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Bipolar Network News

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Diet, Depression, Inflammation and the Brain

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There is evidence that diet, inflammation and depression are all linked. Epidemiological studies by Joe Hiblen have shown that in countries whose populations eat more fish and thus have high levels of omega-3 fatty acids in their diet, there is lower incidence of depression, suicide, and cardiovascular disease such as heart attacks and strokes. This may be because the major omega-3 fatty acids, EPA and DHA, are anti-inflammatory, and inflammation has been linked to depression. EPA inhibits the enzymes phospholipase A2 and cyclo-oxygenase-2 (COX-2), and their subsequent inflammatory effects on cytokines. DHA inhibits the pro-inflammatory cytokine IL6.

Researcher John Davis recently reviewed relevant literature and found that diets high in anti-inflammatory omega-3 fatty acids are associated with lower incidence of depression, cardiovascular disease, and markers of inflammatory processes. Conversely, diets high in fat and in inflammatory omega-6 fatty acids are associated with obesity, depression, and cardiovascular disease.

Various studies have shown the links between inflammation and depression. For example, when patients are given alpha-interferon to treat viral hepatitis, there is a subsequent increase in inflammatory cytokines IL-1 and IL-6, and depression often follows. Also, depressed patients have an increased ratio of pro-inflammatory to anti-inflammatory cytokines in their blood.

Another sign of a link between bipolar illness and inflammation can be seen in biochemical analysis of brain specimens obtained at autopsy. Researcher Rapaka Rao in the laboratory of Stanley Rapoport at the National Institute on Aging at the National Institutes of Health in Bethesda, Maryland, has reported that increased markers of neuronal inflammation and excitotoxicity were found in the brains of people who had had bipolar disorder. Phospholipase A2 and COX-2 were significantly elevated in the brains of those with bipolar illness and those with schizophrenia compared with controls. Pro-inflammatory interleukin I was also significantly increased in the brains of those who had had either illness.

Another finding from the autopsy studies was that excitatory amino acid transporter type 2 was reduced in the frontal cortex of bipolar patients, but not in schizophrenic patients. The reduction in this glial transporter that removes glutamate from the synapse suggests that bipolar illness is associated with a hyper-glutamatergic state. This would increase enzymes in the arachidonic acid cascade, leading to increases in neuronal inflammation in brain.

On the positive side, when patients with rheumatoid arthritis are treated with anti-inflammatory drugs called TNF-alpha inhibitors, the patients experience not only improvement in their arthritis, but lower levels of depression as well, again linking anti-inflammatory effects to antidepressant effects.

Rapoport and colleagues also reported that the mood stabilizers lithium, valproate, carbamazepine and lamotrigine all down-regulate parts of the brain's inflammatory arachidonic acid cascade, suggesting that this could be part of their mechanism of therapeutic action in bipolar illness.

As we have reported in previous *BNN*s, other substances with more direct anti-inflammatory properties, such as the antibiotic minocycline, have been reported to have positive effects on mental health in schizophrenia.

Also in this issue:

See the findings of Bilbo et al. on page 2 for more about the link between diet, inflammation, and depression. The offspring of mother rats fed high fat diets during pregnancy were more obese as adults than offspring of mothers with normal diets. The offspring of mothers with high-fat diets also had more brain inflammation and behavior abnormalities linked to depression and anxiety.

All of these links between diet, obesity, inflammation, and depression suggest the importance of personal, clinical, and public health measures to curb the current trends of increasing obesity and depression in the US. The data suggest the possibility that both dietary and anti-inflammatory interventions may be useful for both depression and obesity.

The Evolving Omega-3 Fatty Acid Story: The Icing on the Cake (And Why You Should Not Eat It)

Omega-3 fatty acids are important for brain development and function and are essential to the human diet since they cannot be synthesized by the body. Omega-3 fatty acids are derived from canola oil, walnuts, flax seed oil, leafy vegetables, and especially fish. The main omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).They have anti-inflammatory effects, unlike omega-6 fatty acids, which are pro-inflammatory. The omega-6 fatty acids come from soy, peanuts, corn oil, and meats, and are associated with increases in obesity, myocardial infarction, and stroke.

