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Bipolar Network News

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Clinical Updates from Recent Meetings: Lithium, Ziprasidone and Risperidone

Study of Lithium Plus or Minus an Atypical for Severe Bipolar Illness in Adolescents Produces Disappointing Results

Vivian Kafantaris and colleagues at the Feinstein Institute of Medical Research, Glen Oaks, New York presented a paper, "What should be the role of antipsychotic medicines in the maintenance treatment of youths with bipolar disorder?" Their study included patients 10 to 18 years old who had bipolar I disorder in addition to either prominent psychotic features or severe aggression. All were treated with lithium and a second-generation atypical antipsychotic agent for at least six months. Olanzapine was the adjunctive second-generation atypical antipsychotic used initially, although switches to risperidone or quetiapine were permitted for non-response or intolerance.

After achieving complete remission for at least eight weeks and a good functional outcome as evidenced by adequate performance in school, participants entered a 48-week placebo-controlled trial in which they stayed on lithium and either continued or discontinued treatment with the second-generation atypical antipsychotic. Subjects randomly assigned to discontinuation had their dose tapered by 25% per week over 4 weeks, while the continuers were maintained on their combination treatment.

The preliminary results were not very encouraging. Of the first 21 subjects who entered the double-blind phase, remission was maintained for the full 48 weeks in only 4 of the 12 subjects who stayed on the combination of lithium and an atypical (33%) and in only 2 of 9 subjects (22%) whose antipsychotic was switched to a placebo. Those randomized to lithium and a second-generation atypical antipsychotic continuation also gained an additional 4% of their body weight compared with those switched to lithium and placebo, who lost 4.3% of their body weight ($p = .006$).

EDITOR'S NOTE: In this severely ill subgroup, the clinical benefit of lithium and the continuation of a second-generation atypical antipsychotic was much smaller than the authors expected, and did not reach statistical significance compared to lithium alone in the initial small group of subjects so far studied. Problems with weight gain remained substantial, even when subjects were switched to risperidone or quetiapine. These data also speak to the importance of clinical trials comparing these agents to aripiprazole and ziprasidone, which tend to cause less weight gain.

Moreover, the most appropriate treatment regimens required for the maintenance of remission in these severely affected adolescents have not been determined. As noted in previous BNNs, *Robert Findling and colleagues at Case-Western Reserve found that the combination of lithium and valproate was effective in about 40% of their patients with childhood- and adolescent-onset mania. This combination deserves further consideration and comparative clinical trials against a mood stabilizer and an atypical antipsychotic. Obviously, the baseline severity of the patients' illness in the studies of Kafantaris et al. and Findling et al. may not have been equivalent, and direct comparative studies of different treatment combinations are urgently needed.*

In this issue:

A Mood Stabilizer Plus or Minus Ziprasidone Successful In Treating Some Patients, Others Remain Ill

Charles Bowden and Edward Vietta and colleagues presented a six-month randomized, placebo-controlled, double-blind trial of ziprasidone plus a mood stabilizer in **adult** subjects with bipolar I disorder. Open-label ziprasidone (800 mg/day) was added to lithium or divalproex, and subjects who achieved eight consecutive weeks of symptomatic stability were randomized to the mood stabilizer, with ziprasidone continued or switched to a placebo.

More patients on added ziprasidone completed the six-month trial (66.1%) compared with those randomized to the placebo plus mood stabilizer (48.2%). Fewer patients on ziprasidone (19.7%) compared with those on placebo (32.4%) required additional therapeutic intervention for a mood episode. The median time before an intervention was needed was also longer for the ziprasidone group (43 days) compared with the placebo group (26.5 days), and the time until discontinuation for any reason also favored ziprasidone. The drug was tolerated

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More Clinical Updates and Promising New Treatments for Bipolar Illness

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well, and the only significant side effect that occurred more often on ziprasidone than placebo was tremor (6.3% vs. 3.6%). The authors state that these results demonstrate that ziprasidone is an effective, safe, and well-tolerated adjunctive treatment to mood stabilizers for the long-term maintenance treatment of bipolar mania.

EDITOR'S NOTE: These findings are noteworthy because of the positive findings about the efficacy of adjunctive ziprasidone. However, what is also noteworthy is the large number of patients who failed to stabilize adequately to the open combination treatment in order to be eligible for the randomization. Of the 586 patients who entered open-label treatment, only 241 (or 41%) stabilized in the 2.5- to 4-month period. This low rate of initial improvement, along with the substantial dropout rate during the randomized double-blind phase, and the moderate need for adjunctive treatment (32.4% even on the ziprasidone and mood stabilizer combination) still leave many questions about optimal treatment regimens that will achieve the goal of maintaining remission in the long term.

However, these data in adults are more promising than those of Kafantari's et al. above using lithium and other atypical antipsychotics in more severely ill adolescents. So far only quetiapine is FDA-approved (as an adjunct to lithium or valproate) for long-term prevention of both mania and depressive episodes in adults.

