavior and patterns of care-giving appear to exert profound and long-lasting effects on the offspring. Studies of Long-Evans rats and rhesus monkeys exposed to neonatal maternal separation display dysfunction of the hypothalamic-pituitary-adrenal axis, anxiety-like behavior, mild cognitive impairments, anhedonia, and proclivity to the acquisition of cocaine and alcohol self-administration.

Many humans experiencing repeated traumatic events early in life appear to suppress their rate of cortisol production, yet they too show a higher incidence of depression, anxiety, and substance abuse, as well as suicide attempts. The new data presented by Dr. Nemeroff mirror those of Dr. R. Yehuda and others, indicating that patients with a history of early severe trauma appear to have a blunted cortisol response to a variety of challenges compared with controls.

DR. J. BREMNER and colleagues at Yale University reported that abused women with post-traumatic stress disorder (PTSD) had lower cortisol levels following both corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) challenge, and that abused women with and without PTSD had a blunted ACTH response to CRF challenge. In a second study, they found that women with PTSD had a decrease in right hippocampal (as well as medial prefrontal) function during traumatic reminders of childhood abuse. The findings were consistent with hippocampal atrophy and dysfunction in PTSD, and suggest long-term dysregulation involving increased central CRF activity but decreased cortisol in the periphery. *(Continued on page 10)*

Life Chart Highlight

(Continued from page 6)

kindled seizures, wherein gabapentin increases the threshold for seizures and lamotrigine is able to inhibit the spread of seizures without changing the threshold.

Two double-blind clinical trials of gabapentin have failed to reveal superiority to placebo. The NIMH clinical trial in refractory affective disorders (Frye et al., 2000; *J Clin Psychopharmacol*, in press) indicated that lamotrigine was superior to both gabapentin and placebo. Used as monotherapy for six weeks, gabapentin was not substantially different from placebo in this highly refractory subgroup of patients. In addition, Dr. A. Pande of Parke-Davis Pharmaceutical Research, reported that gabapentin was no more effective than placebo as an adjunctive treatment for acute mania (see "Meeting Highlights," p. 4).

Nevertheless, a considerable literature of open-label gabapentin augmentation of other mood stabilizers continues to suggest its potential utility for some subgroups of bipolar patients. This utility is convergent with the other documented effects of gabapentin, such as efficacy in anxiety and social phobia syndromes, as well as in paroxysmal pain syndromes, each of which has a moderately high incidence of comorbidity with bipolar illness. Gabapentin also does not have many pharmacokinetic interactions with other drugs, because it is largely secreted unchanged in the kidney. In addition, its side-effects profile is generally relatively benign when used in combination with other agents.

Brodie and Yuen (1997; Epilepsy Res 26:423–432) and others in the neurological literature suggest the excellent efficacy and tolerability of the lamotrigine-valproate combination. However, because of increased risk of serious rash when lamotrigine and valproate are used in combination, this may not be a high priority treatment option for some patients. To the extent that gabapentin shows some biochemical effects similar to valproate (i.e., it increases brain GABA levels), it is possible that the potentiative effects observed for lamotrigine and valproate could also extend to lamotrigine and gabapentin.

This proposition remains to be more systematically explored in more formal clinical trials. However, at present, it would appear that gabapentin monotherapy has little place as a primary mood stabilizer in bipolar illness, but its use as an adjunct may be associated with substantial clinical improvement and, occasionally, a complete remission, as occurred in this patient, at least transiently. Clearly, the optimal choice for combination therapy in patients with refractory affective disorders will require much further research, but the current case at least raises the possibility of combining two drugs with very different mechanisms of action in order to achieve a more complete response than with either alone. ■

Meeting Highlights: ACNP

(Continued from page 9)

DR. M. MEANEY of McGill University, Canada, presented a dramatic example of the potential impact of early environmental experience on lifelong changes in behavior and gene expression, changes that were previously thought to be mediated by hereditary genetics. Dr. Meaney found that in contrast to rat pups undergoing 3-hour separation stress, rat pups that were separated for 15 minutes a day evoked increased licking responses from their mothers upon their return and were protected against age-related cognitive decline and loss of hippocampal cell volume. Because the licking component appeared crucial, he examined spontaneous licking behavior and found that some mothers showed this trait in great quantity, whereas others were minimal lickers. The offspring of rat pups that were minimally licked were hypercortisolemic and showed increased anxiety in a variety of open field studies. When minimally-licked rat pups reproduced, their offspring also were hypercortisolemic and anxious. However, when these rat pups were cross-fostered and brought up by a high-licking mother, they were protected against hypercortisolemia and age-related cognitive decline and, in turn, were able to pass this more positive trait on to their offspring transgenerationally.

