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Bipolar Network News

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Departments

Meeting Highlights

American Psychiatric Association (APA) Annual Meeting

A wealth of new research findings in bipolar and related disorders were presented at the 2004 American Psychiatric Association (APA) meeting in New York (May 1–6, 2004). This article is the first of a two-part summary of those findings; part two will appear in the next issue of the BNN. Editor's comments are in italics.

Antidepressants

The use of antidepressants in bipolar depression continues to be a topic of great debate in the research literature. Dr. J. Amsterdam (University of Pennsylvania School of Medicine) and colleagues are conducting an ongoing, open-label, monotherapy study of the serotonin-selective re-uptake inhibitor (SSRI) fluoxetine (Prozac®; 10–80 mg/day) for up to 10 weeks in bipolar II patients with a major depressive episode. The data on the 71 patients studied so far shows an overall 38% significant reduction in depression rating scale scores, with no significant increased risk of inducing a switch into a manic episode.

Note: Use of antidepressants without mood stabilizers in bipolar illness is not generally recommended.

The relationship between bipolar disorder, substance abuse, and antidepressant-induced mania was investigated by Dr. S. Manwani (Cambridge Hospital, Massachusetts) and colleagues in 108 drug trials in 30 bipolar patients with substance abuse disorder (n=65 trials) and no substance abuse disorder (n=43 trials). This study revealed no statistically significant difference in risk between the two groups for antidepressant-induced mania, even after adjusting for potential confounders. The only factor that predicted antidepressant-induced mania was a history of greater than 10 past manic or hypomanic episodes.

An interim analysis of a study addressing whether or not antidepressants improve remission in patients with bipolar disorder was presented by Dr. T. Pardo (Cambridge Hospital, Massachusetts) and co-investigators. Thirty-three bipolar patients, who had recovered from a major depressive episode for two months (on a mood stabilizer and an antidepressant), were openly randomized to either continue (n=14) or discontinue (n=19) antidepressants (for one year in the data analyzed so far). Time in remission was similar in

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The Second Annual NIMH-sponsored Conference on Pediatric Bipolar Disorder

On Saturday, April 3rd, 2004, the National Institute of Mental Health (NIMH) convened the Second Annual Conference on Pediatric Bipolar Disorder, in Boston, Massachusetts. The following highlights of the meeting were noted by Dr. Robert Post, who attended the meeting. Highlights of the first NIMH-sponsored Conference on Pediatric Bipolar Disorder were given in a previous issue of the BNN (Vol. 8, Issue 3). Editor's comments are in italics.

Dr. B. Birmaher (Western Psychiatric Institute and Clinic, Pittsburgh) began the meeting by describing the naturalistic course of illness in a collaborative cohort of several hundred child and adolescent bipolar patients. This cohort of patients had a mean age of 8.9 ± 4.2 years; 49.7% presented with bipolar I illness, 10.3% with bipolar II, and 39.8% with bipolar not otherwise specified (NOS). These latter children (bipolar NOS) typically have a more chronic illness course with extreme emotional lability from depression to mania, often with a number of changes within a day, and were as impaired by their illness and had as much comorbidity and positive family history (for bipolar illness) as those patients with the more typical bipolar I and bipolar II forms. In the whole cohort there was a 71.4% incidence rate of a positive family history of bipolar illness; 60% of the bipolar children and adolescents had a comorbid diagnosis of attention-deficit hyperactivity disorder (ADHD), 42.4% had a comorbid anxiety disorder diagnosis, and 27.6% presented with psychosis.

Elsewhere during the meeting, a poster presented evidence that pediatric bipolar illness associated with psychosis is highly associated with increased risk of suicidal thinking.

Ninety percent of the bipolar children studied by Birmaher were treated with medications, and the vast majority were taking more than one class of medication. Thirteen percent were on one medication, 31% on two, 23% on three, 14% on four, and 9% on five different classes. Thus, almost half (46%) of the patients were taking three or more medications.

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APA Meeting Highlights

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the antidepressant discontinuation group (74%) vs. the continuation group (67%), suggesting that antidepressant continuation does not lead to increased time in remission in bipolar disorder.

These findings contrast with data from Altshuler et al. (2001, J Clin Psychiatry 62 [8]: 612–616; 2003, Am J Psychiatry 160 [7]: 1252–1262), and further study is needed for clarification.

A meta-analysis of 11 double-blind, randomized, controlled studies of the antidepressant mirtazapine (Remeron®, 1266 patients) versus SSRIs (1272 patients) was performed by Dr. A. Schutte (Organon Inc., New Jersey) and colleagues. These investigators found a statistically significant advantage for mirtazapine in reducing depression rating scale scores, and for a faster onset of action of mirtazapine than SSRIs. These same investigators, along with Dr. M. Thase (University of Pittsburgh Medical Center), also found that in 12 double-blind, randomized, controlled trials of mirtazapine versus SSRIs in more than 2,500 depressed patients, remission rates after six weeks of therapy were statistically significantly higher in the mirtazapine group (38.8%) than in the SSRI-treated groups (34.7%).

"... in a retrospective chart review of [aripiprazole in] 30 children and adolescents... the overall response rate was 67%, without any serious side effects."

Mirtazapine has a propensity for causing sedation and weight gain, however.

Preliminary data from a potential antidepressant that would be the first triple re-uptake inhibitor were presented by Dr. A. Lippa (Dov Pharmaceutical Inc., Hackensack, New Jersey) and colleagues. This potential antidepressant (DOV 126,303) inhibits the re-uptake of the three biogenic amines (norepinephrine, serotonin, and dopamine) most closely linked to depression. A study performed to investigate the safety, tolerability, and pharmacokinetic profile of DOV 126,303 was conducted in France with healthy male volunteers 18-35 years old. There were two studies, a single dose study and a multiple dose study, both of which were randomized, double-blind, placebo-controlled trials. No drug-related effects on vital signs, electroencephalographic (EEG), electrocardiographic (ECG), hematological, or clinical chemistry measures were reported. DOV 126,303 was well tolerated in both the single and multiple studies, with a low incidence of adverse events.

A double-blind, dose-finding study of the omega-3 fatty acid docosahexaenoic acid (DHA) in patents with major depression was conducted by Dr. D. Mischoulon (Massachusetts General Hospital) et al. Thirty-four adult patients with major depression received either 1, 2, or 4 grams of DHA every day for 12 weeks. The group who received 1g/day showed an 83% response rate; the 2g/day group showed a 40% response; and the 4g/day showed a 0% response. The authors therefore concluded that DHA may work best at lower doses in major depression, and that higher doses may be over-correcting a fatty acid imbalance.

Lower doses (1–2 grams) of another form of omega-3 fatty acids, eicosapentaenoic acid (EPA), also have been reported to be more effective than higher doses (4–6 grams).

Atypical Antipsychotics

The efficacy of an intramuscular (IM; injectable) form of the atypical antipsychotic ziprasidone (Geodon®) was studied in six severely agitated adolescents by Dr. S. Klotz (SUNY Stony Brook, New York) et al. IM ziprasidone was effective in all patients and well-tolerated, and showed prompt (within 60 minutes) sedation similar to that shown in adults.

Dr. R. Weisler (University of North Carolina) and colleagues evaluated the efficacy of ziprasidone plus lithium in acute mania and in the long-term treatment of bipolar disorder. In 102 patients, the rate of change was significantly in favor of adjunctive ziprasidone by day 4 of the study, versus placebo (in 103 patients), and long-term improvements were sustained, with good tolerability.