Injectible Long-Acting Risperidone (Risperidol) May Be Effective for Patients Who Relapse Frequently

Wayne McFadden of Ortho-McNeil Jansen Scientific Affairs, in collaboration with others at the University of Cincinnati College of Medicine, reported on predictors of remission for patients with bipolar disorder who relapse frequently. These patients were randomized to receive long-acting injectable risperidone, either 25, 37.7 or 50 mg intramuscularly every two weeks.

By the end of a 16-week open-label phase, 100 of 172 patients (56.5%) who remained in the study had remitted. A higher percentage of patients from India (70.9%) remitted vs. those from the U.S. (32.8%). A higher percentage of males compared with females enrolled in the study remitted, and a higher percentage of those without comorbid substance abuse compared with those with substance abuse also remitted. Another correlate of remission was having initially lower baseline CGI severity scores.

The authors suggested that several of these clinical findings might be useful in ultimately evaluating which patients with an unstable treatment course might respond to intramuscular risperidone administered on an acute biweekly basis.

Methylene Blue Dye Shows Promising Results for Adjunctive Use in Bipolar Illness

Martin Alda of Dalhousie University, Halifax, Nova Scotia, presented information about a randomized trial of methylene blue in patients experiencing residual symptoms or cognitive dysfunction in bipolar disorder. The researchers hypothesized that methylene blue might produce improvement because it affects nitric oxide synthetase and the second messenger system guanylate cyclase, both of which have been implicated in the pathophysiology of bipolar disorder.

It's no joke: Methylene blue might help patients with their blues.

Methylene blue stains the urine blue, so a double-blind placebo comparison is difficult. For this reason, the researchers used a low dose of 15 mg/day as a putative placebo dose against 150 mg/day of methylene blue as the active treatment. Thirty-seven subjects were enrolled in a 26-week trial, and all patients were treated with lamotrigine as their primary mood stabilizer and with any additional medications they had been using, as long as all remained constant throughout the clinical trial.

Compared with the low dose, **high-dose methylene blue improved symptoms of depression** on both the MADRAS and HAM-D scales by 6.6 points and 4.1 points, respectively. This yielded effect sizes of .47 and .42, which are considered moderately large. A similar degree of improvement in anxiety was noted on the HAM-A anxiety scale. There was also a trend toward improvement on several aspects of verbal memory performance,

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Promising New Agents Treat Bipolar Disorder: Methylene Blue, Ketamine

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but not on other measures of executive functioning, selective attention, or early information processing.

EDITOR'S NOTE: This study reports the potential effectiveness of a uniquely acting chemical substance which may be of clinical import in its own right (if blue urine is not a deterrent), but may also point the way towards novel mechanisms of action that could be used as targets in drug development.

Acute Antidepressant Effects of Ketamine May Be Extended

As previously reported in the *BNN*, several groups have found that patients with treatment-resistant depression have responded rapidly and maintained this improvement for three to five days after a sub-anesthetic dose of intravenous ketamine hydrochloride (0.5 mg/kg over a 40-minute period). To make this treatment clinically applicable, methods of sustaining the acute onset of response must be found. Several groups were exploring switching the ketamine responders to another glutamate-active agent such as riluzol, although preliminary results have indicated it is not effective. The following abstract reports another attempt using repeated ketamine infusions.

In the study, ten subjects with treatment-resistant depression were given intravenous infusions of ketamine, and nine of the ten showed a good acute antidepressant response, such that they were then given five additional intravenous infusions on days 3, 5, 8, 10, and 12 following the initial infusion. The researchers, Marije Kaan het Rot and collaborators at Mt. Sinai School of Medicine in New York, in addition to Dennis Charney and Sanjayjay Mathew, reported that the initial **reductions in** Montgomery Asberg Depression Rating Scale (MADRAS) **scores were maintained throughout the two-week period of IV infusions, and for up to 38 days thereafter**. Adverse effects during IV infusions diminished over time and were generally of only mild severity. No psychotic symptoms were reported. (High doses of ketamine are known to cause dissociative symptoms and psychosis.)

EDITOR'S NOTE: These promising data suggest the potential acute and sub-acute effectiveness of intravenous ketamine infusions for those with highly treatment-refractory depression. The fact that substantial improvement in depression can be achieved within hours raises the possibility that the old dictum that antidepressants required several weeks to produce their maximum effects may not be valid for novel treatments with new mechanisms of action. These data converge with observations that sleep deprivation-induced improvement in depressed mood can occur literally overnight, and improvement can also occur acutely in response to some peptides such as thyrotropin releasing hormone (TRH).

The challenge with all of these approaches is how to extend the acute responsivity for a longer term. Considerable evidence suggests that lithium co-treatment may help sustain the acute one-day antidepressant response to sleep deprivation, and it remains to be ascertained what other approaches may be useful for the other potentially rapidly-acting antidepressant agents such as ketamine.