Note: If analogous changes are possible in humans, these data would appear to have tremendous social, cultural, and political implications because effective interventions in one single generation could have very long-lasting effects on the behavior and stress vulnerability of many subsequent generations.

DR. M. DAVIS of Emory University has begun to study the potential for gene therapy of neuropsychiatric syndromes. He was able to increase CREB levels specifically in the basolateral amygdala via herpes simplex viral vector-mediated gene transfer, resulting in near normal long-term memory following massed trials of conditioned fear training which usually result in poor learning. These results show that functional CREB activity in the amygdala may serve as a molecular switch for the formation of long-term emotional memory as reflected in fear conditioning.

Brain Imaging

DR. M. PHELPS from UCLA gave a presentation on "Molecular imaging: from metabolism to gene expression with positron emission tomography (PET)," raising the possibility of ultimately using functional brain imaging to study gene expression in humans, and providing initial evidence from their data that this may soon be possible.

DR. T. KETTER of Stanford University presented data from his work in the Biological Psychiatry Branch of the National Institute of Mental Health (NIMH) as well as his data from the new Affective Disorders Clinic at Stanford. At the NIMH, he found using PET that those patients with baseline hyperactivity in fronto-temporal areas of brain, particularly the left insula, responded better to carbamazepine (Tegretol®), whereas those who were hypometabolic in this area responded better to the L-type calcium channel blocker nimodipine (Nimotop®). Relative hypoactivity at baseline was also associated with response to lamotrigine (Lamictal®), gabapentin (Neurontin®), and 20 Hz (as opposed to 1 Hz) repeated transcranial magnetic stimulation (rTMS) of the brain. Less chronically ill and less treatment-refractory depressed bipolar disorder outpatients at Stanford compared to controls had anterior paralimbic and cerebello-posterior cortical hypermetabolism both at rest and in a (30 minute) sustained self-induced sad state. In antidepressant responders to valproate, decreases in metabolism with the sadness task compared to controls were blunted but were enhanced in the nonresponders to divalproex.

The DR. H. SACKEIM group at Columbia University reported data that showed that those depressed patients who have the greatest decrease in blood flow in frontal cortex, cingulate gyrus, and temporal lobe following electroconvulsive therapy (ECT) have the best antidepressant response. Thus, it is uncertain which areas of brain showing alterations are related to the primary pathophysiological process of depression, and which are compensatory and adaptive and in need of enhancement.

New Treatments

At a panel session addressing endogenous glutamate receptor ligands as novel leads for schizophrenia research and therapy, it was noted that a number of investigators have thought that increasing glutamate agonism indirectly could be helpful in the treatment of schizophrenia because the N-methyl-D-aspartate (NMDA)-type glutamate antagonist phencyclidine (PCP, or"angel dust") is highly psychotomimetic. A presentation by DR. D. GOFF of Harvard University reviewed the clinical implications of endogenous and exogenous glutamate receptor ligands. Attempts to use d-serine or cycloserine have been partially successful and, at this meeting for the first time, it was reported that d-alanine, which more readily crosses the blood-brain barrier, and is converted to d-serine in the brain, is also effective in initial studies. A six-week trial of d-alanine showed improvement in positive and negative symptoms as well as in cognition in patients with schizophrenia.

Note: These data provide another new target of therapeutics in schizophrenia in addition to attempts to decrease the enzyme naladase, as suggested at the meeting by Coyle et al. of Harvard University, or to decrease levels of quinolinic acid, as suggested at the meeting by Schwarcz and associates at the University of Maryland.

(Continued on page 11)

Meeting Highlights: ACNP

(Continued from page 10)

DR. J FRAZIER and colleagues at McLean Hospital presented data on a study of olanzapine (Zyprexa®) in the treatment of bipolar disorder in juveniles. Despite widespread use of antipsychotics in juveniles with bipolar disorder, few studies using these medications have been conducted in this patient population. The primary objective of this study was to assess safety and efficacy of the novel antipsychotic olanzapine after up to 8 weeks of open-label treatment. Twenty-three bipolar disorder patients (currently manic or mixed), ages 5 to 14, received olanzapine (dose range: 2.5–20 mg/day). The response rate (using a >=30% improvement on the Young Mania Rating Scale) was 60.9%. Extrapyramidal symptom measures were not (statistically) significantly different from baseline levels. However, significant increases were observed in weight (4.98 ± 2.32 kg, p<0.001).