The use of the atypical antipsychotic aripiprazole (Abilify®) in pediatric bipolar disorder was evaluated in a retrospective chart review of 30 children or adolescents by Dr. M. DelBello (University of Cincinnati) and colleagues. Patients were treated with aripiprazole at an average final dose of 10.3 mg for an average of four months. The overall response rate was 67%, without any serious side effects.

However, one should start with lower doses (2.5 mg), especially in children.

Anticonvulsants

The use of levetiracetam (Keppra®) in aggressive disorders (e.g., oppositional defiant disorder, conduct disorder, intermittent explosive disorder, and impulse control disorder) was examined in over 100 patients ages 5 to 48 years, with a mean age of 15 (33% female), by Dr. J. Jones (Southwest General, Middleburg Heights, Ohio) et al. The dose range was 125 mg to 4000 mg/day, with an average of 1540 mg/day. Efficacy was found to be good in 45% of the patients, and partially good in an additional 15%. Levetiracetam was safe, well-tolerated, and effective in these aggressive patients, the authors concluded.

This same group of investigators also examined the use of levetiracetam in a 1-year, open-label, retrospective naturalistic study of over 200 patients with bipolar disorder. The dose range of levetiracetam was 125 to 5,250 mg/day, with an average dose of 1856 mg/day. Efficacy was good in approximately 50% of the patients, and partial in another 20%. Side effects were minimal, with the exception

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Bipolar Network News **Editor-in-Chief:** Robert M. Post, MD **Associate Editor:** Gabriele S. Leverich, MSW **Managing Editor:** Chris S. Gavin

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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The opinions expressed in the *BNN* are solely those of the editors, and do not represent the views of the National Institute of Mental Health or any other scientific entity or foundation. For any comments or suggestions you may have, or to be placed on the mailing list, please contact us at: **BNN,** P. O. Box 7925, Charlottesville, VA 22906-7925; **Website:** www.bipolarnews.org; **E-Mail**: info@bipolarnews.org

Meeting Highlights: Society of Biological Psychiatry Meeting

April 29th–May 1st, 2004, New York, NY

The Society of Biological Psychiatry was founded in 1945 to emphasize the medical and scientific study and treatment of mental disorders. Its continuing purpose is to foster scientific research and education and to raise the level of knowledge and comprehension in the field of psychiatry.

To achieve its purpose, the Society sponsors an annual meeting, grants awards to distinguished clinical and basic research workers, and publishes the journal, Biological Psychiatry. The web address for the Society is: www.sobp.org.

BDNF and Mood Disorders

There now is a well established link between brain-derived neurotrophic factor (BDNF) and bipolar disorder. BDNF is necessary for neuronal survival in the hippocampus, and animals that have had BDNF genetically "knocked-out" have impaired learning and memory. Stress decreases BDNF in the hippocampus and all antidepressants increase BDNF. If animals are stressed while on antidepressants, there is an inhibition of the stress-induced decreases in BDNF. Early stressful life events can result in long-term decrements in BDNF in adult animals, and chronic stressors in adult animals also decrease BDNF.

Dr. U. Lang (Charité University Medicine, Berlin, Germany) and Dr. R. Hellweg reported that in a study of the levels of BDNF in 118 healthy volunteers, those with the lowest BDNF levels in serum had more depressive personality traits (such as neuroticism) that have been linked to vulnerability to mood disorders. These results have recently been published (Lang et al., 2004; *Neuropsychopharmacol* 29 [4]: 795–798).

Thus, BDNF can be affected by the environment, but also by genetic vulnerability.

A common gene variant (or polymorphism) in the BDNF promoter region makes BDNF less effective in its function. Individuals with the methionine substitution at position 66 for the usual valine group at this position, called the val66met polymorphism, have problems with specific learning and memory tasks. This phenomenon occurs in normal volunteers, as well as in patients with bipolar illness and schizophrenia. Three previous studies have linked those who inherit the val66met variation to vulnerability to bipolar illness. Data presented by Dr. F. Lohoff (University of Pennsylvania) and colleagues at the Society of Biological Psychiatry meeting have provided another confirmation of these findings. Dr. Lohoff et al. genotyped 345 bipolar patients and 998 healthy controls for the val66met polymorphism, and found that allele frequencies of the val66met polymorphism differed significantly between the bipolar patients and controls, again suggesting that the val66met polymorphism in the BDNF gene might increase susceptibility to bipolar disorder.

Dr. J. Rybakowski (Poznan University of Medical Sciences, Poland) and co-investigators studied 95 patients with bipolar illness in whom the val66met polymorphism of BDNF was genotyped, and found that patients with this polymorphism did significantly worse on a test of prefrontal brain function.

Another study, by Dr. P. Szesko (Zucker Hillside Hospital, New York), reported that the val66met polymorphism was associated with reduced hippocampal volume in both healthy volunteers and in patients with schizophrenia, suggesting that this common variant may not only be associated with changes in vulnerability to bipolar illness, as well as cognitive and physiological alterations, but also in brain anatomy as reflected in hippocampal volume.

A study by Dr. R. Lipsky (National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland) showed that the val 66 allele was seen more frequently in a schizophrenic patient group than in controls, and the met 66 allele group showed the opposite distribution, suggesting that BDNF is also related to an increased risk of schizophrenia.

". . . allele frequencies of the val66met polymorphism differed significantly between the bipolar patients and controls, again suggesting that the val66met polymorphism in the BDNF gene might increase susceptibility to bipolar disorder. . . ."

Neurobiology

Alterations in the amygdala in bipolar illness have been reported, with a number of studies suggesting an increased size of the amygdala, particularly in those with a greater number of hospitalizations for mania. Dr. I. Rosso (McLean Hospital, Massachusetts) led a study investigating the left and right amygdala volumes and hippocampal volumes of 24 inpatients with bipolar I disorder (17 in their first hospitalization) and of 28 demographically-matched comparison subjects, using 1.5 Tesla magnetic resonance imaging (MRI). Dr. Rosso et al. found significantly decreased left and right amygdala volumes in bipolar patients, but no decrease in hippocampal volumes, suggesting an association between bipolar disorder and bilateral reductions of amygdala volumes in the early course of illness and larger volumes later.

These data coincide with data from a study by Dr. S. Caetano (The University of Texas Health Science Center at San Antonio) and colleagues, in which 14 children and adolescents with bipolar disorder and eight healthy controls were studied on a 1.5 Tesla MRI scanner. Bipolar children and adolescents in this study had significantly smaller left and right amygdala volumes compared with healthy controls.

Together, these two studies raise the issue that the amygdala may start off small, but increase in size over the course of the illness. These data would also be consistent with evidence of increased amygdala activity by a variety of investigative groups, including Dr. T. Ketter and associates and Dr. W. Drevets et al. Dr. L. Mah (National Institute of Mental Health, Bethesda, Maryland) working with Dr. Drevets, also found increased glucose metabolism in the amygdala of 10 patients with bipolar II depression.

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Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12-month open-label study

Altamura AC, Salvadori D, Madaro D, Santini A, Mundo E

J Affect Disord 2003; 76 (1–3): 267–271

Methods: Twenty-eight DSM-IV bipolar outpatients were consecutively recruited into the study and were randomized to receive one of two open-label treatments, with quetiapine or classical mood stabilizers at flexible doses for 12 months. Clinical assessment was carried out using BPRS, CGI, YMRS and the 21-item HAM-D at baseline and every 2 months until the end of the study. ANOVAs with repeated measures were applied to the rating scale scores considering the time and the treatment group as main factors.
Results: All patients experienced a significant improvement on the BPRS, CGI and HAM-D scores, with no significant side-effects and a good compliance.