Childhood and Adolescent Treatment Update

Aripiprazole and Ziprasidone: Likely the Best-Tolerated Atypical Antipsychotics In Children and Adolescents

Several abstracts on childhood-onset bipolar disorder were presented at the NCDEU: New Research Approaches for Mental Health Interventions meeting held by the National Institute of Mental Health (NIMH) and the American Society of Clinical Psychopharmacology in the summer of 2008 and reported in the *Journal of the American Academy of Child and Adolescent Psychiatry.*

The abstracts included studies of aripiprazole (Abilify) and ziprasidone (Geodon), which are some of the best-tolerated treatments from the atypical antipsychotic class of drugs for young individuals with bipolar disorder. However, both weight-gain and extrapyramidal side effects (motor symptoms similar to Parkinson's disease resulting from a blockade of dopamine receptors) are more prominent in child and adolescent bipolar patients than in adults treated with these drugs. While not weight-neutral in children, aripiprazole is less likely to cause major problems with weight gain than most of the other atypical antipsychotic agents, and ziprasidone appears largely weight-neutral.

Aripiprazole (Abilify)

Margareta Nyilas presented an abstract entitled, "Long-term efficacy of aripiprazole in children (ages 10-17 years) with bipolar disorder." Two hundred ninety-six children aged 10-17 with a diagnosis of DSM-IV bipolar I disorder with or without psychosis were randomized to receive either placebo or aripiprazole (10 mg/day or 30 mg/day) in a four-week double-blind clinical trial. Children who completed the four-week trial were then administered their assigned treatment for an additional 26 weeks. In the double-blind continuation phase, aripiprazole at doses of 10 and 30 mg showed significant superiority to placebo on the mean change of the Young Mania Rating Scale (YMRS) from baseline ($p < .00001$) at all visits. Response rates were 50% for the 10 mg aripiprazole group, 56%, for the 30 mg aripiprazole group, and 27% for the placebo group ($p < .0001$).

Aripiprazole is FDA-approved for treatment of acute mania and prevention of relapse in children 10-17 years of age.

EDITOR'S NOTE: Largely based on these and related data, aripiprazole was approved for acute and continuation treatment in bipolar I children aged 10-17. In our experience, starting children at a relatively low dose of 2 mg/day aripiprazole results in good initial tolerability and few side effects such as activation, akathisia (restless legs), nausea, or vomiting.

Ziprasidone (Geodon)

Melissa Del Bello presented an abstract entitled, "Safety and efficacy of ziprasidone in pediatric bipolar disorder in a four-week, multi-center, double-blind study of ziprasidone in bipolar children ages 10-17." Patients were randomized at a two–to-one ratio to either flexible dose ziprasidone at 80-100 mg/day or placebo. That process resulted in 150 subjects randomized to ziprasidone, and 88 to placebo. In the intent-to-treat analysis, which analyzes data on each person who began the study rather than just those who completed it, the Young Mania Rating Scale (YMRS) scores decreased significantly more on ziprasidone (-13.8) compared with placebo (-8.6) ($p = .0005$). The most commonly reported adverse events in the ziprasidone group were sedation (22%), somnolence (25%), nausea (13%), fatigue (13%), and dizziness (11%). No changes in mean body mass index, lipids or glucose levels were observed. The mean QT_C interval, which can indicate an increased risk for cardiac arrhythmias, increased compared with baseline by + 8.8 milliseconds in the ziprasidone group compared with -3.5 milliseconds in the placebo group. However, QT_C prolongation greater than 460 milliseconds (thought to be the safe upper limit of normal) was reported in only one subject.

Robert Findling also gave a presentation on the "Long-term safety and tolerability of ziprasidone

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Ziprasidone (cont.)

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in children and adolescents in a 26-week open-label extension" of the previous study summarized above. One hundred fifty-six subjects (mean age 13.4 years) entered the study. Seventy-three percent of subjects experienced an adverse event (i.e. any side effect) and 16% discontinued treatment as a result.

The most commonly reported side effects were sedation (21.8%), headache (17.3%), somnolence (16.7%), dizziness (9%), insomnia (7.7%), nausea (6.4%), and fatigue (5.5%). Five subjects experienced adverse cardiac events, with two subjects experiencing tachycardia, two experiencing palpitations, and one atrial fibrillation, none of which were considered severe. Suicidal ideation was reported in five subjects and homicidal ideation in one subject.

No clinically significant changes in BMI, lipid values, liver enzymes or glucose values were observed. The researchers concluded that ziprasidone is safe and generally well-tolerated for long-term treatment of type I bipolar disorder (manic or mixed) in children aged 10-17 years, and confirmed the metabolic safety of ziprasidone in this population.

EDITOR'S NOTE: Ziprasidone has an efficacy and side-effects profile similar to that of aripiprazole, and both are considerably better tolerated than other atypical antipsychotics, which tend to show substantially greater weight gain and associated increases in lipid values and glucose concentrations, particularly in children. One of the key concerns with ziprasidone had been its ability to increase the QT_C interval, which potentially can predispose a patient to severe cardiac arrhythmias. Severe arrhythmias were not observed in this group of patients. Moreover, as we have previously reported in the BNN, *a study of 18,000 adults randomized to olanzepine (Zyprexa, which does not increase the acute QT_C interval), or ziprasidone found no differences in cardiac abnormalities between the two drugs. Together, these data suggest greater safety of ziprasidone on cardiac indices than had previously been surmised based on its ability to increase the* QT_C *interval.*

Clozapine vs. Olanzepine in Childhood Schizophrenia: Implications for Mania

Sanjiv Kumra presented an abstract entitled, "Clozapine and high-dose olanzapine in refractory early-onset schizophrenia: a 12-week randomized, double-blind comparison." In this study, children aged 10-18 years who met the criteria for schizophrenia (not bipolar disorder) and were also resistant or intolerant to at least two antipsychotic drugs were randomized to either flexibly dosed clozapine (n = 18) or olanzapine at up to 30 mg/day (n = 21) for 12 weeks.