In a recent review of the literature, John Davis and Joe Hiblen found that diets that include high levels of omega-3 fatty acids are associated with decreased incidence of depression, suicide, and cardiovascular disease. The researchers performed a meta-analysis of all the prospective depression treatment studies of omega-3 fatty acids compared to placebo. They found that EPA had antidepressant effects in humans, with moderate effect size and a high degree of statistical significance. DHA, however, did not appear to have an antidepressant effect, and pure DHA was even associated with some worsening of depression.

Editor's note: This meta-analysis helps clarify some of the ambiguities in the literature about the antidepressant efficacy of the omega-3 fatty acids, clarifying that EPA alone is an effective antidepressant. The one study that did not find antidepressant effects with EPA was carried out by the Bipolar Collaborative Network, in which I am an investigator. Our study, published in an article by Keck et al., showed that 6g of EPA was not significantly more effective than placebo in bipolar depression or in rapid cyclers. However, there is some indication that 6g may be too high a dose of EPA, and most of the recommendations now suggest using 1-2g of either EPA or an EPA/DHA combination.

There have been some positive studies of omega-3 fatty acids in schizophrenia including, most impressively, an article published in Australia last year that indicated that omega-3 fatty acids compared with placebo decreased the rate of conversion from prodromal psychotic symptoms to full-blown schizophrenia.

Further support for the role of omega-3 fatty acids in brain development has been found by Jing X. Kang, who studied an animal model in which some animals were genetically engineered to be deficient in DHA. Kang found that the non-engineered control animals had more production of new neurons and more robust neurons (with more neurite formation, greater spine density, and more myelin) and, most importantly, these animals had better spatial memory than the DHA-deficient animals.

In a recent talk about omega-3s, John Davis cited similar evidence from a family study of young offenders. The study showed that low amounts of omega-3 fatty acids in a mother's diet were associated with decreased coordination and decreased IQ levels in her children, particularly in male offspring.

These findings are consistent with a report by Staci Bilbo et al. in the Journal of the Federation of American Societies for Experimental Biology last year that showed that maternal diet and in utero transfer of nutrient substances can have long-term effects on brain development and inflammation in rodents. Bilbo reported that adult offspring of mothers who had high-fat diets while pregnant had increased brain inflammation and behavioral abnormalities compared with those whose mothers had normal diets. This occurred despite the animals beginning normal diets after weaning.

Editor's Note: Together, these studies suggest a variation on the old saw "you are what you eat." You may instead be "what your mother ate," because apparently early dietary influences can have long-term effects on the set point of brain inflammation, depressed and anxious behavior, and obesity in adults.

The ratio of pro-inflammatory omega-6 fatty acids to anti-inflammatory omega-3 fatty acids has dramatically changed with the history of civilized humans. Early in the agricultural revolution there appears to have been a 1:1 ratio of omega-6 to omega-3 fatty acids in the general diet. However, in the 1950s this became a 10:1 ratio and in the 1980s to 1990s it became a 20:1 ratio. This marked change in dietary intake may be one of the factors leading to the current pandemic of obesity, particularly in the

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Bipolar Network News

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Omega-3 Fatty Acids

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U.S. and in other developed countries in which high fat diets predominate.

Since there is a close link between depression and obesity, it appears prudent for those at high risk for depression and bipolar disorder (who may be at even greater risk for obesity than the general population) to attempt to limit dietary intake of fats and proinflammatory omega-6 fatty acids.

There appears to be a progression of influences combining to bring about obesity in those with bipolar disorder. This might start with initial dietary habits (and as noted above, even the maternal diet conveyed to the fetus in utero*). Then depression and weight gain often co-occur (potentially because of both increased appetite and decreased activity in those with atypical depression). Finally, weight gain can result from the number of psychotropic medications with weight gain vulnerability. In the studies of Susan McElroy and colleagues, one of the risk factors for overweight and obesity in outpatients with bipolar disorder was the number of prior exposures to psychotropic medications that increase the risk of weight gain.*

As reviewed at right, not all treatments for bipolar illnes increase risk of weight gain, so choosing drugs with less weight gain potential is beneficial for those patients at high risk for overweight and obesity.

