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Bipolar Network News

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Fourth European Stanley Foundation Conference on Bipolar Disorders

Aarhus, Denmark September 23-25th, 2004

The Stanley Medical Research Institute sponsors the European Conference on Bipolar Disorders and the International Conference on Bipolar Disorder, held in alternating years. Highlights of the Fourth European Stanley Foundation Conference on Bipolar Disorder are noted here; the abstracts of the meeting are available in print in the journal *Acta Psychiatrica Scandinavica*, Volume 110, Supplement 423, 2004.

Neurobiology

Dr. L. Altshuler (University of California Los Angeles School of Medicine) and colleagues studied 72 women with bipolar disorder ages 18–45, who were not taking oral contraceptives, agreed to fill out questionnaires about their menstrual cycle, and agreed to give blood samples to measure a range of reproductive endocrine and metabolic hormone levels. Dr. Altshuler and colleagues found that several hormone levels were low (e.g., estrone, one of three naturally occurring estrogens) and others were high (luteinizing hormone [LH]-to follicle-stimulating hormone [FSH] ratio) across the entire bipolar group. A significantly higher proportion of women taking divalproex (Depakote®) had abnormal LH:FSH ratio values compared with those not taking divalproex. In contrast to a report by the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), the hormone testosterone, a marker for polycystic ovary syndrome, was not elevated in this study. The authors concluded that many women with bipolar disorder have endocrine abnormalities, regardless of drug treatment, which may contribute to high rates of menstrual disturbance reported in this group. The full set of findings from this study were just recently published (Rasgon et al., 2005; *Bipolar Disord* 7 [3]: 246–259).

"... many women with bipolar disorder have endocrine abnormalities, regardless of drug treatment, which may contribute to high rates of menstrual disturbance reported in this group."

A previous study by Kupka et al. (2002; *Biol Psychiatry* 51 [4]: 305–311) found an increased incidence of antithyroid antibodies in bipolar patients. Dr. R. Padmos (Erasmus MC, Rotterdam, The Netherlands) et al. investigated the prevalence of three other antibodies: antibodies to hydrogen/potassium (H/K) adenosine triphosphatase (ATPase); glutamic acid decarboxylase 65 (GAD-65), which is critical for the synthesis of the main inhibitory neurotransmitter in brain gamma-aminobutyric acid (GABA); and GAD-67, in 239 patients with bipolar disorder, 74 patients with schizophrenia, and 220 controls. The prevalence of antibodies for H/K ATPase and GAD-65 were increased in bipolar patients compared with controls; schizophrenic patients did not show any significantly higher prevalence. Dr. Padmos et al. have published the full results from this study (2004; *Biol Psychiatry* 56 [7]: 476–482)

Together with the previous study of Kupka et al., these data suggest that there is an increased incidence of several different types of endocrine and neural autoimmunity in patients with bipolar illness, and further study of the relationship of these findings to treatment outcome is clearly warranted.

The relationship between genetic risk and brain structural variation was studied by Dr. C. McDonald (Institute of Psychiatry, London, UK) and colleagues in: a) 25 patients with schizophrenia; b) 36 of their unaffected first-degree relatives; c) 37 patients with bipolar I disorder who had experienced psychotic symptoms during episodes of illness exacerbation; and d) 50 of their unaffected first-degree relatives. Using magnetic resonance imaging (MRI), Dr. McDonald et al. found that decreased volume of white matter areas in the frontal, temporal, and parietal regions of the brain was a genetic risk factor for both bipolar illness and schizophrenia, but only a gray matter volume deficit in the right anterior cingulate gyrus and ventral striatum was associated with a genetic risk for bipolar disorder. The full results of this study have been published (McDonald et al., 2004; *Arch Gen Psychiatry* 61 [10]: 974–984).

The serotonin transporter gene-linked polymorphic region (5-HTTLPR) is considered to play a

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major role in serotonin-mediated effects; some studies have found that the short form of 5-HTTLPR (short/short allele, or s/s) results in decreased efficacy of serotonin-selective reuptake inhibitors (SSRIs). In 50 treatment-refractory depressed patients (11 bipolar, 39 unipolar) using lithium augmentation, Dr. T. Stamm (University Medicine Berlin, Germany) et al. reported that the s/s form of 5-HTTLPR was the most significant predictor of remission in these patients.

"Dr. S. Dittmann . . . and colleagues reported an association of cognitive deficits in euthymic patients with bipolar illness who had elevated levels of plasma homocysteine."

Because the s/s genotype seems to predict nonresponse to the SSRIs, other approaches such as lithium or pindolol augmentation might be considered in those patients with this genotype who have an inadequate response to antidepressant monotherapy.

Neurocognitive Impairment

Dr. V. Balanza (University of Valencia, Spain) et al. reported on persistent cognitive impairment in euthymic bipolar I patients in a follow-up study. Twenty-three euthymic bipolar I patients and 39 schizophrenic outpatients were followed for one year, and tested twice with a battery of cognitive tests. Both groups were found to show a persistent cognitive dysfunction compared with healthy subjects, in the areas of verbal memory, verbal fluency, and motor and attentional/executive domains.

These data confirm a growing series of studies indicating that, even when euthymic, bipolar patients on average have deficits in verbal memory and fluency, and in motor and executive functioning compared with normal controls. Most importantly, in the study of Dr. Balanza, the number of past episodes predicted 36–47% of the variance in working memory and attentional/executive domains. These studies replicate and extend the earlier findings of Denicoff and colleagues (1999; J Affect Disord 56 [1]: 67–73) that a number of cognitive deficits are related to duration or number of episodes in bipolar patients. In a large epidemiological study involving more than 20,000 patients in the Danish Case Registry, Kessing and colleagues (2004; J Neurol Neurosurg Psychiatry 75 [12]: 1662–1666) found that one affective episode in unipolar or bipolar disorder did not alter one's chances of becoming cognitively impaired (i.e., acquiring a dementia syndrome) in old age, whereas having four or more episodes increased the risk approximately two-fold. All of these studies suggest the importance of early preventive pharmacological strategies to not only modify the subsequent course of illness, but also to prevent some of these cognitive and neurobiological alterations that may be associated with having greater numbers of episodes.

Dr. S. Dittmann (University of Munich, Germany) and colleagues reported an association of cognitive deficits in euthymic patients with bipolar illness who had elevated levels of plasma homocysteine. High plasma levels of homocysteine have been associated with cognitive impairment, Alzheimer's disease, and white matter lesions in healthy elderly individuals. Homocysteine has also been reported to be higher in bipolar patients who did not get well between episodes, and increased levels of homocysteine are a risk factor for cardiovascular disease, including an increased incidence of myocardial infarction.

Dr. Dittmann and colleagues' finding of an association between plasma homocysteine and cognitive impairment in euthymic bipolar disorder further supports the rationale for treatment of many patients with refractory affective disorders with folic acid supplements. Folic acid, as well as vitamin B12, decreases elevated levels of homocysteine. Coppen and Bailey (2000; J Affect Disord 60 [2]: 121–130) reported that folic acid, compared with placebo, increased the degree of antidepressant efficacy of fluoxetine (Prozac®) in patients with major depression, and Coppen et al. (1986; J Affect Disord 10 [1]: 9–13) found that folic acid increased the efficacy of lithium carbonate in long-term prophylaxis.