Significantly more clozapine-treated adolescents met the response criteria (defined as at least a 30% decrease in BPRS (Brief Pscyhiatric Rating Scale) score and a CGI (Clinical Global Impressions) improvement rating of *much* or *very much improved*). **Sixty-six percent responded to clozapine while 33% responded to the high-dose olanzapine.** However, both treatments were associated with significant weight gain and related metabolic abnormalities.

EDITOR'S NOTE: For children with treatment-refractory schizophrenia who have failed to improve after being treated with two prior second-generation antipsychotic drugs, clozapine is clearly superior to olanzapine. However, both drugs are associated with the greatest degree of weight gain and associated metabolic abnormalities among atypical antipsychotics in both adults and children.

Developing interventions to limit weight gain and these metabolic side effects is necessary to enhance the risk/benefit profile of either drug. Some data have suggested that metformin *co-treatment is helpful on these indices. Based on data in adults, we would also recommend the consideration of co-treatment with the anticonvulsants* topiramate *or* zonisamide, *both of which have been associated with the potential beneficial side effect, in this instance, of weight loss.*

These drugs are of particular interest for co-treating children on clozapine, because increased risk of seizures is a potential side effect of clozapine, and at higher doses it is conventionally co-treated with an anticonvulsant to lower the seizure risk. Thus one might achieve a double benefit from the adjunctive use of either drug (i.e. protection against both seizures and weight gain).

Course of Illness and Comorbidity

Substance Abuse By Bipolar Patients May Increase Medical Comorbidity

David Kemp and colleagues from Case-Western Reserve presented an abstract entitled, "Substance dependence is associated with an elevated risk of high medical burden and rapid cycling bipolar disorder." The data were derived from two open-label clinical studies using lithium and valproate for up to 24 weeks to achieve mood stabilization. The authors found that **the odds of having a high burden of general medical problems was more than doubled in the presence of a recent diagnosis of substance dependence.** Age and body mass index (BMI) were also associated with increased medical burden, but the presence of substance dependence had a markedly greater impact. Moreover, higher BMI was negatively associated with rates of favorable clinical response, and notably, greater severity of baseline depression was positively correlated with the number of organ systems affected by medical illness.

EDITOR'S NOTE: These data are particularly striking from several perspectives. Patients with bipolar illness are already at substantially increased risk for a greater medical burden, and the likelihood of heart attack in depressed patients is double that of the general population. Studies show that in most states in the US, and to a lesser extent in Europe as well, patients with serious psychiatric illness, including those with depression, bipolar disorder, or schizophrenia, have a life expectancy one to two decades less than that of the general population. Thus, it would appear that the burden of general medical problems is even more prominent in those with an associated substance dependence problem.

These data again speak to the importance of early intervention in adults with a bipolar illness onset in order to attempt to exert primary prophylaxis against their adopting a substance abuse problem, to which they are at extremely

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Preclinical Studies About Substance Abuse: Inhibition of Cocaine Use

N Acetyl Cysteine Inhibits Cocaine Seeking in Rodents and Has Shown Promising Results in Humans

Peter Kalivas of the Medical University of South Carolina presented an abstract entitled, "N acetyl cysteine produces enduring reductions in cue- and cocaine-induced drug seeking and normalizes cocaine-induced plasticity in dendritic spines."

Dr. Kalivas found that cocaine "reinstatement" in rodents (restarting to bar press for an intravenous injection of cocaine once bar pressing had been extinguished) was associated with marked increases in glutamate release in the reward area of the brain (nucleus accumbens) of rodents. He reasoned that N acetyl cysteine acting at a cysteine-glutamate exchanger in the area would prevent the excess glutamate increases and prevent cocaine-induced drug-seeking behavior.

Kalivas had found that this was indeed the case in animal studies, and his finding led to the use of **N acetyl cysteine in cocaine-abusing patients, who also reported decreased urges to use cocaine**.

In this animal study, Dr. Kalivas's group first created cocaine addiction in the animals. They then treated the animals with N acetyl cysteine treatment two hours prior to placing in the animals in a two-hour extinction session designed to break the addiction, and continued this treatment for three weeks. Those animals treated with N acetyl cysteine showed decreased reaction to a light or tone cue, which had signaled cocaine in the past, or a small dose of cocaine designed to reinstate lever pressing to get more cocaine. This effect lasted for at least two weeks after discontinuing N acetyl cysteine.

The diameter of dendritic spine heads on GABAergic medium spiny neurons in the n. accumbens was enlarged by a cocaine challenge after withdrawal from chronic cocaine administration. This increase in dendritic spine diameter by cocaine was blocked by N acetyl cysteine as well.