Another option to limit weight gain from medications is the use of drugs with weight loss side effects to counteract those with weight gain effects. Drugs with weight loss side effects include the anticonvulsants topiramate (Topamax) and zonisamide (Zonegran), both of which are associated with weight loss in patients with seizure disorders and affective disorders. The anti-diabetic drug metformin also helps limit weight gain when used in conjunction with atypical antipsychotics while helping to sensitize insulin receptors and treat insulin resistance in type II diabetes.

Atypical Antipsychotics with the Lowest Risk of Weight Gain

There is a major problem of overweight and obesity in the US, with about 50% of the population affected. Patients with mood disorders, and particularly bipolar disorder, appear to be at increased risk for weight gain, which often accompanies depression. Thus, it is important that when treating these patients, doctors prescribe medications with low likelihood of weight gain.

Among the atypical antipsychotics that are widely used not only in schizophrenia but also in bipolar disorder and sometimes as adjunctive treatments in unipolar depression, there are wide differences in potential for weight gain and alterations in metabolic indices such as cholesterol, triglycerides, and blood glucose. Clozapine and olanzapine convey the greatest risk for abnormalities in these indices; risperidone and quetiapine convey moderate risk, and aripiprazole and ziprasidone are the least likely to affect metabolic indices. Newly approved lurasidone also has a mild side-effects profile. See page 5 for more details.

Aripiprazole, ziprasidone, and newly approved lurasidone are the atypicals least likely to cause weight gain.

The atypical ziprasidone (Geodon) appears to be truly weight-neutral and to have minimal impact on metabolic indices, but is not widely used due to two potential complications, neither of which must necessarily cause problems. One is the difficulty of dose titration with this drug. Surprisingly, low doses of the drug may be somewhat activating. (Atypicals are usually sedating.) Studies suggest that starting treatment with higher doses or increasing doses more quickly may be better tolerated. So rather than starting at 20mg twice a day, 40mg twice a day with rapid increases towards the range of 80mg twice a day may be associated with better tolerability.

Ziprasidone must be taken with food, because absorption on an empty stomach leads to much lower bioavailability and lower blood levels of the drug, which could further obscure the therapeutic efficacy of the drug.

The other reason for hesitation about prescribing ziprasidone is concern about its ability to increase the QTc interval, a measure of electrical activity in the heart. An increased QTc interval is theoretically associated with an increased risk of serious cardiac arrhythmias. However, there is ample recent data from post-marketing surveillance and formal clinical trials that suggest that the ability of ziprasidone to increase the QTc interval is not likely to be problematic. Among these studies was a randomization of 18,000 patients, half to olanzapine, which does not increase the QTc interval, and half to ziprasidone, which does. Incidence of cardiac events was similar in both groups. These and other data suggest that initial concerns about increases in the QTc interval precipitating cardiac arrhythmias should no longer preclude the use of this drug.

In addition to data from formal controlled clinical trials, new data on the naturalistic use of ziprasidone in a substantial number of patients in the STEP-BD Network is also available (see page 4).

Ziprasidone Useful as an Adjunctive Treatment for Bipolar Disorder

In an open study of bipolar disorder treatment, Shefali Srivastava, Terence Ketter and colleagues at Stanford University evaluated ziprasidone as an aid to patients unresponsive to other medications. This study was part of the multi-center research program Systematic Treatment and Evaluation Program for Bipolar Disorder, or STEP-BD.

During naturalistic treatment, ziprasidone was added to an average of 3.6 other psychotropic medications and 1.2 other nonpsychotropic medications patients had already been prescribed. The researchers found substantial improvement in mood with ziprasidone, particularly in the patients who had symptomatic levels of depression at baseline. The research team also observed a mean weight decrease from 195 ± 50lbs at baseline to 183 ± 47lbs at the final visit, with 34.3% of the patients achieving at least a 7% weight loss with ziprasidone.