Dr. A. Martinez-Aran (Stanley Medical Research Institute Center, Barcelona, Spain) et al. attempted to determine whether the report of cognitive complaints in bipolar patients was associated with objective neuropsychological impairments. Sixty euthymic bipolar patients were assessed through a neuropsychological battery, and 30 healthy controls were also included in the study. Dr. Martinez-Aran et al. reported that bipolar patients with more subjective complaints of cognitive impairment had more previous episodes, a longer duration of illness, and an earlier age of onset. Also, bipolar patients with subjective cognitive complaints had lower scores on several cognitive measures related to attention, memory, and executive function compared with the control group.

Neurocognitive dysfunction in the first-degree relatives of bipolar disorder patients was examined by Dr. U. Goswami (Lady Hardinge Medical College, New Delhi, India) and co-investigators. They found that 31 first-degree, non-symptomatic *relatives* of bipolar patients had more depression, mania, and neurological soft signs than control subjects, and did significantly poorly on a few neurocognitive test measures of immediate memory and executive function.

New Data on Atypical Antipsychotics

Zotepine (Nipolept®) is a broad spectrum atypical antipsychotic drug that has been approved for use in Germany since 1990. Dr. B. Amann (Ludwig Maximilian University, Munich, Germany) and co-investigators tested the efficacy and tolerability of zotepine (up to 600 mg/day) for a maximum of three weeks in 12 patients with an acute and severe manic

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Bipolar Network News

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The *BNN* is published three times a year by investigators working with patients with bipolar disorder to better understand the long-term course and treatment of the illness. The newsletter is available free of charge to all who request it.

Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in summary or pre-publication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact, omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the *BNN*.

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episode. Nine of the 10 patients who remained in the study were classified as responders (five of them responding within four days), and no patient switched into a depressive episode. There were dose-dependent extrapyramidal side effects, increases in weight, and autonomic side effects in some patients.

Dr. P. Keck Jr. (University of Cincinnati Hospital) and colleagues conducted an analysis of 315 rapid cycling bipolar patients who participated in the large 8-week, double-blind study of olanzapine (Zyprexa®) versus olanzapine/fluoxetine (Prozac®) combination (OFC, or Symbyax®) therapy versus placebo in 833 patients by Tohen et al. (2003; *Arch Gen Psychiatry* 60 [11]: 1079–1088). Keck et al. found that in these rapid cycling patients, OFC was significantly better than placebo and olanzapine at weeks 4, 6, and 8 of the study. OFC also showed higher response and remission rates at endpoint, and treatment-emergent mania (i.e., switching into mania) did not differ significantly between groups.

An open-label, 6-month extension of the acute olanzapine versus OFC trial was conducted in 562 patients. One analysis of this 6-month extension by Keck et al. found that, as in the subset of rapid cycling patients noted above, treatment-emergent mania was low and did not differ between groups in the acute phase (6.4% for OFC, 5.7% for olanzapine, 6.7% for placebo), and remained low in the extension phase (4.7% for OFC).

In another analysis of the 6-month OFC extension study, Dr. T. Ketter (Stanford University) and co-investigators examined the efficacy of either OFC or olanzapine in patients with bipolar depression. Dr. Ketter found that of the 192 patients who were in remission after the 8-week acute trial, 120 (62.5%) remained free from relapse over the 6-month maintenance period.

Dr. E. Mick (Massachusetts General Hospital, Boston) et al. conducted an 8-week, open-label comparison of the atypical antipsychotics olanzapine, quetiapine (Seroquel®), risperidone (Risperdal®), and ziprasidone (Geodon®) for monotherapy treatment of pediatric bipolar disorder. One hundred and one patients were enrolled in the study, and were an average of 10.2 years old. The study data showed that risperidone was associated with a 75% much or very much improved rate in pediatric bipolar disorder, followed by ziprasidone (57%), quetiapine (56%) and olanzapine (50%). Olanzapine was associated with a marked increase in weight (4.9 kg), which was significantly greater than the weight gain for risperidone, quetiapine, or ziprasidone.

In a second study, Dr. Mick and collaborators evaluated the efficacy of risperidone (maximum dose 2 mg/day) or olanzapine monotherapy (maximum dose 10 mg/day) in 12 preschoolers (average age = 4.5 years old) with bipolar disorder in an 8-week, open-label trial. Both olanzapine (75% improvement) and risperidone (63% improvement) were moderately to highly effective, with mild and infrequent side effects for each drug in this small study.

Epidemiology, Course, and New Treatments of Bipolar Disorder

As part of the Jorvi Bipolar Study, Dr. O. Mantere (National Public Health Institute, Helsinki, Finland) and colleagues screened 1,630 non-schizophrenic psychiatric inpatients and outpatients in three Finnish cities, and found 191 bipolar patients. The majority (54.5%) of the bipolar II subjects and 28.9% of the bipolar I subjects were previously undiagnosed, and the remainder of the patients had a median of 8.2 years delay from first episode to diagnosis (and presumably treatment). More complete results from this study have been published (Mantere et al., 2004; *Bipolar Disord* 6 [5]: 395–405).

These investigators sadly confirm what appears to be a worldwide under-recognition of bipolar I and bipolar II disorders, even in psychiatric settings. The data of Hirschfeld and colleagues (2003; J Clin Psychiatry 64 [2]: 161–174) also strikingly emphasizes how common this diagnostic delay is in the U.S..; data from the former Stanley Foundation Bipolar Network showed an average delay of ten years between first symptoms that impaired function and first treatment.

Dr. T. Suppes (University of Texas Southwestern Medical Center, Dallas) and co-investigators examined a large database from 908 patients with bipolar disorder who participated in studies with the Stanley Foundation Bipolar Network (now called the Bipolar Collaborative Network). These investigators reviewed the frequency and gender relationship of the co-occurrence of depression and hypomania. During patient visits with a hypomanic state, 57% had mixed symptoms (hypomania with depression symptoms as well); 72% of women showed mixed symptoms if hypomanic, and only 42% of patient visits showed depression with no hypomania.

Two extensive studies by Dr. I. Kandemir (SSK Hospital-Buca, Izmir, Turkey) and colleagues investigated the differences between bipolar I and bipolar II, and the characteristics of bipolar depressive patients. In the first study, all of the bipolar patients over a 5-year period were followed in an outpatient clinic after discharge from 1993 to 1998. Nineteen patients had a bipolar II diagnosis, and 90 had a bipolar I diagnosis. Age of onset of first symptoms, first psychotropic drug use, first antidepressant use, and first hospitalization were significantly higher in bipolar II patients. The average duration of depressive episodes was significantly longer in patients with bipolar II depression, and there was a tendency to have a family history of non-bipolar mood disorders in bipolar II patients. In the second study, characteristics of bipolar depression treatment were evaluated over 5 years, during a transition period from tricyclic antidepressants (TCAs) to second generation antidepressants in Turkey. Rates of non-response, full response, and manic switch with TCAs vs. SSRIs were 25% vs. 21.6%, 50% vs. 52.9%, and 17.9% vs. 35.2%, respectively.