Combination of mood stabilizers with quetiapine for treatment of acute bipolar disorder: an open label study

Bahk WM, Yoon BH, Lee KU, Chae JH

Hum Psychopharmacol 2004; 19 (3): 181–185

Method: This study was a 4-week, open-label, add-on, prospective investigation using

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Special Report

Antidepressant effects of the atypical antipsychotic quetiapine (Seroquel®)

The new atypical antipsychotic quetiapine was approved by the Food and Drug administration (FDA) in early 2004 as a monotherapy, and as an adjunct therapy with lithium or divalproex (Depakote®), for treatment of acute (short-term) manic episodes associated with bipolar I disorder. Several open-label, nonrandomized studies in the last several years that used quetiapine as an adjunct in the acute and prophylactic (preventive) treatment of bipolar disorder episodes have found significant effects of quetiapine in both manic and depressive phases (see margins).

We review the antidepressant effects of quetiapine in this issue of the *BNN* for several reasons. A recent study presented by Dr. J. Calabrese (Case Western Reserve University, Cleveland) at the 2004 American Psychiatric Association (APA) meeting showed remarkable degrees of antidepressant efficacy of quetiapine in bipolar depression. As we and others have noted, depression is the mood state that contributes the predominant amount of breakthrough symptomatology in outpatients treated in a naturalistic fashion; three times more time depressed than time manic is typically observed (Post et al., 2003, *J Clin Psychiatry* 64 [6]: 680–690; Judd et al., 2002, *Arch Gen Psychiatry* 59 [6]: 530–537).

Depression in Bipolar Illness: Role of Atypical Antipsychotics

Depression is a major cause of dysfunction, disability, and serious suicide attempts. Traditional antidepressants widely used in the treatment of recurrent unipolar depression, such as serotonin-selective re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), carry some risk when used in bipolar illness for associated episode switches into hypomania or mania or increasing the rapidity of cycling. A related problem in bipolar illness is that all of the major mood stabilizers, with the exception of lamotrigine (Lamictal®), appear to be more effective in mania than in depression; thus, new approaches to bipolar depression are clearly needed.

A significant question in bipolar disorder research has been to what extent the atypical antipsychotics (such as quetiapine, risperidone [Risperdal®], olanzapine [Zyprexa®], and others) will help fill this void. All of the recent atypical antipsychotics have now been shown in at least two or more controlled clinical trials to be effective antimanic agents (although clozapine [Clozaril®] is supported only by an extensive non-controlled trial literature). Less apparent is to what extent the atypical antipsychotics will, as a class, possess antidepressant effects.

Promising data have emerged for olanzapine, which in a large study of more than 800 patients with bipolar depression, showed small but significantly better antidepressant effects than placebo in monotherapy. However, more marked effects were observed in this study in a smaller number of patients when olanzapine was used together with the antidepressant fluoxetine (Prozac®)(Tohen et al., 2003; *Arch Gen Psychiatry* 60 [11]: 1079–1088). This study led to the subsequent approval by the FDA of the olanzapine-fluoxetine combination under the brand name Symbyax®.

In a naturalistic study presented by Dr. Paul Keck at the 2001 APA meeting, the Stanley Foundation Bipolar Network (now renamed the Bipolar Collaborative Network) found that quetiapine exerted significant improvement in clinical ratings of bipolar depression in the first month, and improvement continued in the next two months thereafter. Parallel trials of the atypical antipsychotics risperidone and clozapine did not show this same degree of improvement in bipolar depression.

This initial promising set of adjunctive, open-label, retrospective observations led the pharmaceutical industry to conduct a carefully controlled, 8-week, double-blind study of quetiapine (300mg/day and 600mg/day) compared with placebo in 539 patients with bipolar depression (358 bipolar I, 181 bipolar II; Calabrese et al., 2004, APA meeting). Surprisingly, quetiapine monotherapy exerted antidepressant effects of equal or greater magnitude to that of the olanzapine-fluoxetine combination. Quetiapine showed highly statistically significant ($p < .001$) improvement in depression, anxiety, and sleep compared with placebo by the first week of treatment. Both doses of quetiapine showed virtually identical degrees of antidepressant efficacy, suggesting that an optimal dose might be 300mg or lower and that going beyond 300mg/day contributed little extra to the rate of clinical improvement.

Although it is not clear what mechanisms contributed to this dramatic antidepressant effect of quetiapine monotherapy in bipolar depression, it is noteworthy that all atypical antipsychotics exert effects on other neurotransmitter systems thought to be involved in depression, including blockade of serotonin $(5\text{-HT})_2$ receptors. In addition, Dr. H.

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Quetiapine

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Xu et al. have shown that in rodents, quetiapine blocks the reductions in brain derived neurotrophic factor (BDNF) that are induced by repeated stressors (Xu et al., 2002; *Neurosci Lett* 321 [1–2]: 65–68). This is a particularly interesting finding, because all of the known effective antidepressant modalities (TCAs, MAOIs, second generation antidepressants, and electroconvulsive therapy [ECT]) are capable of increasing BDNF and preventing stress-induced decrements in BDNF in the hippocampus. This finding raises the question as to whether the antidepressant effects of quetiapine are related to this BDNF protective effect or some other mechanism of action.

Clinical Implications

The new data on olanzapine and quetiapine raise the question as to what are the most effective treatment strategies of bipolar patients with depression breaking through one or more mood stabilizers. Twenty years ago, antidepressants were uniformly added to lithium for problems with depression, although this was not always a successful treatment strategy. Whether the addition of another mood stabilizer—such as lamotrigine, lithium, carbamazepine (Tegretol®), or valproate—would be more effective than an antidepressant has not been adequately addressed and answered in the literature.

The FDA recently approved lamotrigine for the prevention of depressed, mixed, and manic episodes; therefore, lamotrigine may be a potential useful alternative to antidepressants, particularly given its excellent side-effects profile for bipolar depression (non-sedating, lack of sexual dysfunction), as long as one titrates the dose upward extremely slowly in an attempt to avoid the risk of a severe rash (1 in 5000 incidence rate requiring emergency medical treatment and usually hospitalization). Controlled clinical trials indicate that lamotrigine does not increase the incidence rate of switching into mania over that of placebo, and may actually have some preventive effects on manic episodes as indicated in the FDA approval. A randomized comparison of the efficacy of adding an antidepressant vs. lamotrigine to ongoing mood stabilizer therapy is clearly needed.

The high potency benzodiazepines have been used for anxiety and insomnia breaking through bipolar illness either as a precursor or concomitant to a depressed or manic episode. In many case series, approximately 50% of patients use adjunctive benzodiazepines, usually of the high potency variety such as lorazepam (Ativan®) or clonazepam (Klonopin®). The long-term efficacy of this approach in augmenting the treatment for bipolar depression has not been well studied or established, however.

The new evidence of the efficacy of two of the atypical antipsychotics in the depressed phase of the illness provides another alternative to both antidepressants and benzodiazepines. Both olanzapine and quetiapine are moderately sedating and the use of these agents in single nighttime dosing can be useful for addressing problems of insomnia and minimizing problems with daytime sedation.