DR. M. SAJATOVIC of Case Western Reserve University reported on quetiapine (Seroquel®) in neuroleptic-dependent mood disorders. In this prospective, open-label, 12-week trial of quetiapine therapy in patients with neuroleptic-dependent mood disorders, twenty individuals (10 with bipolar disorder and 10 with schizoaffective disorder) received quetiapine therapy at a mean dosage of 202 mg/day. Overall, patients did well on quetiapine therapy with significant improvement compared to previous antipsychotic medication therapy. Most individuals in the study had substantial depressive symptoms, which improved on quetiapine therapy. Simpson-Angus ratings of neurological side effects also decreased significantly from a baseline of 5.5 to an endpoint score of 1.9 (p = 0.02).

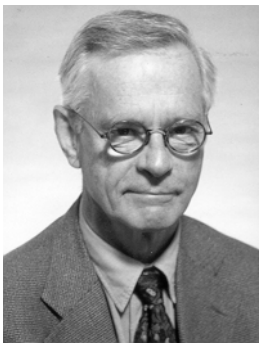
DR. E. VIETA of the University of Barcelona, Spain, presented data on risperidone (Risperdal®) as add-on therapy in bipolar disorder. Risperidone has shown efficacy in treating affective symptoms of schizophrenia and in patients with schizoaffective disorder and bipolar disorder. They conducted an open study in 598 patients with either schizoaffective disorder, bipolar type, or bipolar disorder, type I or II. Inclusion criteria were age between 18 and 65 years and DSM-IV symptoms of an episode of acute mania, hypomania, or mixed symptoms, and a Young Mania Rating Scale score >7. Each patient was receiving mood-stabilizing medication. Of the patients initially recruited, 541 were eligible for evaluation using various measures of treatment efficacy. During the 6-month follow-up, 111 patients dropped out for several reasons, including lost to follow-up (4%), side effects (3%), hospitalization (3%), lack of response (3%), poor compliance (1%), patient's decision (1%), and other (6%).

At 6 months, the mean dose of risperidone was 3.9 mg/day. According to a last-observation-carried-forward analysis, significant improvements were seen in scores on the Clinical Global Impressions scale (p<0.0001), total and positive, negative, and general psychopathology subscales of the Positive and Negative Syndrome Scale (p<0.0001), Young Mania Rating Scale (p<0.0001), and Hamilton Rating Scale for Depression (p<0.0001). Significant improvements were also seen in most neurological side effects, including scores on the Udvalg for Kliniske Undersogelser subscale for neurological side effects (p<0.0001). By the end of the study period, over 40% of patients were asymptomatic. These results suggest that risperidone may have mood stabilizing properties and prove useful in the treatment of patients with bipolar disorder and schizoaffective disorder, in conjunction with mood-stabilizing medication.

In a special plenary symposium celebrating the first 50 years of experience with lithium, DR. MULLER-OERLINGHAUSEN of the Freie University, Berlin, indicated that although there is a 30 to 50-fold increased risk of suicide in the unipolar and bipolar affective disorders compared with the general population, lithium greatly lowers this risk back toward that of the general population. In this regard, lithium appears superior to carbamazepine because, in a prospective randomized study, no suicidal acts occurred in the lithium-treated group (146 patients), but four suicides and five attempts were reported in 139 patients on carbamazepine. These data are consistent with a recent meta-analysis of Dr. Baldessarini and colleagues (see "Meeting Highlights," p. 3). ■

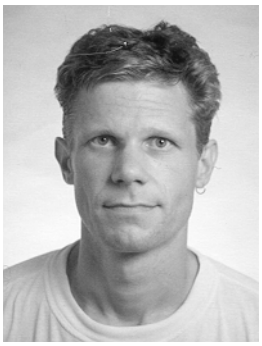
Investigator Spotlight

Dr. Tom G. Bolwig, Dr. Lars V. Kessing
Rigshospitalet, Copenhagen, Denmark



DR. TOM G. BOLWIG obtained his medical degree in 1964 and his advanced degree in 1977 from the University of Copenhagen; he was Senior Lecturer in Psychiatry from 1977 to 1982, and has been a Professor of Clinical Psychiatry from 1982 to the present. Dr. Bolwig's career is distinguished by both its breadth and depth. He has made major contributions to clinical psychiatry, psychopharmacology, and experimental neurobiology. He has published 215 papers and edited three books. He is also the Associate Editor of the *Journal of ECT* and *Acta Psychiatrica Scandinavica*. Because ECT is widely used in the treatment of refractory depression, Dr. Bolwig and his colleagues have studied its potential mechanisms of action, revealing alterations in neuropeptides, receptors, and the activation of glial cells following this treatment in experimental animals. His finding evidence of glial activation with seizures is particularly interesting in relation to recent findings of deficient numbers and decreased activation of glial cells in depression reported by many groups, including in autopsy specimens of depressed patients in the Stanley Foundation Brain Bank collection.