"... data showed that risperidone was associated with a 75% much or very much improved rate in pediatric bipolar disorder, followed by ziprasidone (57%), quetiapine (56%) and olanzapine (50%)."

Previous studies have found that lithium reduces the risk of suicide in patients with bipolar disorder. Dr. L. Sondergard (Rigshospitalet, Copenhagen, Denmark) and co-investigators conducted an observational cohort study of all patients prescribed lithium (13,170) and all recorded suicides in Denmark from 1995-1999. Dr. Sondergard and colleagues found that in this cohort,

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purchasing lithium at least twice was associated with a 0.44 reduced rate of suicide compared with the rate when purchasing it only once, with no interaction between gender and age. They concluded that continued lithium treatment (at least two prescriptions filled), as reported in many other studies using other methodologies, was associated with a reduced risk for suicide regardless of age and gender.

Dr. M. Franks (Stanley Research Centre, Newcastle-upon-Tyne, United Kingdom) and colleagues conducted a retrospective examination of the impact of withdrawal of maintenance medications in bipolar disorder. Patients were included if at least one medication was withdrawn after six months of documented remission, and recurrences in the three months after medication withdrawal were recorded. These investigators found that of 48 patients who met inclusion criteria, 34 (68%) experienced recurrence within three months of withdrawal. Twenty-two of the 39 episode recurrences required hospital admission.

In a previous issue (*BNN* Vol. 9, Issue 1), we reported that Dr. P. Keck and associates found a failure of 6 grams/day of the omega-3 fatty acid ethyl-eicosapentanoate (EPA) to significantly improve mood in patients with bipolar depression and in patients with rapid cycling, in two 4-month, randomized, placebo-controlled trials. At the Aarhus meeting, Dr. Keck reported that response in these two studies was not related to blood concentrations of omega-3 fatty acids.

This study, which used six grams EPA/day, is consistent with several other studies suggesting that lower doses may be more effective than higher doses, even in the treatment of unipolar illness or schizophrenia. Thus, if one were to consider using omega-3 fatty acids, it would appear prudent at this point to choose low doses of EPA, docosahexaenoic acid (DHA), or their combination, rather than attempt to achieve the very highest levels of these compounds.

A small study (12 subjects) by Dr. M. Comes (Hospital Clinic De Barcelona, Spain) and colleagues examined the use of the anticonvulsant oxcarbazepine (Trileptal®) for six months in patients with bipolar II disorder currently experiencing a hypomanic episode. Although five patients dropped out for various reasons, the remaining subjects showed a statistically significant improvement in hypomanic symptoms from week two forward.

Ms. G. Leverich (National Institute of Mental Health, Bethesda, Maryland) et al. and Dr. R. Post (NIMH) et al. reported on different aspects of a randomized study of the second-generation antidepressants bupropion (Wellbutrin®), sertraline (Zoloft®), or venlafaxine (Effexor®) added to a mood stabilizer for the treatment of bipolar depression in 184 patients. These three antidepressants were associated with moderate acute response rates (62–67%) and moderate rates of switching into hypomania or mania (9–38%). On a variety of analyses, venlafaxine was more likely to be associated with switching into

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Drugs Currently FDA-approved for Use in Bipolar Disorder

Medication Name	Bipolar Disorder Indication
Lithium (Lithobid®, Eskalith®)	• Acute mania in adults and children 12 years or older • Maintenance treatment of bipolar disorder in adults and children 12 years or older
Carbamazepine Extended Release Capsules (Equetro®)	• Acute manic and mixed episodes in adult patients with bipolar I disorder
Sodium Valproate (Depakote®, Depakene®, Divalproex®, Valproic Acid®)	• Acute bipolar mania in adults
Lamotrigine (Lamictal®)	• Maintenance treatment of adult patients with bipolar I disorder
Aripiprazole (Abilify®)	• Acute bipolar mania in adults, including manic and mixed episodes • Maintaining efficacy in patients with bipolar I disorder with a recent manic or mixed episode who have been stabilized and then maintained for at least six weeks.
Quetiapine (Seroquel®)	• Acute bipolar mania in adults with bipolar I disorder
Risperidone (Risperdal®)	• Acute bipolar mania, including manic and mixed episodes, in adults with bipolar I disorder, alone or in combination with mood stabilizers.
Olanzapine (Zyprexa®)	• Acute mania in adults with bipolar I disorder, including manic and mixed episodes, as monotherapy and in combination therapy with both divalproex and lithium • Maintenance treatment in bipolar disorder
Olanzapine and Fluoxetine HCL Capsules (Symbyax®)	• Treatment of depressive episodes in patients with bipolar disorder
Ziprasidone (Geodon®)	• Acute mania in adults with bipolar I disorder, including manic and mixed episodes

Special Report

Aripiprazole: An unusual atypical antipsychotic

Aripiprazole (Abilify®) is the latest atypical antipsychotic to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania (in October, 2004). All of the older typical antipsychotics (such as chlorpromazine [Thorazine®] and haloperidol [Haldol®]) clearly possess acute antimanic effects, and this is now true for all of the newer atypical antipsychotics as well (clozapine [Clozaril®], risperidone [Risperdal®], olanzapine [Zyprexa®], quetiapine [Seroquel®], ziprasidone [Geodon®], and aripiprazole [Abilify®]). In March of 2005, aripiprazole was also FDA-approved for maintenance therapy in bipolar I disorder patients with a recent manic or mixed episode, who had been stabilized and then maintained for at least six weeks.

Pharmacology and Pharmacokinetics

With the exception of aripiprazole, all of the typical and atypical antipsychotic drugs are thought to exert their primary action via direct blockade (antagonism) of the dopamine D_2 receptor. Aripiprazole appears to be an even more "atypical" atypical, because it is a partial agonist (rather than a full antagonist) at dopamine D_2 receptors. Full agonists (used to treat Parkinsonism) directly stimulate the dopamine receptor, and full antagonists directly block the dopamine receptor (and can cause parkinsonian side effects). As a partial agonist, aripiprazole occupies the dopamine receptor, but only stimulates it approximately 20% of the amount of a full agonist, regardless of how high the dosage is increased.

However, because aripiprazole is occupying the dopamine receptor (like a key in a lock), it is preventing excess dopamine from reaching the receptor, and is thus exerting an 80% functional blockade (or relative antagonism) of the dopamine receptor. These differences in agonist, antagonist, and partial agonist effects are illustrated in the figure on page 6.

In addition to partial agonism at the dopamine D_2 receptor, aripiprazole is also a partial agonist at dopamine D_1 and D_3 receptors, as well as at serotonin $(5\text{-HT})_{1A}$ receptors. These latter receptors are thought to be important for the antidepressant and antianxiety effects of drugs such as buspirone (Buspar®), which are agonists at the 5-HT_{1A} receptor. As such, it is hoped that the 20% stimulating effect of aripiprazole at dopamine and 5-HT_{1A} receptors will be associated not only with acute antimanic efficacy, but also with antidepressant and antianxiety efficacy.