The atypical antipsychotics carry a range of liabilities for weight gain. Clozapine and olanzapine are the most problematic, risperidone and quetiapine intermediate, and ziprasidone (Geodon®) and aripiprazole (Abilify®) are weight neutral (see table above). Given this asset of the latter two compounds in

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Preliminary Global Evaluation of Antipsychotics in Bipolar Depresson[1]

Drug	Strength of Evidence as an Antidepressant[a]	Safety Rating: Acute/Chronic[b]	Priority/Utility Rating for Depression[c]	Side effect considerations
Typical Antipsychotics				
Low Potency: Chlorpromazine (Thorazine), Thioridazine (Mellaril)	±	C / C	D–	Orthostatic **9** blood pressure; extrapyramidal symptoms (EPS) and tardive dyskinesia (TD)
High Potency: Haloprido l (Haldol)	— —	A– / C	D	EPS and TD, anti-cholinergic treatment often needed
Molindone (Moban)	?	C / C+	C	EPS and TD; weight neutral however
Atypical Antipsychotics				
Clozapine (Clozaril)	++	D / D+	C-	Weekly white blood cell monitoring, seizures, significant weight gain
Risperidone (Risperdal)	±	A– / C–	D	**8** Prolactin, **8** EPS at doses >/= 6 mg/day, moderate weight gain
Olanzapine (Zyprexa)	(+++)*	B+ / C–	C+	Sedation, significant weight gain
Quetiapine (Seroquel)	+++	A– / C	B+	Sedation, moderate weight gain
Ziprasidone (Geodon)	(+)**	B / B+	B+	Activation, no weight gain
Aripiprazole (Abilify)	(+)**	B+ / A–	B+	Akathisia, partial agonist at dopamine $(D)_{2,3}$ receptors and serotonin $(5\text{-}HT)_{1A}$ receptors, blocks $5\text{-}HT_2$ receptors, no weight gain

[1] Based on one investigator's opinion (Editor-in-Chief)

[a] = +++, Excellent; based on controlled trials; ++, Good; based on extensive open series; +, Some evidence; mostly case series; ±, Equivocal; — —, may worsen depression; ( ), other ambiguities present; * FDA-approved in combination with fluoxetine; **, mechanisms of action suggest possible utility in depression.

[b] = Grades: A, Excellent; B, Good; C, Fair; D, Poor.

[c] = Grades: A, Highest priority; B, moderately high priority; C, average priority; D, low priority

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quetiapine in addition to mood stabilizers. Data on 18 patients fulfilling DSM-IV diagnostic criteria for bipolar I disorder were analyzed. The Young Mania Rating Scale (YMRS), the Hamilton Scale for Depression (HDRS), the Brief Psychiatric Rating Scale (BPRS) and Extrapyramidal Symptom Rating Scale (ESRS) were applied at baseline and at weeks 1, 2 and 4. The Clinical Global Impression scale (CGI) was evaluated at baseline and week 4. **Results:** The addition of quetiapine produced a statistically significant improvement on the YMRS, HDRS, BPRS and CGI score at week 4 from baseline ($p<0.005$). Quetiapine was well tolerated, with no subjects discontinuing because of side effects.

Quetiapine alone and added to a mood stabilizer for serious mood disorders

Sajatovic M, Brescan DW, Perez DE, DiGiovanni SK, Hattab H, Ray JB, Bingham CR

J Clin Psychiatry 2001; 62 (9): 728–732

Method: Participants in the study were inpatients or outpatients with a DSM-IV diagnosis of bipolar or schizoaffective disorder. Baseline psychopathology was evaluated with the Brief Psychiatric Rating Scale (BPRS), the Young Mania Rating Scale (YMRS), and the Hamilton Rating Scale for Depression (HAM-D). Involuntary movements were rated with the Simpson-Angus Neurologic Rating Scale. Quetiapine was added on an open-label basis and increased to optimum clinical dosage. Psychopathology and Abnormal Involuntary Movement Scale ratings were repeated weekly for the first 4 weeks and then again at weeks 8 and 12.

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Other Data on Quetiapine from the 2004 American Psychiatric Association (APA) Meeting

There were over 60 presentations concerning some aspect of the new atypical antipsychotic quetiapine (Seroquel®) at this year's APA meeting. Below are selected highlights from those presentations.

Efficacy in Bipolar Disorder

In addition to the randomized, double-blind, placebo-controlled trial of quetiapine (300 mg and 600 mg/day) versus placebo noted in the article on page 4, other presentations on quetiapine and bipolar disorder were given at the meeting. An analysis of the **antianxiety effects** of quetiapine in the Calabrese et al. study from the APA meeting by Dr. W. Macfadden (AstraZeneca Pharmaceuticals, Wilmington, Delaware) found that quetiapine was significantly more effective than placebo and well tolerated in the treatment of anxiety symptoms in patients with bipolar depression, as measured on the Hamilton Rating Scale for Anxiety. Preliminary results from an ongoing 8-week, open-label trial of adjunctive quetiapine (dose range 50–400 mg/day) in adult **bipolar I or bipolar II depression** were presented by Dr. R. Milev (PCC, Ontario, Canada) and co-investigators. Of the five patients who have completed the eight weeks of treatment, a significant drop in depression rating scores occurred by week 4, and an even greater reduction by week 8.

Dr. M. Carta (University of Cagliari, Italy) and colleagues evaluated open-label quetiapine in the **long-term adjunctive treatment** of refractory bipolar I disorder. Twenty-one bipolar I outpatients inadequately responsive to standard treatments were treated with adjunctive quetiapine (average dose 518 mg/day) for 26–78 weeks (13 patients > 52 weeks). Highly significant differences in overall relapse rates between before versus during quetiapine treatment were found, as well as in relapse rates into a manic/mixed episode, and in relapse rates into a depressive episode. An overall clinical score showed a significant improvement during quetiapine treatment, and remained significant for improvement over a 52-week maintenance period.

A number of studies presented at the meeting involved quetiapine and **bipolar mania**. Dr. J. Goldberg (Zucker Hillside Hospital, New York) found that the average doses of quetiapine in responders in double-blind studies of mania were (on average) 598 mg/day in monotherapy, and 584 mg/day when quetiapine was used in combination with lithium or divalproex (Depakote®). A study comparing quetiapine with divalproex sodium for the treatment of acute mania by Dr. D. Fleck (University of Cincinnati) found that quetiapine and divalproex sodium were equally effective for treating mania, but quetiapine was more effective in reducing depressive symptoms.

Two randomized, placebo-controlled, double-blind studies by Dr. R. McIntyre (University of Toronto) evaluated the efficacy of quetiapine for acute mania in patients with bipolar I disorder; one study examined quetiapine **alone** (up to 800 mg/day for 12 weeks), and another study examined quetiapine **in combination with lithium** (0.7–1.0 mEq/L, for three weeks) **or divalproex** (50–100 g/mL for six weeks); quetiapine monotherapy and in combination were more effective than placebo from the first week of treatment onward. In these same two studies, Dr. H. Nasrallah (University of Cincinnati) found that adverse side effects (including akathisia, the inability to sit still) of quetiapine monotherapy were no different from placebo, and that adverse events with quetiapine plus lithium or divalproex were no different from lithium or divalproex monotherapy.

Mechanisms of Action

Dr. A. Baskys (VA Health Care Systems, Long Beach, California) et al. investigated the effects of quetiapine on **neuronal survival** in rats, and found that in two cell death models, quetiapine was neuroprotective (reduced cell death). The authors believe that this property of quetiapine may contribute to its efficacy in treating psychoses of dementia.

Dr. X. Li (University of Saskatchewan, Canada) and co-investigators examined the effects of quetiapine, clozapine (Clozaril®), and haloperidol (Haldol®) on **cell growth, cell mortality**, glial fibrillary acidic protein (GFAP) expression, and glial cell-derived neurotrophic factor (GDNF) release in rat C6 glioma cells. Dr. Li et al. found that: (a) C6 cell number was reduced by quetiapine and clozapine; (b) none of the antipsychotics increased cell mortality; (c) only quetiapine decreased GFAP protein levels significantly; and (d) all three antipsychotics increased GDNF release in varying doses. These authors concluded that quetiapine may be useful for regulating astrogliosis (an abnormal increase in the number of astrocytes due to the destruction of nearby neurons) that occurs after brain injury and in some neurodegenerative diseases.