These findings further support the evaluation of repeated N acetyl cysteine administration as a potential treatment for clinical cocaine addiction, especially since Mike Berk (Biological Psychiatry, 2008) has also found that N acetyl cysteine (1 gram BID) helps stabilize mood in bipolar patients.

Aripiprazole Inhibits Cocaine Use in Rodents

In another abstract, Mathew Feltenstein, also from Medical University of S. Carolina, reported that chronic aripiprazole (Abilify) attenuates cocaine-seeking behavior in an animal model of relapse.

Feltenstein found that pretreatment with aripiprazole significantly attenuated response during relapse testing and blocked both cue- and cocaine-primed reinstatement in a dose-dependent fashion. He reasoned that studies of aripiprazole would be particularly important in patients with bipolar illness and schizophrenia who had comorbid cocaine abuse disorders, and that such clinical trials had substantial preclinical support.

Course of Illness and Comorbidity

Lithium May Prevent Cognitive Dysfunction In Older Bipolar Adults

Ariel Gildengers and colleagues from the University of Pittsburgh presented a study on the longitudinal course of cognitive function in older adults with bipolar disorder. Bipolar subjects and comparators were average age 70 at baseline. Subjects with bipolar disorder performed significantly worse on the dementia rating scale at baseline and over the course of longitudinal follow-up compared with the controls. There was a significant interaction, indicating that **older adults with bipolar disorder had even more cognitive dysfunction and more rapid decline than expected for their age and education.**

EDITOR'S NOTE: These data are of considerable interest in regard to recent findings of Kapczinski and colleagues, who reported that brain-derived neurotrophic factor (BDNF) measured in the blood of subjects with bipolar disorder declined with age more rapidly than that of control subjects. BDNF is a neuroprotective factor that is important for the maintenance of long-term memory. BDNF decreases during each acute episode of depression and mania, in proportion to the severity of that episode. These data suggest the possibility that the accelerated declines in BDNF in bipolar patients could be associated with the performance deficits noted above.

In fact, as reported in other issues of the BNN, *Lars Kessing, using the extensive national Danish Case Registry, reported that having four or more hospitalizations for a depressive episode is associated with a doubled incidence of dementia in late life compared to patients with just two prior depressive episode hospitalizations for either unipolar or bipolar depression. These data, taken with the fact that lithium, valproate, and carbamazepine not only are known mood stabilizers with efficacy in preventing manic and depressive episodes, but also increase BDNF, should encourage earlier and more concerted long-term prophylaxis in an effort to both prevent episodes and episode-related decrements in BDNF as well as to increase BDNF directly.*

Manic and depressive episodes decrease BDNF and are bad for the brain. Lithium and other mood stabilizers increase BDNF and may protect the brain.

Effective treatment might prevent the more rapid cognitive decline seen in bipolar patients compared with controls--a cognitive decline that has consistently been correlated with greater numbers of prior episodes. These data and the BDNF data present additional important reasons for patients to be particularly scrupulous about monitoring their long-term follow-up, modifying treatment regimens when needed to achieve and sustain maximal effectiveness, and hopefully prevent cognitive decline.

As reported in previous issues of the BNN, *other data from Kessing and colleagues suggested that* **those who were maintained on lithium treatment were significantly less likely to have a future diagnosis of Alzheimer's dementia** *compared with those patients not treated with lithium. These observations support a great number of others in preclinical and clinical studies suggesting that lithium, and possibly some of the other mood stabilizers, are, in fact, neurotrophic (supportive of neurons) and neuroprotective.*

Increased Medical Morbidity with Substance Abuse (cont.)

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high risk. Studies also consistently indicate that substance dependence makes treatment of both bipolar illness and the comorbid medical illness more difficult.

Investigators from this same group also found a very high incidence of undiagnosed bipolar illness and substance abuse in people incarcerated in nearby jails in the Cleveland area. Taken together, the major difficulties associated with bipolar illness and comorbid substance abuse deserve considerable new attention in order to reduce their adverse impact on psychiatric and medical syndromes and on longevity.

Neurobiology Update

Increased Arachidonic Acid and Inflammatory Markers in Bipolar Brains

Stanley Rapoport of the National Institute on Aging (NIA) at the National Institutes of Health (NIH) in Bethesda, MD reported that arachidonic acid metabolism is involved in mechanisms and treatment of bipolar disorder. Arachidonic acid metabolism is part of a second messenger system of cell regulation that is related to inflammation.

Rapoport found that antimanic drugs lithium, valproic acid, and carbamazepine all downregulate markers of brain arachidonic acid (AA) metabolism when given chronically to rats, but that topiramate (which is not antimanic) did not change AA metabolism. This group hypothesized that: 1) AA metabolic markers would be increased in the brains of patients who died with bipolar disorder, and that 2) antidepressant agents, which can cause switching into mania, would increase AA markers in rat brain.