Like many other atypical antipsychotics, aripiprazole is also a full agonist at 5-HT_{2A} receptors. Inhibition of these receptors is thought to be associated with antidepressant effects, and also with enhancement of deeper phases of sleep (slow wave sleep), similar to trazodone (Desyrel®) and nefazodone (Serzone®), which also block 5-HT_{2A} receptors.

Aripiprazole has a relatively long half-life of 75 hours, so that it can be given in once-a-day dosing. It can be given in the morning if patients are slightly activated, or in the evening if they are more sedated on the drug. Aripiprazole is metabolized by two kinds of hepatic enzymes, cytochrome (CYP) 2D6 and CYP3A4. Inhibitors of 2D6 such as fluoxetine (Prozac®) and paroxetine (Paxil®) may notably increase aripiprazole levels, and inhibitors of 3A4 metabolism such as erythromycin and verapamil (Calan®), will do likewise. Carbamazepine (Tegretol®), which induces 3A4, will lower aripiprazole levels.

Dopamine is important for inhibiting prolactin secretion. In contrast to all of the typical antipsychotics, which increase prolactin because of a blockade of dopamine D_2 receptors, aripiprazole will actually produce slight decreases in prolactin, consistent with its partial agonist properties.

Aripiprazole in Mood Disorders

Mania

Aripiprazole was FDA-approved for use in acute bipolar mania, including manic and mixed episodes, based on three different 3-week, double-blind, multicenter studies in 899 patients with acute mania, randomized to aripiprazole (n=515) or placebo (n=384). Significantly more patients responded with aripiprazole (45%) as compared with placebo (30%), and significantly more patients attained remission by study endpoint with aripiprazole (42%) versus placebo (28%). One of these studies has been published (Keck et al., 2003; see table, page 7).

Depression

As noted in the previous issue of the *BNN*, the atypical antipsychotics as a class appear to be increasingly used as adjuncts to antidepressants in refractory unipolar and bipolar depression (see Vol. 10, Issue 1, table, p. 5). Controlled studies have not yet been performed with aripiprazole in depression, but preliminary open case series suggest its possible utility in this illness phase as well (see table, page 7). Dr. J Barbee et al. (2004; *Ann Clin*

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Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole

Brown ES, Jeffress J, Liggin JD, Garza M, Beard L

J Clin Psychiatry 2005; 66 (6): 756–760

OBJECTIVE: Substance abuse is extremely common in patients with bipolar disorders, although minimal data are available on the treatment of this important clinical population. Aripiprazole is an atypical antipsychotic that is approved for the treatment of mania and that has a novel mechanism of action, acting as a dopamine-2 receptor partial agonist, thereby increasing dopamine release in some parts of the brain and decreasing dopamine release in other brain regions. Dopamine release is implicated in substance use, and both dopaminergic agonists and antagonists have been examined for the treatment of substance abuse. To our knowledge, dopamine receptor partial agonists have not been investigated for treatment of substance abuse in humans.

METHOD: Twenty antipsychotic-treated patients with bipolar or schizoaffective disorder and current substance abuse were switched to open-label aripiprazole using an overlap and taper method. At baseline, diagnoses were confirmed using the Mini-International Neuropsychiatric Interview based on DSM-IV criteria. Psychiatric symptoms, side effects, and substance use and craving were assessed over 12 weeks. Psychiatric symptoms were assessed with the Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS), and Brief

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Aripiprazole

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Psychiatry 16 [4]: 189–194) conducted a retrospective chart review of 30 treatment-resistant unipolar depressed patients with documented failure to at least one other atypical antipsychotic (risperidone, olanzapine, quetiapine, or ziprasidone) as an augmentation treatment to their antidepressant, who then received antidepressant augmentation with aripiprazole. Following the addition of aripiprazole, 14 (46.7%) of 30 patients in the intent-to-treat analysis responded (much or very much improved). The mean time to obtain a response was 3.1 weeks. The mean dose among responders was 13.0 mg/day.

In another study, Dr. J. Worthington et al. (2005; *Int Clin Psychopharmacol* 20 [1]: 9–11) retrospectively examined whether treatment-resistant depression (n=6) and anxiety disorder (n=11) patients, who had an incomplete response to a variety of serotonin-selective reuptake inhibitors (SSRIs), responded to and tolerated augmentation with aripiprazole for an average of almost 5 weeks. Ten (59%) of 17 patients were much or very improved at doses between 7.5 and 30 mg/day.

This possible efficacy in depression might be expected, not only based on aripiprazole's drug class (i.e., potentially similar to that of olanzapine and quetiapine where there are strong data for acute antidepressant efficacy), but also based on its partial agonist properties at dopamine and serotonin receptors. Dr. J Goldberg et al. (2004; *Am J Psychiatry* 161 [3]: 564–566) and Dr. C. Zarate et al. (2004; *Biol Psychiatry* 56 [1]: 54–60) have both reported that pramipexole (Mirapex®), which is a *full* agonist of dopamine D_2 and D_3 receptors, exerts

Schematic of the Receptor Modulating Effects of Partial Agonists

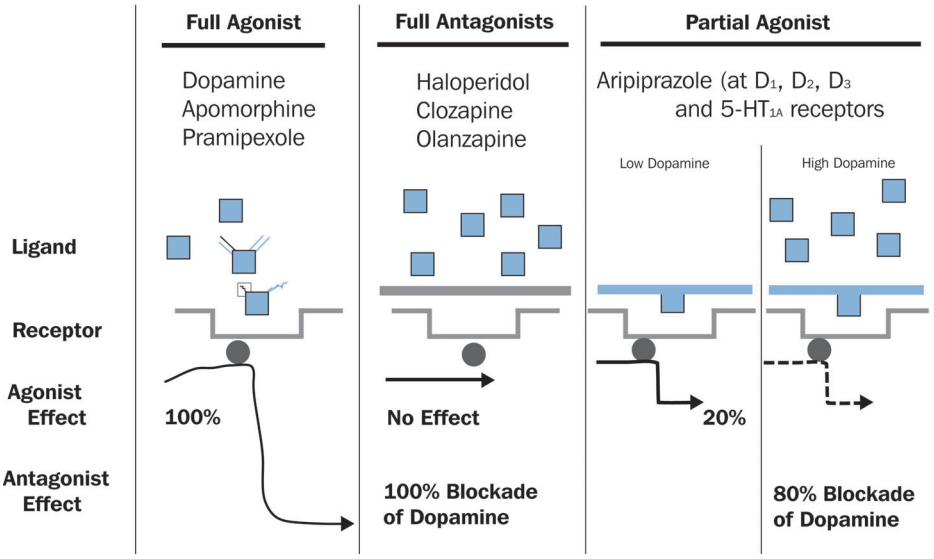

Figure Legend: Dopamine and direct agonists used in the treatment of Parkinson's disease fit into the dopamine receptor and cause increases in activation (left column). Conversely, antagonists (grey bar in second column) block the receptor and prevent excess dopamine (squares) stimulation that could lead to mania or psychosis. Aripiprazole is a partial agonist, meaning that part of the molecule acts like dopamine, but no matter how high the dose, it never stimulates more than 20% of a full agonist (blue bar with part of square attached, third column). Yet when the partial agonist occupies the receptor, it prevents any further dopamine stimulation, thus yielding an 80% functional blockade (last column). Aripiprazole is a partial agonist at serotonin 5-HT_{1A} receptors, as well as at dopamine D_1, D_2, and D_3 receptors.

antidepressant effects in bipolar depression. As a partial agonist with 20% inherent dopamine and 5-HT_{1A} stimulatory properties, aripiprazole might, on a theoretical basis, also be expected to be a useful antidepressant.