The effects of quetiapine on **cortisol** in healthy volunteers were studied by Dr. S. Cohrs (University of Goettingen, Germany) and co-investigators, who found that acute administration of low doses of quetiapine in an acoustic stress paradigm in humans reduced the total amount of cortisol excretion and urinary cortisol excretion. These results have recently been published (Cohrs et al., 2004; *Psychopharmacol* 174 [3]: 414–420).

In a retrospective chart review of 70 male youth patients at a residential treatment center, Dr. P. Kymissis (Manhasset, New York) and colleagues found that in 50 patients taking risperidone (Risperdal®) and in 20 taking quetiapine, **serum prolactin** levels increased in 68% on risperidone and in 20% on quetiapine; duration of treatment was not associated with prolactin levels.

Side Effects

One of the well-known side effects of quetiapine is **somnolence** (sleepiness, drowsiness). Dr. J. Goldstein (AstraZeneca Pharmaceuticals) and Dr. K. Zhong retrospectively analyzed data from 76 different trials involving quetiapine (12 placebo-controlled) for reports of somnolence. They found that out of 7,894 patients treated, 25.5% reported somnolence, 62% of which resolved by the end of treatment. Somnolence in these cases was mild or moderate in 94.9%.

A large case-controlled study of the use of second-generation antipsychotics (clozapine, risperidone, olanzapine

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Quetiapine Data

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[Zyprexa®], and quetiapine) and the incidence of **diabetes mellitus** was undertaken by Dr. L. Citrome (Nathan Kline Institute, New York) et al. In 7,546 patients who were hospitalized for at least 60 days and not prescribed anti-diabetic medication in the past, statistically significant elevations in risk for diabetes were observed for those patients taking clozapine, quetiapine, and more than one second-generation antipsychotic. Results from a larger sample from this study have recently been published (Citrome et al., 2004; *Psychiatric Serv* 55 [9]: 1006–1013).

However, another study of the association between **diabetes** and treatment with risperidone, olanzapine, quetiapine, or conventional antipsychotics found different results. Dr. F. Gianfrancesco (Hecon Associates, Montgomery Village, Maryland) and associates reviewed his published data (Gianfrancesco et al., 2003; *J Clin Psychopharmacol* 23 [4]: 328–335) that assessed claims data for over 6,000 patients with psychosis treated with antipsychotics. The study screened for preexisting diabetes, identification of diabetes with prescription claims only, and requirement of antipsychotic monotherapy, to better control for confounding influences. Under a weaker study design, all antipsychotics were associated with significantly higher odds of diabetes relative to patients untreated with antipsychotics. But under the stronger study design criteria noted above, relative odds of risperidone and quetiapine declined, becoming statistically insignificant, while odds ratios for diabetes with olanzapine and conventional antipsychotics increased and remained significant.

Use in Other Disorders

A study by Dr. J. Doree (Hospital P. Legardeur, Repentigny, Canada) et al. investigated the effects of augmenting antidepressant treatments using quetiapine or lithium in patients with **treatment-resistant major depression** (eight patients in each group). This 8-week, single-blind study found that with both quetiapine and lithium, depression significantly improved, but to a greater extent with quetiapine; a greater number of patients responded to treatment (88% vs. 50%) and were in remission (88% vs. 38%) in the quetiapine group compared with the lithium group, respectively.

The adjunctive use of quetiapine with **cognitive-behavior therapy** (CBT) was evaluated by Dr. Y. Chaput (McGill University, Montreal, Canada) and colleagues in 30 patients who had experienced at least two 8-week treatments with two different classes of antidepressants at maximal dosages. After a 3-week lithium augmentation phase, nonresponders were withdrawn from all antidepressant medication and randomized to either CBT (12 weekly sessions) + placebo or CBT + quetiapine (25 mg/day, titrated up to a maximum of 400 mg/day). Twenty-two patients failed lithium augmentation, and were randomized (11 in each group). CBT significantly improved all efficacy variables at endpoint by up to 25%, but the CBT + quetiapine group showed significant improvement in all rating scale scores, whereas the CBT + placebo group did not. ■

Quetiapine

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the long-term maintenance of bipolar illness, these agents (ziprasidone and aripiprazole) are being increasingly used clinically for inadequately-stabilized bipolar patients, despite the current lack of formal efficacy studies for bipolar depression.

Bipolar 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.

euthymia Without any hypomanic, manic, depressive, or other negative mood symptoms; balanced, stable.

open-label A study in which there is no control or placebo group; typically used in pilot studies; non-blind.

mixed symptoms Symptoms of both mania and depression at the same time.

controlled trial A study in which there is a control group given the alternative medication or treatment (such as a placebo) on a double-blind basis, instead of the primary treatment being investigated.

odds ratio A statistical term, meaning the ratio of the odds of an event occurring in one group to the odds of it occurring in another group, or to a data-based estimate of that ratio.

naturalistic A term usually referring to studies in which the investigator passively observes the course of illness in patients as conventionally treated.

comorbidity Occurrence of more than one disease or illness at one time.

adjunctive Essentially means "together with;" used in research to describe one treatment added-on to another.

Note: A highly-personalized (by the editor) overall utility grade is offered in the table on page 5 in an effort to integrate the limited, preliminary available data on potential efficacy and long-term tolerability. Many other clinicians and investigators would rate these drugs differently, especially if they were relying solely on randomized controlled clinical trials that have been considered the gold standard for strict evidence-based medicine. ■

(Continued from Page 5)

Results: Ten individuals with bipolar disorder and 10 with schizoaffective disorder received quetiapine therapy. Overall, patients improved, with significant improvement in BPRS ($p < .001$), YMRS ($p = .043$), and HAM-D scores ($p = .002$). Simpson-Angus score also significantly decreased ($p = .02$). Overall, quetiapine was well tolerated by patients in this group with serious mood disorders. The mean +/- SD quetiapine dose was 202.9 +/- 124.3 mg/day (range, 50-400 mg/day). Mean weight gain was 10.9 lb (4.9 kg).

Use of quetiapine in bipolar disorder: a case series with prospective evaluation.

Suppes T, McElroy SL, Keck PE, Altshuler L, Frye MA, Grunze H, Leverich GS, Nolen WA, Chisholm K, Dennehy EB, Post RM

Int Clin Psychopharmacol 2004; 19 (3): 173–174

Methods: Quetiapine, a new atypical antipsychotic, was added to ongoing treatment of bipolar I outpatients (n=15) for symptoms of illness (mood lability, irritability, psychosis and/or difficulty sleeping). **Results:** All evaluations were prospectively obtained, with the majority of patients (n=9) showing much or very much improvement on the Clinical Global Impression for Bipolar Disorder (CGI-BP). Somatic complaints were limited. Mean (SD) duration before changes in medication regimens was 134 (100) days.

Biological Psychiatry

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Dr. S. Kaur (University of Texas Health Science Center at San Antonio) and colleagues investigated corpus callosum signal intensity in the brains of 16 children and adolescents (average age 15.5 years) with bipolar illness. Similar to findings in adult bipolar patients, these investigators found significantly lower corpus callosum signal intensity in bipolar patients. Interestingly, among the 13 healthy control subjects who received four weeks of lithium treatment after an initial MRI scan, there were no significant effects of lithium administration in signal intensity.