Mean trial duration was 860 ± 700 days, with no subsequent psychotropic agents added in 51.2% of the patients who had a mean trial duration of 221 ± 272 days. Ziprasidone was discontinued in 57.3% of the 82 trials after a mean of 208 ± 364 days. This was due to side effects in 26.8% of the participants and due to inefficacy for mood in 23.2%.

The investigators concluded that in bipolar patients treated naturalistically with complex pharmacotherapy, ziprasidone decreased overall bipolar illness severity, was helpful in patients with substantial depression at baseline, and also yielded clinically significant weight loss in about one-third of the patients.

Editor's note: These data are notable because they support ziprasidone's pattern of weight neutrality (also discussed on page 3) and because of the overall improvement in mood symptomatology the drug brought about.

Moreover, in this case ziprasidone was added to a mean of 4.8 other prescribed medications, re-affirming the need for complicated pharmacological regimens in most patients with this disorder. These data mirror what my colleagues and I found while providing naturalistic treatment to bipolar outpatients in the Stanley Bipolar Network. Complex regimens were typically required in order to achieve substantial long-term mood stabilization. (We published this research in the Journal of Clinical Psychiatry *last year in the article, "Complexity of pharmacologic treatment required for sustained improvement in outpatients with bipolar disorder.") The ziprasidone study also highlights the general need to study complicated treatment regimens in order to assess which combinations are most effective and how to develop the best treatment algorithms for achieving good long-term responses.*

Most of the atypical antipsychotics have been studied in combination with a mood stabilizer, such as lithium or valproate, in formal randomized controlled clinical trials, and this combination has shown significant superiority over mood stabilizers alone. More complicated treatment regimens have not been systematically studied, despite the fact that many patients with bipolar illness require such regimens. Therefore, careful sequential augmentation trials to assess individual responsiveness and tolerability including detailed longitudinal self-ratings on the NIMH-LCM (or personal calendar, which can be found on our website http://bipolarnews.org) are the most practical way to proceed to maximize chances of clinical remission.

Ziprasidone Does Not Seem to Cause Arrhythmias, As Once Feared

A comprehensive review of ziprasidone's effect on the QTc interval, a measure of electrical activity in the heart, has been completed by John Kane of the Zucker Hillside Hospital in Glen Oaks, NY. He and his colleagues reviewed relevant data that had been published over the past decade. Ziprasidone can prolong the QTc interval, which theoretically puts a person at risk for cardiac arrhythmias. Kane and colleagues concluded that the effect of ziprasidone on the QTc interval is related to dose and to the patient's baseline QTc interval.

The QTc prolongation appears to plateau at the higher end of the usual clinical dose range of ziprasidone. In their review, the researchers found no cases of a QTc interval greater than 480 milliseconds, which is thought to be the threshold for developing vulnerability to arrhythmias. Additionally, no deaths were attributed to ziprasidone in any of the studies reviewed.

Ziprasidone side effects differ in different mood states

Keming Gao from Case-Western Reserve University reviewed the adverse effects of ziprasidone monotherapy in the treatment of patients with bipolar depression, mania, or schizophrenia. Gao noted that akathisia (restless legs) and other extrapyramidal side effects (such as tremor or speech problems) during mania were more common among patients on ziprasidone than among those on placebo, and these effects were more often found in patients with mania than those with depression.

Editor's note: The finding that these extrapyramidal side effects are more common during mania is interesting because it runs contrary to findings on another atypical antipsychotic, aripiprazole. Aripiprazole is a partial dopamine agonist, meaning it partially activates dopamine receptors, and bipolar depressed patients on aripiprazole experience more akathisia than patients taking aripiprazole for mania or schizophrenia do.

Ziprasidone fully blocks dopamine receptors, and this may explain why its effects on dopamine turnover may, in contrast to aripiprazole, convey greater risk for extrapyramidal side effects in mania than in depression. This is unusual since most side effects tend to be more prominent during the depressive phases than manic phases of the illness. The reasons for this reversal with ziprasidone deserve further investigation and clarification.