Maintenance Treatment

In March of 2005, aripiprazole was approved for use in maintenance therapy in bipolar I disorder patients with a recent manic or mixed episode, who had been stabilized and then maintained for at least six weeks. As noted in a previous issue of the *BNN* (Vol. 9, Issue 2, ACNP highlights, p.10), the maintenance study was a double-blind, placebo-controlled study in 161 patients with bipolar disorder who had experienced a manic episode and had been stabilized on aripiprazole for 6-18 weeks, and then were randomized to maintenance treatment with either aripiprazole or placebo for 26 weeks. Of those patients who experienced a relapse, patients treated with aripiprazole relapsed significantly later than placebo-treated patients. Also, the total number of relapses was significantly fewer in patients treated with aripiprazole than with placebo (25% vs. 43%, respectively). There were insufficient data in this study to know whether aripiprazole was effective in delaying the time to occurrence of depression in patients with bipolar I disorder.

Pediatric Bipolar Disorder

Two different retrospective chart reviews and one prospective study of the use of aripiprazole in pediatric bipolar disorder have revealed positive effects in this population (see table, page 7). As noted in a previous issue of the *BNN*, Dr. D. Barzman et al. (2004; *J Child Adolesc Psychopharmacol* 14 [4]: 593–600) found aripiprazole to be effective in 67% of 30 patients with pediatric bipolar disorder in a retrospective chart review. In the other retrospective study, Dr. J. Biederman et al. (2005; *CNS Spectrums* 10 [2]: 141–148) found aripiprazole to be effective in 71% of 41 pediatric bipolar patients. Dr. J. Durkin (2004; *J Child Adolesc Psychopharmacol* 14 [4]: 505–506) prospectively followed 24 pediatric bipolar patients treated with aripiprazole adjunctively; 14 (58%) were identified as responders.

Side Effects

The partial agonist properties of aripiprazole appear to be associated with a generally benign side-effects profile. Typical side effects include somnolence (sleepiness), akathisia (restless legs), nausea, and vomiting, and these effects are more likely to occur in the first week of treatment than thereafter. Although the recommended daily dose is 10-15 mg/day, it appears that many patients with bipolar disorder are more sensitive to the initial side effects of aripiprazole than observed in the original clinical trials in schizophrenia. Thus, it may be advisable to start patients at low doses (5 mg) or very low doses (2.5 mg, particularly for children), and then slowly titrate the drug

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Aripiprazole

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upward toward clinical efficacy and appropriate target doses of 8-15 mg/day in adults, and lower doses in children.

The atypical antipsychotics as a class have a considerable range of side-effects liability for weight gain. Clozapine and olanzapine are most problematic in their risk for increased weight. Quetiapine and risperidone are less problematic, whereas ziprasidone and aripiprazole appear to be relatively weight neutral. There is increasing concern about the problem of overweight and obesity in children and adults in the U.S. in general, and in those patients on many psychotropic drugs in particular; ziprasidone and aripiprazole may provide options for children and adults where it is important to avoid this side effect.

Some of the atypical antipsychotics have been associated with the presence of the "metabolic syndrome," which in addition to weight gain and increased waist size, includes increases in cholesterol, triglycerides, and blood pressure, and increased likelihood of diabetes, based on relative decreases in insulin sensitivity. Similar to the problem of obesity and weight gain, the metabolic syndrome appears less likely to occur on aripiprazole and ziprasidone compared with the other agents in this class, although more data are required to confirm this possibility. ■

ARIPIPRAZOLE IN MAJOR DEPRESSION

Authors	Study type	# of Patients	Dose (mg/day)	Trial Length	# of Responders
Barbee et al., 2004	Retrospective chart review; aripiprazole as adjunct	30 adults	13 (mean in responders)	6 weeks	14/30 (47%)
Worthington et al., 2005	Open-label; aripiprazole as adjunct to SSRI	17 (6 depression, 11 anxiety)	7.5 - 30 (mean 16.9)	4.9 weeks (mean)	10/17 (59%)

ARIPIPRAZOLE IN BIPOLAR DISORDER

Authors	Study type	# of Patients	Dose (mg/day)	Trial Length	# of Responders
Pediatric Bipolar					
Durkin, 2004	Prospective; aripiprazole as adjunct	24 (ages 5 - 17)	5 - 20	Varied	14/24 (58%)
Barzman et al., 2004	Retrospective chart review; 9 pts. with aripiprazole monotherapy	30 (ages 5 - 19)	5 - 15 (mean 9)	1 - 9 months (mean 4.4 months)	20/30 (67%)
Biederman et al., 2005	Retrospective chart review; both monotherapy and adjunctive	41 (mean age 11.4)	16 (mean)	4.6 months	71%
Mania					
Keck et al., 2003	Placebo-controlled, double-blind; aripiprazole monotherapy in acute mania	262 adults	27.9 (mean)	3 weeks	40% vs. 19% (placebo)
Maintenance					
Marcus et al., 2003 (unpublished)	Placebo-controlled, double-blind; aripiprazole in maintenance treatment after an acute manic episode	161 (adults)	15-30	26 weeks	25% relapsed vs. 43% with placebo

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Psychiatric Rating Scale (BPRS). Substance craving was assessed with visual analogue scales, and side effects were monitored using the Abnormal Involuntary Movement Scale, Simpson-Angus Scale, Barnes Akathisia Scale, and patient report. Study enrollment was from April 2003 to February 2004.

RESULTS: Significant baseline-to-exit improvement in HAM-D ($p = .002$), YMRS ($p = .021$), and BPRS ($p = .000$) scores were observed without a significant change in antipsychotic-induced side effect scales. In 17 participants with current alcohol dependence, significant reductions in dollars spent on alcohol ($p = .042$) and alcohol craving ($p = .003$) were found. In 9 participants with cocaine-related disorders, significant reductions in cocaine craving ($p = .014$), but not use, were found.

CONCLUSION: A change to aripiprazole was associated with symptomatic improvement. Limitations of the study include a small sample size, high attrition, and an open-label design. Controlled trials in dual-diagnosis patients are needed to confirm these findings.