The researchers reported that, convergent with their hypotheses, AA markers including protein and mRNA levels of cytosolic phospholipase A2 (PLA2) and cyclo-oxygenase (Cox 2 and their/its transcription factor subunits AP-2A and 2B and NF kappa B) were significantly higher in postmortem brains of those with bipolar disorder, although Cox 1 levels were lower. They also found that excitotoxicity and neural inflammatory markers were significantly increased in the brain of those with bipolar disorder.

In conjunction with the second hypothesis, the group found fluoxetine and imipramine did increase brain AA turnover and phospholipase A2 expression in awake rats. However, lamotrigine and bupropion, which are less likely to induce switches into mania, did not change AA turnover.

Thus, the researchers report that AA cascade markers increased in the postmortem brain of patients with bipolar disorder and these markers are reduced when given antimanic mood stabilizers (including lithium, valproate, and carbamazepine) and increased with some antidepressants.

In a related poster, Dr. J. Rao, also of the NIA, reported that increased excitatory and neuroinflammatory markers were found in the postmortem frontal cortices of patients with bipolar disorder. Rao's research group reported that it is well-documented that activation of the interleukin I beta (IL-I beta) receptor cascade triggers expression of the arachidonic acid cascade enzymes of phospholipase A2 and Cox 2 and other neuroinflammatory markers via activation of nuclear factor kappa B (NFκB), an activator protein of transcription factors in animals. They suggested that such an upregulation of AA might involve neural inflammation and excitotoxicity.

Consistent with this hypothesis, they found significantly higher levels of protein and mRNA for levels of IL-1 beta and the IL-1 receptor as well as MYB88 and inducible nitric oxide synthetase, as well as glial fibullary acidic protein (GFAP) in bipolar patients' frontal cortices compared with controls. There was also a significant decrease in expression of glutamate NMDA receptor subunits NR1 and NR3A.

The researchers suggest that changes in bipolar brain may be due to the disease itself or to chronic drug administration, but the presence of neural inflammation and excitotoxicity could account for elevation in the AA cascade enzymes. They concluded that the data suggest a potential neurodegenerative component of the disorder.

EDITOR'S NOTE: This evidence of inflammatory markers in brain is consistent with an increase in peripheral inflammatory markers measured in the blood of both childhood- and adult-onset bipolar disorder. As such, these findings raise potential targets for clinical therapeutics aimed at decreasing inflammation.

Neurobiology Update

Medications Increase Amygdala Volume

Jonathan Savitz of the National Institute of Mental Health (NIMH) in Bethesda, Maryland completed a study of amygdala volume in bipolar disorder, as assessed using high-resolution 3T MRI. His research group found that in unmedicated subjects with bipolar disorder, amygdala volumes were smaller than matched controls without bipolar disorder. However, conversely, the group who were undergoing treatment with medication for bipolar diorder had larger right amygdala volumes (and a trend towards larger left amygdala volumes) than the matched controls or the unmedicated bipolar sample.

The researchers noted that previous studies had shown that bipolar patients treated with lithium displayed increased grey matter volume of the cortex and hippocampus, and they suggest that this may also occur in the amygdala. They suggest that stress-induced dendritic remodeling of the amygdala (which results in larger amygdala volumes in rodents exposed to stress compared with litter mate controls) could also be affected by mood-stabilizing medicines such as lithium and divalproex.

EDITOR'S NOTE: A series of studies have generally supported the view that the amygdala in childhood-onset bipolar disorder is smaller than in normal controls, while many studies report increased volume of the amygdala in adults. One interpretation of these observations is that illness-related variables resulted in relatively greater amygdala volumes with age. This new study raises another possibility, that some of the increases in size of the amygdala may be driven by the mood stabilizers lithium and valproate, which are known to increase BDNF and neurogenesis. This study stresses the importance of assessing medication effects in evaluation of the size of the amygdala.

Neurobiology Update

More Abnormalities in White Matter Tracts (Myelin Coating of Axons) in Bipolar Patients Compared to Unipolar Depressed Patients

Amelia Versace of the University of Pittsburgh reported that white matter connectivity in neurocircuitry for sensory motor and emotional processing is different in bipolar depression versus unipolar depression. Bipolar patients showed more significant abnormalities than unipolar depressed patients in left-side white matter tracts important for sensory motor processing, and bilaterally in white matter tracts important for emotional processing.

Using diffusion tensor imaging (DTI), which shows how well-aligned neurons are in these white matter tracts, the researchers found decreased fractal anisotropy (FA), a measure of longitudinal fiber alignment. The researchers also found increases in FA in white matter tracts linking amygdala and ventral striatum, suggesting an increased number or longitudinal alignment of fibers in these tracts, potentially resulting in increased amygdala influence on emotional processing.

EDITOR'S NOTE: Several meta-analyses had previously indicated that there was an increase in incidence of white matter hyper-intensities (abnormal white specks on the MRI) observed on MRI scans in bipolar disorder compared with unipolar disorder or normal volunteer controls. This study begins to delineate a more fine-grained analysis of the nature of the white matter connectivity alterations using the new technique of diffusion tensor imaging to measure fiber alignment within important white matter tracts. These studies are consistent with the view that subtle alterations in sensory motor and emotional processing observed in bipolar illness may have an anatomical correlate, as revealed by these measures of white matter connectivity.