Protein kinase C (PKC), a regulatory enzyme involved in important neuronal functions and a key component of the phosphoinositide signaling system, may be a target of therapeutic actions of mood stabilizing drugs. However, direct evidence of PKC involvement in bipolar disorder is not available. Dr. G. Pandey (University of Illinois at Chicago) et al. studied PKC, as well as myristoylated alanine-rich C-kinase substrate (MARCKS, a key substrate for phosphorylation by PKC), phospholipase C (PLC), and cyclic response element binding protein (CREB, a transcription factor), in the platelets and neutrophils of patients with bipolar disorder during a drug-free baseline period. They found that PKC and PLC activity was significantly decreased in platelets from bipolar patients; that protein expression levels of MARCKS were significantly increased in platelets of bipolar patients; and that protein expression levels of CREB (which is activated by PKC) were significantly lower in neutrophils of bipolar patients. The authors proposed that these findings suggest an abnormality of PKC in bipolar patients, which may lead to further abnormalities of phosphorylation of MARCKS and levels of CREB.

Dr. J. Crayton (Loyola Medical School, Illinois) and Dr. W. Walsh studied zinc and copper circulating blood levels in 574 women and 328 men with a primary complaint of depression. These investigators found that overall, women had significantly higher copper levels than men, but that zinc levels were not significantly different between the sexes. Depressed women had significantly higher copper levels than non-depressed women, but there were no differences in zinc levels. Higher copper levels were most clearly associated with a history of post-partum depression.

"Although it was a small study involving only 21 [bipolar depressed] patients for six weeks, 60% of the patients taking pramipexole versus 9% of those on placebo responded."

New Treatments

New data of Dr. S. Kendell (Yale University) showed statistically significant antidepressant effects of the N-methyl-D-aspartate (NMDA) antagonist riluzole (Systemic®) as an adjunctive treatment for patients with treatment-refractory depression at doses of 50 mg twice a day.

Results from this 12-week, open-label study parallel those of a previous study by Zarate et al. (2004; Am J Psychiatry 161 [1]: 171–174), indicating positive antidepressant effects of riluzole in 19 treatment-resistant patients. These data add to the growing support that weak inhibition of glutamate NMDA receptor activity (such as in riluzole) could be associated with antidepressant effects. Further controlled studies are clearly needed and indicated.

A randomized, controlled trial comparing electroconvulsive therapy (ECT) with repetitive transcranial magnetic stimulation (rTMS) by Dr. D. McLoughlin (Institute of Psychiatry, London) found a marked reduction in depression rating scale scores in both groups, with no difference between ECT and rTMS. ECT was performed using the stimulus dosing method, and a course length decided by the referring physician; rTMS was applied to the left dorsolateral prefrontal cortex at 20 trains a day, 5 seconds at 10 Hz, and 110% of motor threshold.

This marks the fourth randomized study showing equal efficacy of ECT and rTMS. Though there is considerable controversy about the overall effectiveness of rTMS compared with ECT, this series of four randomized studies provides highly suggestive evidence that attempting rTMS (if available) prior to a trial of ECT would be worth consideration. Moreover, a recent cost-benefit and risk analysis by Kozel and associates (Kozel et al., 2004; CNS Spectrums 9 [6]: 476–482) also suggested the potential utility of rTMS in this regard. However, it should be noted that rTMS is not yet available to the general public because the apparatus is not FDA-approved for use outside of specific controlled experiments.

Previous work of Dr. J. Goldberg et al. (2004; *Am J Psychiatry* 161 [3]: 564–566) suggested significant effects of the dopamine agonist pramipexole (Mirapex®) in bipolar depression. Similar results were reported by Dr. J. Singh (NIMH, Bethesda, Maryland) et al. in a double-blind, placebo-controlled trial of pramipexole in bipolar II depression. Although it was a small study involving only 21 patients for six weeks, 60% of the patients taking pramipexole versus 9% of those on placebo responded. Full results of this study were recently published (Zarate et al., 2004; *Biol Psychiatry* 56 [1]: 54–60).

These data are of considerable interest because the dopamine-active antidepressant bupropion (Wellbutrin®) is widely used in the treatment of bipolar patients by clinicians because of its generally positive side-effects profile, equivalent efficacy to other antidepressant modalities, and possible decreased switch rate compared with older tricyclic antidepressants such as desipramine (Norpramine®). In contrast to bupropion, which is an indirect dopamine agonist (it increases levels of dopamine in the caudate and ventral striatum of animals upon acute and chronic administration), pramipexole is a direct agonist, since it stimulates dopamine receptors (both those of the D_2 and D_3 subtype). These studies suggest the possibility that direct dopamine agonism of D_2 and D_3 receptors, as adjunctive treatment to mood stabilizers such as lithium and valproate (Depakote®), could provide another route to antidepressant response in patients with bipolar illness.

Dr. M. Pavuluri (University of Illinois at Chicago) conducted a 6-month, open-label trial examining the safety and efficacy of two combination therapies for manic or mixed episodes of pediatric bipolar disorder: divalproex sodium and risperidone (Risperdal®), or lithium and risperidone. In 37 bipolar patients (ages 5–18) in

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Pediatric Bipolar

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Similar to the pharmacological treatment of adult bipolar disorder, the approach to childhood and adolescent bipolar disorder typically involves polypharmacy, and in many instances, very complex combination therapy. These data also parallel those of Kowatch and collaborators (2003; Biol Psychiatry 53 [11]: 978–984) in childhood bipolar disorder, indicating that it often takes several mood stabilizers, in combination, to adequately treat the illness, and occasionally after mood stabilization, small doses of psychomotor stimulants are also necessary to treat residual comorbid ADHD.

Dr. T. Wilens (Massachusetts General Hospital) presented convincing data from his research showing that adolescents (ages 11-18) with bipolar illness were at markedly increased risk for developing a substance abuse disorder. Compared with controls (non-bipolar adolescents) in his study, there was a four-fold increased risk of cigarette smoking (5% vs. 20%), a six-fold increased risk of developing alcohol-related problems (4% vs. 25%), and a nine-fold increased risk of having substance abuse (2% vs. 18%). The children in this study had an average age of onset of 7.4 years, 8.4 years of age at first treatment, and were 13.3 years of age on average during this study. More complete results from this study were just recently published (Wilens et al., 2004; *J Am Acad Child Adolesc Psychiatry* 43 [11]: 1380–1386).

These data reinforce the importance of treating adolescent-onset bipolar illness as a very high risk factor for comorbid substance abuse. Attempting to avert such substance abuse comorbidities in bipolar children and adolescents would be indicated in an effort to prevent a more severe and complicated course of illness associated with this substance abuse comorbidity.

The psychopathology of 117 offspring of parents with bipolar disorder compared with the offspring of 171 non-affectively ill control subjects was studied by Dr. A. Henin and colleagues (Massachusetts General Hospital). The mean age of the children in the study was 13.5 years. In the children of the controls versus the children of the bipolar parents, there was a 13% vs. a 39% incidence rate of depression (odds ratio 4.4), respectively; a 2% vs. 20% incidence rate of bipolar illness (odds ratio 13.9); a 22% vs. 41% incidence rate of any anxiety diagnosis (odds ratio 2.6); an 8% vs. 22% incidence rate of ADHD (odds ratio 3.4); and a 4% vs. 28% incidence rate of oppositional defiance disorder (ODD) (odds ratio 8.9). Thirty-one percent of these patients required special classes for schooling.

This study emphasizes that offspring of bipolar parents are at a very high risk for an affective illness diagnosis and an anxiety disorder diagnosis, as well as ADHD and ODD diagnoses. These data should alert parents and clinicians to screen potentially at-risk children earlier, and treat where appropriate.