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hypomania or mania acutely. This association of venlafaxine and switching continued to be evident in the continuation phases of treatment when responders were offered an additional year of antidepressant treatment. Bipolar I patients were found to be more likely to switch than those with bipolar II. Venlafaxine was also associated with a three-times greater ratio of full to brief hypomanic switches compared with bupropion. If one examined all of the intent-to-treat randomized antidepressant trials (n = 228) in this study, disappointingly only 16% of them were shown to have persistent antidepressant responses in continuation without a switch.

These data highlight the need for alternative treatment approaches for bipolar depression other than use of adjunctive, and even second-generation, antidepressant augmentation strategies. These data are consistent with those of Sachs et al. (2003, unpublished data) indicating a less-than-ideal response to antidepressant augmentation.

Lymphoblasts are young, immature cells that mature into lymphocytes, which are white blood cells formed in lymphatic tissue throughout the body. Dr. A. Thiruvengadam (University of Maryland School of Medicine, Baltimore) et al. tried a new technique to see if a blood lymphoblast test could differentiate bipolar patients from their siblings and controls, and if it could differentiate bipolar patients from unipolar and schizophrenic patients

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Brain-Derived Neurotrophic Factor (BDNF): What is it, why is it important, and how does it affect the course and treatment of bipolar illness?

In the last issue of the BNN (Vol. 10, Issue 1), we noted that a common gene variant of brain-derived neurotrophic factor (BDNF) is being investigated by a number of research groups as a potential genetic marker of bipolar illness. A more detailed explanation of this finding might be useful to our readership.

For many years, scientists believed that the brain cells of the central nervous system couldn't regrow after damage or trauma. However, scientists have recently discovered a family of proteins called neurotrophic factors that play a critical role in the development and survival of nerve cells, or neurons. Neurotrophic factors also support adult neurons and keep them healthy throughout life, and can make neurons grow.

BDNF is one of the most common neurotrophic factors in the brain. BDNF is important both to initial central nervous system neuronal development and growth, and to later plasticity (adaptive changes) and learning and memory in animals.

Animal Studies

Research in animals has shown that chronic stress can reduce BDNF levels in the hippocampus. Interestingly, all of the antidepressants, as well as the mood stabilizers lithium and valproate (Depakote®), increase BDNF levels in animals, as do electroconvulsive seizures. Chronic (long-term), but not acute (short-term), administration of antidepressants, and the atypical antipsychotic quetiapine (Seroquel®), can prevent the stress-induced decreases in BDNF levels. Direct infusion of BDNF into animals produces an antidepressant-like effect. Repetitive transcranial magnetic stimulation (rTMS), a potential treatment for depression in humans, also increases BDNF in animals.

Human Studies

In four human studies, depressed patients had low serum (blood level) BDNF that correlated with the severity of their depression, which improved with recovery from depression. In two of these four studies, treatment with antidepressants (venlafaxine [Effexor®] or serotonin-selective reuptake inhibitors) increased the serum BDNF concentrations in these patients, and BDNF concentrations increased as depression rating scale scores decreased. In an autopsy study, brain BDNF was found to be low in depressed patients who had not been previously treated with antidepressants, compared with those so treated.

The Val66met Allele

Therefore, the important role of BDNF in the brain has been suggested in many areas that could be related to mood disorders. A number of genes have been reported as potential risk factors for bipolar illness, but until recently no well-replicated findings have emerged. A number of studies have now indicated that a common gene variant, called a single nucleotide polymorphism (SNP), is associated with a risk of bipolar disorder in North American subject populations. Normally, at the 66th position of the BDNF gene promoter, there is a nutritionally-essential amino acid called valine, written as val66val. Genetic studies have recently begun examining the SNP in which there is a substitution of methionine for valine at the 66th position, called val66met, which is less common than the val66val form; the met66met form is very rare. The val66met form of BDNF has been associated with cognitive deficiencies, decreased volume of the hippocampus, and increased activation of the hippocampus during learning and memory tasks in normal volunteers.

Several studies have found an association between the val66met allele and learning and memory. One study found a significant decrease in memory performance in 64 healthy subjects with the val66met versus the val66val allele. Dr. M. Egan in 2003 found that in schizophrenic patients, unaffected siblings, and normal volunteers, those patients with ether the val66met allele or met66met allele had difficulties with selective processing of some types of learning and memory tasks, such as those involving episodic or working memory.

Also in 2003, Dr. J. Rybakowski et al. published a study that tested a possible association between the val66met BDNF polymorphism and performance on the Wisconsin Card Sort Test (WCST) in 54 bipolar patients; the WCST is a test that measures cognitive performance. Dr. Rybakowski and colleagues found that the val66met allele was associated with poorer performance in all domains of the WCST, even though these patients had a later onset of bipolar illness than those with the val66val allele.

BDNF Alleles and Early Onset Bipolar Disorder

In addition to the study by Rybakowski et al., other recent studies have found an association between the val66met allele and early onset mood disorders. Dr. B. Geller and colleagues investigated the transmission of the BDNF val66val allele in 53 biological trios (child or adolescent with bipolar disorder + both biological parents). In this patient sample, with a child or early adolescent mean age of 10.7 years, the BDNF val66val allele was preferentially transmitted to the children or adolescents with bipolar disorder, suggesting that the BDNF val66val allele genetically predisposes children or adolescents to prepubertal or early adolescent bipolar disorder. These results of Geller et al. and Rybakowski et al. both suggest that the val66met form of BDNF protects people from early onset bipolar disorder.

Paradoxically, Dr. M. Skibinska et al. (2004) found, in a subset of schizophrenic (N=62) and bipolar (N=28) patients with early onset (18 years or younger), no significant difference between schizophrenic patients and controls, but did find an association between the met66met allele and early onset in the bipolar disorder subgroup.

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BDNF

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BDNF Alleles and Vulnerability to Bipolar Disorder

In 2002, two studies were published that found an association between the val66met BDNF SNP and an increased incidence of bipolar disorder. Dr. M. Neves-Pereira et al. in 2002 found an association between those subjects with the val66val SNP and the presence of bipolar disorder. The second study in 2002, by Dr. P. Sklar et al., found that out of 76 genes tested in bipolar disorder, only the val66val allele was significantly associated with bipolar disorder.

Two later studies supported a role of this gene variant and an association with bipolar disorder. The study by Geller et al. (2004) noted previously found an increased incidence of the val66val allele and child and adolescent bipolar disorder. And also in 2004, Dr. F. Lohoff et al. presented data at the Society of Biological Psychiatry meeting from a replication study of the 2002 studies, in 345 bipolar patients and 998 healthy controls, and found that the val66val allele of BDNF was again significantly more common in bipolar disorder. Thus, four different studies found that the val66val allele was associated with bipolar disorder; all four of these studies were in populations from North America. These four studies also indirectly show that individuals with the val66met form of the BDNF allele may be protected from bipolar disorder.

However, five studies in non-North-American populations have found no association between the val66met allele and bipolar disorder. The study by Skibinska et al. (2004) noted previously, using the entire cohort of 336 patients with schizophrenia, 352 with bipolar disorder, and 375 healthy controls, found no association between any of the three groups and the val66met allele in a Polish population.