The myelin sheath surrounding axons of neurons is produced by one of the glial subtypes, oligodentrocytes, further implicating glial alterations in bipolar disorder.

Genetics Update

Genes Involved in Circadian Rhythms and Bipolar Disorder

Coleen McClung of Southwestern Medical Center completed a study of the distinct functions of the genes NPAS2 and CLOCK in reward pathways and reward-related behaviors. She and the other investigators in her research group found that the CLOCK gene is expressed in high levels in the dopaminergic ventral tegmental area (VTA), which is the origin of the dopamine neurons that go to the frontal cortex and limbic areas. They found that **CLOCK deficient mice had an overall behavioral profile similar to patients with bipolar disorder, including hyperactivity and an increase in cocaine-related reward behavior.** NPAS2 mutants, in contrast, have a decrease for cocaine preference compared with wild type controls. Chronic cocaine treatment leads to an increase in NPAS2 expression in striatal regions, but has no effect on CLOCK gene expression.

While both CLOCK and NPAS2 bind to the PER gene (another critical circadian clock gene), only NPAS2 binding is increased by cocaine treatment, and only NPAS2 binding is necessary for the cocaine-induced increase in expression of these genes. Dysfunction in the CLOCK gene in the VTA alters cocaine preference and other behaviors such as mood, activity, and motivation that are altered in bipolar patients. The author reasoned that alteration in the circadian timing genes in this reward area of brain could account for the high comorbidity of bipolar disorder with drug abuse and addiction.

Sandra Villasuerte et al. of the University of Michigan reported that the CLOCK gene is associated both with an endophenotype and with differential expression *in vitro* in bipolar disorder. These investigators found an additive genetic association between a specific allele of the CLOCK gene (rs1801260 C allele) with higher scores on extraversion in a sample of 997 individuals from 412 families in whom personality traits were tested.

They also performed a micro-array analysis, which found that siblings affected with bipolar disorder expressed significantly lower levels of this CLOCK gene compared with their unaffected siblings. The researchers concluded that their evidence supports other work that shows the CLOCK gene may be involved in bipolar disorder. Previous studies had implicated the C allele with "eveningness" (i.e. evening activity, higher episode recurrence rates, insomnia, and decreased need for sleep in bipolar disorder).

Here, they report the C allele is associated with activity scores and that such individuals move about quickly, energetically, and vigorously and are involved in many types of activities. They suggest that this high active trait might be an endophenotype of bipolar disorder that could be studied in both those with the illness and in normal volunteer controls.

NEUROBIOLOGY UPDATE ON EPIGENETICS:

Gene Sequence Is Inherited, But Recent Evidence Shows Lasting Environmental Influences On DNA Availability and Gene Structure

As reported in previous issues of the *BNN*, investigators have found that neonatal stressors in rodents can lead to long-lasting alterations in neurochemistry (such as decreased BDNF levels in frontal cortex) and behavior (such as increases in anxiety-like behavior and higher levels of corticosterone, the rat equivalent of the human stress hormone cortisol) throughout adulthood. Some of the mechanisms of these long-lasting changes are now becoming apparent and appear to involve alterations in the fine structure of DNA (rather than the DNA sequence that codes specific proteins).

Environmental stressors can affect how tightly DNA is wound around histones (by adding methyl or acetyl groups either to the DNA or to the histones), and can thus alter the ease of gene expression in a long-lasting fashion. If the DNA is wound more tightly around histones, initiating expression of all the genes encoded in this area of tight coiling is inhibited. (The enzyme that reads the DNA code, which is known as RNA polymerase, cannot reach the tightly bound DNA to read out the gene sequences.) Conversely, if DNA is more loosely wound around the histones, gene expression is facilitated by this easier access. It is believed that different environmental contingencies and stressors can affect gene structure in this fashion in what is considered epigenetic gene regulation, as opposed to the usual genetic influences that are mediated only through the inheritance of different gene sequences from one's parents.

Epigenetic changes involve, most often, adding methyl groups to DNA, which inhibits gene transcription, or adding acetyl groups to histones, which opens up DNA for greater ease of transcription (turning on of genes). This provides a mechanism by which, for example, sufficient neonatal exposure of rodents to a stressor can result in their producing decreased numbers of neurons throughout the rest of their lives in association with decreases in BDNF levels and decreases in brain volume.

Altering Epigenetic Changes for Therapeutic Purposes

What is particularly exciting about the new findings of epigenetic regulation is that these changes in methylation and acetylation of DNA and histones had been thought to persist in a life-long fashion, but are now found to be alterable or plastic. Some drugs can lead to increases in histone acetylation and/or prevent histones from getting deacetylated and therefore enhancing DNA transcription.

Interestingly, the mood-stabilizing anticonvulsant valproic acid is a histone deacetylase inhibitor, meaning that it prevents acetyl groups from being taken off the histones and thus leaves DNA more open for transcription. It is now thought that illnesses such as fragile X, other forms of mental retardation, and some forms of autism could be related to these types of epigenetic changes, raising the possibility of new therapeutic approaches to these abnormalities which were previously thought to be permanent.