Dr. R. Perlis (Massachusetts General Hospital) presented data (briefly summarized in the last issue of the *BNN*) from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a 5-year bipolar outpatient research project on optimal treatment sponsored by the NIMH. Age-of-onset retrospective data in adults with bipolar illness in the STEP-BD program was broken down into three groups: (1) those with an age of onset before age 13 (very early onset); (2) those with an age of onset from 13 to 18 years of age (early onset); and (3) those with onset over age 18 (adult onset). Dr. Perlis and colleagues found more depressive episodes in the prior year as a function of age of onset, with an average of 2.8 vs. 2.5 vs. 1.7 depressive episodes in the very early onset, early onset, and adult onset groups, respectively. There was also an increased incidence of lifetime suicide attempts as a function of age of onset in the three groups (49.8% vs. 37.0% vs. 24.6%, respectively), i.e., much higher incidence rates in the groups with very early and early onsets. There was also an increased incidence of comorbid anxiety disorders in the first two early onset groups (69.2% vs. 53.9% vs. 38.3%, respectively). And lastly, the data in this cohort showed that increased numbers of prior depressive episodes led to poorer functioning and more syndromal presentations when entering into the study. The results of this study have recently been published (Perlis et al., 2004; *Biol Psychiatry* 55 [9]: 875–881).

Although these were retrospective data, they are convergent with a variety of other studies in the literature indicating relatively greater morbidity in those with the earliest ages of onset.

Dr. J. Biederman (Massachusetts General Hospital) presented data from a study on 38 preschool children with an average age of onset of bipolar disorder of 2.0 ± 1.2 years, with a range of 1–4 years (very early onset). These children were treated in an open-label fashion for eight weeks with either risperidone (Risperdal®; average dose of 1.5 ± 0.5 mg) in 21 children vs. olanzapine (Zyprexa®; average dose of 6.5 ± 2.6 mg) in 14 children. All of the children were between ages 4 and 6 years. They had very high incidences of comorbid ADHD and conduct disorder (greater than 80%), and 20–40% were psychotic. Both groups showed significant improvement from baseline, but after monotherapy for eight weeks on either treatment, only 40–50% of the children achieved a 50% reduction in a mania scale score. There was a significantly higher dropout rate on olanzapine (43%) vs. risperidone (10%). Weight gain on risperidone in the eight weeks was 1.6 ± 0.4 kg and on olanzapine it was 3.4 ± 0.8 kg. Dr. Biederman concluded that both of these atypical antispychotics improve manic symptoms in preschoolers, but the effects were somewhat less robust than those documented in older children. There was more weight gain on olanzapine, but higher levels of prolactin on risperidone.

"Dr. T. Wilens. . . presented convincing data from his research showing that adolescents (ages 11–18) were at markedly increased risk for developing a substance use disorder."

These early systematic data in very young children with bipolar illness are important in documenting both the partial effectiveness and side-effects profiles of these agents in children with very substantial difficulties from their bipolar illness and associated comorbidities. The importance of comparative studies with other (perhaps better tolerated) atypical antipsychotics, as well as with other mood stabilizing anticonvulsants and lithium, will be of considerable importance in finding the best treatment approaches to these highly impaired children.

Dr. J. Wozniak (Massachusetts General Hospital) gave a presentation on the topic "Are cardinal symptoms (in childhood bipolar illness) really cardinal," i.e., are they the primary indicators of bipolar disorder. It had been proposed by Dr. B. Geller and Dr. E.

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Pediatric Bipolar

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Liebenluft that euphoria, grandiosity, and cycling were cardinal symptoms. Dr. Wozniak studied 107 probands with childhood-onset bipolar disorder and 296 of their relatives in an attempt to address these questions empirically. Her primary finding was that there was nothing "cardinal" about these particular symptoms; on the contrary, when the probands were stratified for criteria B mania symptoms (such as grandiosity, decreased need for sleep, talkativeness, racing thoughts, distractibility, psychomotor agitation, and others) and the rates of bipolar disorder in first degree relatives were examined, it appeared that grandiosity, decreased sleep, pressured speech, flight of ideas, racing thoughts, and distractibility showed significant familiality (association with affected relatives) in the bipolar probands.

Dr. Wozniak concluded that non-irritable euphoria is rare, occurring in about 1% of her patients with childhood bipolar disorder, whereas non-euphoric irritability is more common, occurring in 62%. Examining chronic vs. episodic courses defined several different ways in the study also did not make any difference in terms of familiality. Twelve percent of the bipolar children in the study had rapid cycling (four or more episodes in one year), 27% had ultra-rapid cycling (multiple episodes within a few days or weeks), and only 1% of these children had ultradian cycling (distinct mood shifts within 24 hours) as opposed to a much higher percentage in the studies of Dr. B. Geller and colleagues (Geller et al., 2004; *Arch Gen Psychiatry* 61 [5]: 459–467).

Because Dr. Wozniak found a similar pattern of symptoms in children independent of whether they had euphoric, irritable, chronic or episodic courses, and there were no differences in family history, she concluded that these presumptive cardinal symptoms are not really cardinal at all. She also concluded that it is important to have consensus on defining episodicity and chronicity.

Regarding this last point of a consensus, it would appear extremely important to have daily prospective longitudinal data from the NIMH Life Chart Method (NIMH-LCM™), so that the accurate patterns of mood fluctuations can be documented and defined. Such a longitudinal approach to some of the diagnostic and cyclicity ambiguities in bipolar children has not yet been adequately explored. As demonstrated in Dr. Wozniak's presentation, detailed prospective LCM data could have superseded theory and speculation. Dr. R. Findling (Case-Western Reserve University, Cleveland) is examining some of his data in children with bipolar disorder in this regard, but we are not yet aware of other investigators pursuing this detailed longitudinal rating approach.

Dr. J. Soares (The University of Texas Health Science Center at San Antonio) reported data showing a decreased volume in the left anterior cingulate cortex of the brain in unmedicated children with bipolar illness compared with healthy controls. Interestingly, those children with a history of lithium treatment had normal volumes of this brain region, further suggesting the possible neurotrophic and neuroprotective effects of lithium in children, as has previously been reported in adults (Chuang et al., 2002; *Bipolar Disord* 4 [2]: 129–136). These data of Dr. Soares and colleagues have recently been published (Sassi et al., 2004; *Biol Psychiatry* 56 [7]: 467–475).

Dr. A. Doyle (Massachusetts General Hospital) presented neuropsychological functioning data in pediatric bipolar disorder, finding impairments in a number of neuropsychological tests. She indicated that these results suggest impairments in attention and working memory, processing speed, abstract problem solving, and math in bipolar youth. She concluded that these findings would appear to support deficits in frontal striatal pathways in the brain, and that youth with bipolar disorder may require special education support in addition to their treatment for bipolar disorder. It is noteworthy that 47% of the subjects in this study were taking mood stabilizing anticonvulsants, 31% were taking atypical antispychotics, and 20% were taking lithium, as well as a variety of other treatments.

Abnormal facial emotion recognition in children with bipolar illness was investigated by Dr. D. Dixon (NIMH). Based on his neuropsychological data from this study, Dr. Dixon suggested that there were abnormalities in the temporal lobe and frontal cortex in pediatric bipolar disorder. Patients in this study were taking an average of 3.4 medications.

A work group discussion meeting on collaborative treatment studies, led by Dr. M. Fristad and Dr. T. Wilens, found considerable support for, and consensus on, the creation of a clinical trials network for pediatric bipolar disorder. ■

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the study, response rates were 80% in the divalproex and risperidone group, and 82.4% in the lithium and risperidone group. Both combinations were well tolerated.