Dr. K. Nakata et al. (2003) investigated the genetic association between two different polymorphisms of the BDNF gene and bipolar disorder in 132 unrelated Japanese patients and 190 healthy Japanese controls, and found neither the C270T polymorphism nor the val66met polymorphism was significantly different in the bipolar patients versus the controls. In the other study of Japanese patients, Dr. H. Kunugi et al. (2004) performed a 6-center study of 519 Japanese patients with bipolar disorder and 588 control subjects, and also found no significant differences between bipolar patients and controls with regard to the val66met allele, including age of onset.

In a Chinese population, Dr. C. Hong and colleagues (2003) examined the association between the val66met polymorphism and mood disorders, age of onset, and suicidal behavior in 192 patients (84 with major depression, 108 with bipolar disorder). No significant differences were found in either patient group for presence of mood disorders, age of onset, or suicidal history, and the val66met allele. Dr. Neves-Pereira et al. (2005), in a recent study of 321 Scottish patients with schizophrenia and 263 with bipolar disorder, found a positive association with the val66met allele and schizophrenia, but not with bipolar disorder.

Potential Roles of BDNF in Bipolar Illness and Treatment

BDNF Variations and Neurobiology:

Genetic Vulnerability: Val66met allele of BDNF is associated with:	• Decreases in working memory in patients with schizophrenia, bipolar illness, and in normal controls • Reduced hippocampal N-acetylaspartate and volume, increased activation of the hippocampus, and reduced dorsolateral prefrontal grey matter volume, in normal controls • Less efficient BDNF transport to synapses • Protection from early onset bipolar disorder
Val66val allele associated with:	• Increased risk of bipolar illness (4 studies in North American populations) • Early onset bipolar disorder
Personality Vulnerability: Decreased BDNF in serum associated with:	• Personality trait of neuroticism
Depressive Episode: Depression found to be associated with:	• Decreased BDNF in serum (correlated with severity of depression) • Decreased BDNF in the hippocampus of non-treated patients vs. patients treated with antidepressants in an autopsy study

BDNF and Relationships to Treatment:

Antidepressants: All antidepressants, lithium, valproate, and ECT:	• Increase BDNF in animals
Venlafaxine and serotonin-selective reuptake inhibitors:	• Increase low serum BDNF levels in depressed patients to normal levels, and degree of increase is correlated with improved depression ratings (2 studies)
BDNF Direct infusion of BDNF:	• Produces an antidepressant-like effect in animals (2 studies)
rTMS: rTMS, used as a treatment for depression in humans:	• Increases BDNF in animals

Conclusions

What conclusions can we draw from these varied findings of BDNF in bipolar and other mood disorders? New findings reviewed here indicate that BDNF: (1) is altered in affective illness and by stressors; (2) is increased by a range of effective treatments; and (3) is a risk factor for cognitive dysfunction and for bipolar illness onset in North American populations. These findings help to reconceptualize bipolar disorder in two different ways. First, these findings help to show that bipolar disorder is a genetically- and neurochemically-based complex, recurrent, and potentially progressive neuropsychiatric disorder involving multiple brain systems at the level of neurochemistry, physiology, and structure. Second, these findings support that the pharmacological agents used in the treatment of this illness not only prevent manic and depressive episodes, but through their effects on BDNF, may also help prevent or reverse pathological changes in the brain associated with bipolar illness.

The role of BDNF in the diagnosis and treatment of bipolar disorder is clearly intriguing, as this article has noted with many examples. More genetic linkage studies of the BDNF SNP will be needed to determine the predictive value of the val66val, val66met, and met66met alleles in bipolar disorder cognitive function vulnerability and early onset in the future. But the current data are promising signs that future genetic studies will greatly assist in predicting bipolar illness onset, course, and possibly (along with a number of SNPs) response to treatment in the future. ■

Selected Highlights from the 2004 American Psychiatric Association Meeting: Part II

Child and Adolescent Bipolar Illness

Dr. K. Wagner (University of Texas Medical Branch, Galveston) and colleagues examined the clinical validity of the 15-item self-rated screening instrument for bipolar symptoms known as the Mood Disorder Questionnaire (MDQ; Hirschfeld et al., 2000, *Am J Psychiatry* 157 [11]: 1873–1875) for adolescents. Parents and adolescents (104 total) from four outpatient child psychiatry clinics completed the MDQ. Although the parent and adolescent versions of the MDQ had good internal reliability, only the parent reports correlated with another scale, the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). The investigators concluded that the adolescents with bipolar disorder may lack insight into their condition, and that parent reports from the MDQ may be useful in screening bipolar disorder in this age group.

Parents of very young children with bipolar illness should consider rating their children's illness using the Kiddie Life Chart Method (K-LCM). Pre-adolescents or their parents can daily rate the course of illness and medications on the adult prospective version of the LCM (LCM-P); see the life charting section of the website (www.bipolarnews.org) for forms and instructions.

Dr. C. Glod (Northeastern University) et al. presented preliminary data from 18 adolescents enrolled in a double-blind, placebo-controlled, 8-week trial comparing the efficacy of bupropion (Wellbutrin®) and citalopram (Celexa®), showing a greater antidepressant effect for bupropion than citalopram; 43% of subjects lost weight with bupropion, and 29% lost weight with citalopram.

Dr. G. Swope (Mountain West Clinical Trials LLC, Boise, Idaho) and colleagues evaluated the safety and efficacy of lamotrigine (Lamictal®) in the treatment of adolescent bipolar I disorder, with the most recent episode depressed or mixed. A single-center, 12-week, open-label study in adolescent outpatients (ages 13–17) diagnosed with bipolar I disorder was conducted. Twenty-three patients entered the trial and 13 completed the 12 weeks of therapy. Lamotrigine appeared to be safe and effective at the conclusion of the study, according to improvements in depression, mania, and global scores.

Lamotrigine must be titrated very slowly in children because of the increased risk of serious rash, i.e., 1 in 2,500 children versus 1 in 5,000 adults.

A study comparing 117 children with at least one bipolar parent with 171 children without mood-disordered parents was conducted by Dr. A. Nierenberg (Massachusetts General Hospital, Boston) and colleagues. These investigators found that children with a bipolar parent were at a greater risk for depression (odds ratio = 4.39), bipolar disorder (odds ratio = 13.85), generalized anxiety disorder (odds ratio = 9.24), separation anxiety (odds ratio = 6.18), attention-deficit hyperactivity disorder (odds ratio = 3.38), oppositional-defiant disorder (odds ratio = 8.93), and substance abuse (odds ratio = 4.15) compared with controls.

Bipolar illness in parents should raise awareness of bipolar and a variety of other disorders in their children.

Research Updates

An ongoing NIMH-funded, randomized, multicenter trial is evaluating the speed of a course of bilateral electroconvulsive therapy (ECT) in relieving psychotic symptoms in psychotic depression. Dr. C. Kellner (UMDMJ New Jersey Medical School, Newark) et al. reported results from the 444 patients who had completed the trial. Approximately 45% of the patients had all psychotic symptoms resolved after 3 ECT sessions, and 68% resolved after six ECT sessions; only 22% failed to resolve all of their psychotic symptoms over the course of ECT.