Dr. Bolwig has also demonstrated that repeated episodes of alcohol withdrawal would result in increased seizure susceptibility, as predicted from the kindling model. In examining the Danish case registry in collaboration with Dr. Lars Kessing, he has found the strongest evidence to date of sensitization phenomena in the affective disorders (see p. 13). These data add to a growing list of evidence that suggests the importance of early and effective intervention and long-term prophylaxis in the recurrent affective disorders based on the finding that the number of prior episodes is a strong predictor of subsequent relapse and rehospitalization. We look forward to further important contributions of Dr. Bolwig and colleagues to the better understanding and treatment of the refractory affective disorders. ■



DR. LARS V. KESSING received his M.D. from Copenhagen University in 1986, becoming a specialist in psychiatry in 1999. He has studied the psychiatric symptomatology of the human immunodeficiency virus (HIV), the consequences of epilepsy surgery, and cognitive impairments in primary affective disorder in relation to illness characteristics.

His series of studies (along with Dr. Bolwig) based on the data in more than 20,000 patients in the Danish case registry has added a crucial perspective to factors that contribute to the recurrence of affective disorders. He found that the best predictor of the incidence and rate of rehospitalization in both unipolar and bipolar disorder was the number of prior episdodes (see p. 13). Again, these data speak to the importance of long-term prophylaxis in attempting to alter this course of recurrent affective disorders.

Most recently, Dr. Kessing has studied factors related to the development of dementia in affective disorder patients as well as individual heterogeneity of illness characteristics that are associated with recurrence. These data will enable one to better anticipate high degrees of illness vulnerability and recommend more effective long-term prophylactic strategies. Dr. Kessing will defend his thesis in Medical Science at the University of Copenhagen this summer, and we look forward to his continued major contributions to the field. ■

Dr. Bolwig and Dr. Kessing are the lead investigators at the new Stanley Foundation Bipolar Network European Center in Denmark. An example of their groundbreaking collaborative work is summarized on the following page.

Recurrence in affective disorder I. Case register study

Lars Vedel Kessing, Per Kragh Andersen, Preben Bo Mortensen, Tom Gert Bolwig

Full Article Appeared in the Journal: Br J Psychiatry 172: 23–28, 1998

BACKGROUND: In recent years, studies of the risk of recurrence in affective disorder in relation to the number of prior episodes have given contradictory results. Some investigators have found that the duration of time to recurrence decreases as a function of the number of prior episodes; other investigators have failed to demonstrate this relation in bipolar disorder. To investigate changes in the risk of recurrence with successive episodes it is necessary to study a large sample of patients followed through many years. Psychiatric case registers make this possible and data can now be analysed with survival analysis. The aim of this study was to describe the rate of recurrence, expressed as the rate of readmission after successive discharges in unipolar and bipolar disorders, by applying life-table methods in a larger sample from a psychiatric case register.

METHOD: In Denmark, all psychiatric admissions have been registered in a nationwide register. Since there are no private psychiatric hospitals or clinics in Denmark, all admissions for the 5.1 million inhabitants are included in the register. The study sample was defined as all inpatients with a manic-depressive main diagnosis, depressive or manic/cyclic episode, at first discharge. The sample was divided into two, according to the type of manic-depressive disorder at a given time (unipolar or bipolar). The type of disorder was thus time-dependent and some patients changed type during the study. The risk of readmission originates from a sum of two other risk factors: the risk of relapse, i.e., the return of an episode during remission (before recovery) and the risk of recurrence, i.e., the appearance of a new episode during recovery. The first eight weeks after discharge was defined as the period of remission, and readmission after these first eight weeks as a new episode (i.e., recurrence).

RESULTS: A total of 20,350 patients constituted the study sample meeting the diagnoses requirements. Time to recurrence decreased with the number of previous episodes for unipolar as well as for bipolar patients. Initially, the two types of disorders followed markedly different courses, but later in the course of the illness the rate of recurrence was the same for the two disorders. The progressive course of the illness was partly due to a selection phenomenon, since patients with many episodes demonstrated a high risk of recurrence from the first episode. However, this selection bias did not explain the whole deteriorating pattern, since the high initial risk of recurrence for patients with many episodes also increased further with every new episode. Further analysis revealed that other selection biases were caused by age and gender, since younger patients and female patients constituted an increasing proportion of patients and in addition experienced greater risk of recurrence as the number of episodes increased. However, if the sample was divided on gender and on age categories, all subpopulations demonstrated the same deteriorating pattern for each new episode. (Kessing et al., 1998; Br J Psychiatry 172:29–34)

CONCLUSIONS: The course of unipolar and bipolar disorder as reflected in hospitalizations seems to be progressive in nature despite naturalistic treatment in the community, and stresses the great need for further, earlier, and more effective prophylactic interventions. ■

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