Dr. Pavuluri also examined the effects of divalproex monotherapy in pediatric mixed mania in a 6-month open-label trial. In 34 patients with an average age of 12.3 years and current mixed mania, the response rate to divalproex monotherapy was 73.5%.

In a secondary analysis of a clinical trial examining lamotrigine (Lamictal®) versus placebo, Dr. J. Goldberg (Zucker Hillside Hospital, New York) and colleagues examined data for 182 bipolar outpatients with rapid cycling who had initially stabilized with open-label lamotrigine, and were then randomized to receive either lamotrigine monotherapy or placebo for up to six months. Dr. Goldberg et al. found that in both bipolar I and bipolar II disorder, significantly more time was spent in euthymia during the study period for patients taking lamotrigine than placebo, and that those taking lamotrigine spent significantly less time with mild hypomania or with moderate levels of depression, as well as less time with dysphoric mania.

Dr. J. Dunn (Pfizer Inc., New York) and co-investigators analyzed primary results from a 2-year open-label extension of a 21-day placebo-controlled trial of adjunctive ziprasidone (Geodon®) in mania associated with bipolar I disorder. In 127 patients, the mean dosage of ziprasidone was 122.4 mg/day. Although only 30% of the patients remained in the study after one year, scores on the mania scale and the overall global scale continued to improve from baseline through the last visit. Fourteen patients gained weight, and 20 lost weight. ■

APA Meeting Highlights

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of sedation in 9%, which was used as an advantage by dosing at night.

A systematic chart review of the adjunctive use of levetiracetam in 19 adults and 11 children with bipolar disorder, by Dr. A. Ahmadi (Macon Psychiatry Center PC, Georgia) and Dr. S. Ekhtiari, found a moderate to excellent response; patients with bipolar II and bipolar not otherwise specified benefitted slightly more from levetiracetam than patients with bipolar I. Also, patients 16 and older showed more improvement, although the difference was small.

Two previous studies in adult bipolar patients have shown the efficacy of extended-release carbamazepine (ERC-CBZ; Carbatrol®) (Ketter et al., 2004, *J Clin Psychiatry* 65 [5]: 668–673; Weisler et al., 2004, *J Clin Psychiatry* 65 [4]: 478–484); Dr. L. Ginsberg (Red Oak Psychiatry, Houston, Texas) performed a retrospective chart review of 79 children and adolescents ages 7–17 with bipolar disorder (40.5% bipolar I, 29.1 % bipolar II, 30.4% bipolar not otherwise specified [NOS]) who were treated with ERC-CBZ in a private practice setting. Marked to moderate improvement was seen in 53.2% of patients, and no patients experienced moderate to marked worsening; relapse was seen in 28% of the patients. The mean dose was 620.5 mg/day, and ERC-CBZ was well-tolerated; dizziness (10.1%) and nausea (8.9%) were the most frequently reported side effects.

The American Psychiatric Association is a medical specialty society recognized worldwide. Its over 35,000 U.S. and international member physicians work together to ensure humane care and effective treatment for all persons with mental disorder, including mental retardation and substance-related disorders.

The efficacy of the adjunctive use of zonisamide (Zonegran®) in depressed and bipolar adults was examined in a retrospective chart review of outpatients in a private practice by Dr. A. Mech (Mech Psychiatric Associates, Plano, Texas). Forty patient charts were reviewed (32 with major depression, 8 with bipolar disorder); improvements in both mania and depression rating scale scores were found with zonisamide treatment. Seventeen patients lost weight, 11 gained weight, and 12 had no weight change.

Two new studies found evidence for additional uses of the anticonvulsant topiramate (Topamax®). Dr. Ait-Daoud (University of Texas Health Science Center, San Antonio) et al. found that during a randomized trial of 150 patients receiving topiramate or placebo for treatment of alcohol dependence, patients were significantly more likely to become abstinent from nicotine as well. An open-label study by Dr. J. Bobes (University Oviedo, Spain) and colleagues in 75 patients diagnosed with substance dependence found that topiramate significantly reduced craving and consumption of substances of abuse after six months.

Neurobiology

Dr. Y. Kim (Seoul National Hospital, South Korea) and colleagues reviewed their published data (Kang et al., 2004; *FEBS Lett* 560 [1–3]: 115–119) that clozapine (Clozaril®), like lithium and valproate (Depakote®), regulates the phosphorylation of glycogen synthase kinase (GSK)-3 through Ser-9. GSK-3 is the key component of Wnt (wingless) and P13K-Akt signaling pathways. The authors suggested that clozapine may have neurotrophic effects and may enhance cell survival through regulation of Wnt signaling.

Previous studies have found decreases in white matter in the brains of adult bipolar patients. Dr. J. Adams (University of Cincinnati) and colleagues looked at white matter changes in 27 adolescent bipolar patients versus 17 healthy controls, using diffusion tensor imaging. These investigators found decreased white matter in several brain regions of the adolescent bipolar patients, unrelated to gender and age; these changes were even found in first-episode patients.

As noted previously in the *BNN*, lithium has recently been shown to have both neuroprotective and neurotrophic effects in humans and animals. A study presented by Dr. S. Shim (Case Western Reserve University, Cleveland, Ohio) and Dr. R. Russell showed that two weeks of lithium treatment in rats increased synaptic efficiency and plasticity in the hippocampus.

Novel Treatments

The first double-blind, placebo-controlled study of the antiarrhythmic drug mexiletine (Mexitil®) in bipolar mania or hypomania was conducted by Dr. A. Schaffer (Sunnybrook Health Science Center, Toronto) et al. This 3-week study in 10 bipolar manic or hypomanic patients (six bipolar I, four bipolar II) found a significant reduction in mania scale scores after treatment with mexiletine. ■

White Coat Anxiety?

An interesting abstract at the 2004 APA meeting investigated the patient's perspective on physical attire worn by a treating psychiatrist. Dr. N. Nihalnai (State University of New York, Syracuse) and colleagues conducted a 7-question survey in an adult outpatient psychiatry clinic, and found that **none** of the 52 patients surveyed thought psychiatrists should wear a white coat, and 50% thought a white coat was a bad influence on doctor-patient relationships.

Mailing List Problems

The mailing service the newsletter uses made some mistakes in mailing the last issue, and a small number of current subscribers may not have received the last issue. We have tried to mail out issues to those subscribers who may have been omitted, but if you were supposed to receive the last issue, but did not, please send us an e-mail at info@bipolarnews.org, or send us a letter, and we will send you a copy of the last issue. We apologize for this mistake; steps have been taken to ensure it will not happen again.

Website Update

We are in the process of updating and re-designing our website (www.bipolarnews.org). If you have any suggestions for new material that you would like to see, please send us an e-mail at: info@bipolarnews.org. Remember that the very latest bipolar research abstracts are updated Monday through Friday, every week, and you can find all the information you need to use the Life Chart Method (LCM™) to begin keeping a detailed record of your illness and treatment history, and important life events, on one simple form.

Next Issue

Topics expected to be covered in the next issue include:

- The second part of our highlights of the 2004 American Psychiatric Association meeting.
- Highlights from the Fourth European Stanley Conference on Bipolar Disorders, which brings together researchers in bipolar disorder from around the world.
- A detailed look at the new atypical antipsychotic aripiprazole (Abilify®), which was recently approved by the U.S. Food and Drug Administration for use in acute mania.

BNN
P. O. Box 7925
Charlottesville, VA 22906-7925

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