These epigenetic changes may also be relevant for long-lasting alterations in biochemistry and behavior that occur in adult animals in response to stress. Eric Nestler of the Mount Sinai Brain Institute and his research group have shown that if an adult mouse is subjected to repeated defeat stress by a larger, more aggressive animal, it shows depressive-like behaviors that are associated with decrements in BDNF in the hippocampus and increases in BDNF in the n. accumbens. If either of these regional changes in BDNF is prevented with appropriate genetic manipulations or with antidepressant co-treatment, the defeat stress behaviors are not observed.

However, some of the epigenetic changes in histone methylation and acetylation that occur with defeat stress behaviors are not ameliorated by the antidepressant treatment, even though the antidepressants themselves reverse the defeat stress behaviors, increase BDNF, and prevent stress from decreasing BDNF. This suggests the possibility that the repeated episodes of defeat stress may leave more long-term markers at the level of epigenetic changes in histones, which would convey a long-lasting vulnerability to reactivation of the depressive behaviors.

We now know that greater numbers of prior affective episodes are associated with an increased vulnerability to relapse into a new episode. The preclinical data raise

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No Link Between Autism and MMR Vaccines: Original Data Were Fabricated

In 1998, a British research team led by Andrew Wakefield, MD reported in *The Lancet* medical journal that eight children in a group of 12 who received the Measles-Mumps-Rubella (MMR) vaccination developed symptoms of autism within a few days. This past February, Jim Deer, an investigative reporter for the *Times* of London, determined that the data in the study had been altered, and that **most of the children in the group showed signs of autism before they received the vaccine**. The research group also fabricated reports that the vaccine caused inflammatory bowel disease in the children.

In the *LA Times*, Thomas H. Maugh II reported that "In 2004, 10 of the 13 original authors on the *Lancet* paper requested that the paper be withdrawn, concluding that 'no causal link was established between MMR vaccine and autism because the data was insufficient.'" A link between autism and MMR vaccines has not been found in other studies.

Several newspapers report that since the time of the *Lancet* article, MMR vaccinations have fallen from a rate of 92% to a rate of 80% in the United Kingdom, and at least a few of these children have since died of measles.

According to the *LA Times*, "Wakefield and two other co-authors, Dr. John Walker-Smith and Dr. Simon Murch, are now defending themselves against allegations of professional misconduct brought by England's General Medical Council, which oversees physicians. Those charges are not related to the data in the newspaper, but to the researchers' ethics in using the children."

Editor's Note: Parents should note that study after study has been conducted to examine any data linking vaccination and autism, and have consistently found that there is ***no link****. Hollywood stars and others nonetheless have continued to believe that there is a causal link and speak out to this effect. Now that it is clear the original evidence connecting vaccinations to autism was fabricated, hopefully this claim will end.*

P.S. Even after thermisol mercury (the proposed cause) was removed from the vaccines, children in California continued to have a persistently rising rate of autism.

We need to find the real reasons why autism is increasing so dramatically in the population so we can prevent it. What we do know now is that it is not because of vaccinations.

In the meantime, it appears to be a very good idea to ***vaccinate your children so they don't get measles and other potentially lethal illnesses!***

Deep Brain Stimulation Approved for OCD: First Time Approved for Treatment of a Psychiatric Disorder

The Washington *Post* reported in February that a device for deep brain stimulation (DBS) was approved by the Federal Drug Administration (FDA) for use by patients with highly treatment-resistant obsessive-compulsive disorder (OCD).

DBS uses electrodes implanted in the brain, which are controlled from outside the body by a pacemaker-like apparatus. The electrodes are aimed at a forebrain structure (the anterior limb of the internal capsule) that is involved in the overactive cortical-striatal-thalamic circuits that occur in OCD. A high frequency of 110 cycles/sec. is used to stimulate this area, but causes minimal side effects.

According to the *Post*, this is the first time that DBS has been approved to treat a psychiatric disorder. In a study of 26 OCD patients, a 67% response rate was observed. The technique has been successful in the treatment of Parkinson's disease and other movement disorders when targeted toward other areas of the brain. The newly approved device is called Reclaim and is manufactured by Medtronic Inc. of Minneapolis.

A number of groups are studying the efficacy of DBS targeted to the prefrontal cortex or ventral striatum for treatment-resistant depression, also with promising initial results. However, DBS is not FDA-approved for refractory depression.

Environmental Affects on Gene Structure (cont.)

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the possibility that this accumulated vulnerability, to the extent that it is based on epigenetic changes in histone or DNA acetylation and methylation, could, in fact, be reversible. If this is the case, one could envision lessening the long-term vulnerabilities to episode recurrence at a more fundamental level.

Currently, we know that patients with recurrent unipolar or bipolar disorder require lifetime preventive treatment with medications to continue to suppress this tendency for episode recurrence. The changes now revealed at an epigenetic level at least raise the possibility that ways of reversing the long-term vulnerability to recurrence in the affective disorders could be developed in the future that act at the level of DNA methylation and acetylation, such that some patients might no longer require life-long preventive treatment.

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