An analysis of pooled data from six placebo-controlled and serotonin-selective re-uptake inhibitor (SSRI)-controlled clinical trials of the new dual reuptake (serotonin and norepinephrine) inhibitor duloxetine (Cymbalta®) was conducted by Dr. R. Swindle (Eli Lilly and Company, Indianapolis) and colleagues. These investigators found that, based on the mean change in the Hamilton depression rating scale total and subscale scores, the efficacy of duloxetine was superior to that of SSRIs in the treatment of major depression.

These results parallel those of venlafaxine in unipolar depression (but see p. 4 for bipolar depression).

Costs of Illness

Dr. A. Fu (University of North Carolina, Chapel Hill) and colleagues sought to characterize episodes of care (for either a depressed or manic episode) in a bipolar sample, and compared outpatient, pharmacy, and inpatient costs. During the 4-year study period, 13,118 patients experienced 14,069 bipolar episodes. Annual outpatient bipolar depression costs were four times as high, and inpatient bipolar depression costs were twice as high, as those for bipolar mania. Depressive episodes occurred three times more frequently than manic episodes.

These data add to the growing consensus that in bipolar illness, depressive phases are more difficult to treat and impart greater illness morbidity, disability, and (given the data from Dr. Fu) cost than the manic phase.

Neurobiology

As noted in the last issue of the BNN and on page 8 of this issue, the neurotrophic factor called brain-derived neurotrophic factor (BDNF) is important for learning and memory, and necessary for the survival of neurons and glia in the hippocampus. Dr. S. Kim (Chungang University Medical School, Seoul, Korea) and colleagues assessed the levels of BDNF in the blood of 49 schizophrenic patients and in 50 healthy controls. These investigators found significantly increased levels of BDNF in the serum of schizophrenic patients, and the direction of BDNF change was proportional to that observed in the brains of schizophrenic patients in autopsy studies.

In a study of four different treatments for schizophrenia—1) olanzapine (Zyprexa®) monotherapy, 2) olanzapine in combination with divalproex (Depakote®), 3) risperidone (Risperdal®) monotherapy, or 4) risperidone in combination with divalproex—in 249 patients, Dr. M. Jafari (Abbott Laboratories,

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Newport Coast, California) and other investigators found that adding divalproex to olanzapine or risperidone resulted in no change or a decrease in total cholesterol compared with increases in monotherapy.

These findings are similar to observations in patients with bipolar disorder. Valproate may moderate the increases in cholesterol seen with some atypical antipsychotics.

Predictors of Response

Dr. G. Goodwin (University of Oxford, United Kingdom) and collaborators re-analyzed data from the two recently-completed, large, controlled trials of lamotrigine (previously detailed in *BNN* Vol. 9, Issue 1). Dr. Goodwin found that in these two clinical trials, previous positive response to lithium was predictive of subsequent response to either lithium or lamotrigine.

The predictors of time to relapse in bipolar I disorder were determined by Dr. M. Tohen (Eli Lilly and Company, Indianapolis) and colleagues in a pooled analysis of data from two bipolar maintenance studies. The patients were 779 subjects who achieved symptomatic remission from a manic or mixed index (first) episode and entered double-blind maintenance therapy for up to 48 weeks with olanzapine, lithium, or placebo for up to 48 weeks, following 6-12 weeks of acute, open-label treatment with either olanzapine (1st study) or olanzapine-lithium combination therapy (2nd study). The strongest predictors of relapse in these two studies were: (1) a history of rapid cycling; (2) a mixed index episode; and (3) >1 manic episode in the past year.

A post hoc analysis was performed on three randomized, fixed dose, placebo-controlled studies of divalproex for acute mania by Dr. M. Allen (University of Colorado, Denver) and colleagues to determine whether there was a linear relationship between higher serum levels and greater reduction in manic symptoms. These investigators found that efficacy was significantly greater than placebo beginning at the 71-85 µg/ml range and for all higher levels. Using linear modeling to estimate maximal effect, Dr. Allen et al. found that a median blood level of 87 µg/ml was associated with being a responder to divalproex.

Comorbidity

Two 26-week, placebo-controlled trials of 937 patients assessed the ability of topiramate (Topamax®) to prevent migraine headaches. Significantly reduced mean monthly migraine frequencies were observed throughout the entire double-blind phase for 100 mg/day of topiramate and for 200 mg/day of topiramate versus placebo. Patients receiving topiramate in doses of 50 mg/day (37.3%), 100 mg/day (51.6%), and 200 mg/day (49.6%) exhibited $ 50% monthly migraine frequency reduction versus placebo.

Although topiramate is not an antimanic agent, it may still be useful for many comorbidities that commonly occur with bipolar disorder, including weight gain and bulimia, alcohol and cocaine abuse, post-traumatic stress disorder (PTSD), and now migraine. ■

Research Words

Readers have asked us to provide definitions for some technical or medical terms we often use in the context of describing bipolar disorder research. Here are a few terms used in this and other issues of the *BNN* and their meanings in the context of bipolar disorder research:

allele Any one of a number of alternative forms of the same gene occupying a given position on a chromosome.

autonomic side effects In the human body, the autonomic nervous system is responsible for maintaining a relatively constant internal environment by controlling such involuntary functions as digestion, respiration, perspiration, and metabolism, and by modulating blood pressure; autonomic side effects include orthostatic hypotension (a sudden drop in blood pressure that occurs when a person assumes a standing position) and tachycardia (abnormally rapid beating of the heart).

executive function The cognitive ability, mediated by the prefrontal cortex, to control other cognitive processes, such as planning, abstract thinking, and inhibiting inappropriate actions.

extrapyramidal side effects In human anatomy, the extrapyramidal system is a neural network located in the brain that is part of the motor system involved in the coordination of movement; extrapyramidal side effects are movement disorders that can result from taking antipsychotic drugs. These disorders include: parkinsonism (stiffness, slowing, and tremor); acute dystonias (writhing movements); akathisia (restless legs); and the long-term side effects of tardive dyskinesia (involuntary repetitive movements of the mouth, tongue, or fingers). All of these are more common with the older typical antipsychotics than the newer atypical antipsychotics.

ligand In biochemistry, a ligand is a small molecule that binds to a larger macromolecule, such as a neurotransmitter binding to a receptor.

post hoc analysis An analysis run after the experiment has been completed that was not part of the original hypothesis of the experiment.

Sources: Modified from Stedman's Medical Dictionary (www.stedmans.com); and Wikipedia (en.wikipedia.org).

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and controls. Dr. Thiruvengadam et al. found that the membrane potentials of lymphoblasts from bipolar patients were significantly hyperpolarized when compared with those of their siblings or controls, and that the ratio of potentials of bipolar cells was significantly different from those of unipolar and schizophrenic patients and controls. ■

Next Issue:

Highlights from the following 2005 Research Meetings:

- **American Psychiatric Association**
- **Biological Psychiatry**
- **Sixth International Conference on Bipolar Disorders**

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