A New Atypical Antipsychotic: Lurasidone (Latuda)

A study by a research group that included Antony Loebel of pharmaceutical company Sunovion, Steven Potkin of the University of California, Irvine, and Herbert Meltzer from Vanderbilt University summarizes data on a new atypical antipsychotic FDA-approved for treatment of schizophrenia and likely to be available this month. This agent, lurasidone (Latuda), was studied in a double-blind, placebo-controlled six-week trial in patients with schizophrenia.

The drug is a new psychotropic agent that has a high affinity for dopamine D_2 receptors and serotonin $5HT_{2A}$, $5HT_{1A}$, and $5HT_7$ receptors. (New data suggest that antagonistic effects on $5HT_7$ receptors may be related to antidepressant efficacy.)

In the study, patients were randomized to receive lurasidone at 80mg/day, lurasidone at 160mg/day, quetiapine XR at 600mg/day, or placebo. Evening dosing was used. Both dose levels of lurasidone resulted in significant degrees of improvement compared with quetiapine XR and placebo.

The side effects profile for lurasidone was also promising; patients were no more likely to gain weight on lurasidone than on placebo, while there was a mean 2kg weight increase on quetiapine XR. In addition, total cholesterol and triglycerides on both doses of lurasidone were similar to that on placebo, in contrast to small but significant increases on quetiapine XR.

There were significant increases in levels of prolactin (a hormone related to lactation, sex function, and bone demineralization) on lurasidone at both 80mg (+ 0.8mg/dl) and 160mg (+ 3mg/dl), while small decreases in prolactin were observed on quetiapine XR (-0.3 mg/dl) and on placebo (-0.8 mg/dl).

The data suggest that lurasidone is effective in the treatment of patients with acute exacerbation of schizophrenia, with significant effects occurring as early as day 4. This study had a low rate of adverse events.

Another study on the long-term safety and tolerability of lurasidone in subjects with schizophrenia was completed by Stephen Stahl of the University of California, San Diego. In that study, 246 patients who successfully completed a 6-week double-blind trial of lurasidone (at 40mg and 120mg) compared with olanzapine (at 15mg) went on to participate in a six-month open label extension phase in which all subjects were switched to lurasidone at 80mg daily. After one week, flexible dosing was permitted in the range of 40-120 mg/day. Clinical improvement in most areas of psychopathology continued during the open label extension phase.

Lurasidone appears to be effective in schizophrenia without causing weight-gain side effects.

Only two types of adverse events were common. Akathisia (restless legs) was observed in 13% of patients, and insomnia was observed in 11%. Twelve percent of participants discontinued the study due to an adverse event during the six-month open label extension. Body weight and BMI remained stable in the open extension phase, except in those who had been randomized from olanzapine to lurasidone, in whom a loss of 1.8kg was observed. Cholesterol, low-density lipoproteins, triglycerides, and whole blood hemoglobin A_1C did not change in a clinically meaningful fashion, and prolactin, which had increased + 0.32 ng/ml in the acute double-blind phase of the study, showed an overall median decrease of -1.3 ng/ml during the open label extension. These data suggest that flexibly dosed lurasidone between 40 and 120mg daily was well tolerated for up to eight months and shows a low potential for weight gain and lipid abnormalities.

Editor's note: While studies of lurasidone for the treatment of acute mania have not yet been published, it should be noted that without exception, all typical and atypical antipsychotics that have been introduced initially with acute efficacy in schizophrenia have eventually proven to have acute antimanic efficacy as well. Thus, lurasidone is likely to join this group and ultimately be used in the treatment of acute mania.

In addition, because of its overall tolerability, including lack of weight gain or increase in metabolic indices, long-term prophylactic studies in bipolar disorder are eagerly awaited.

In terms of other side effects, lurasidone exhibits little or no affinity for the for the acetylcholine M_1 receptor, which is associated with anticholinergic side effects such as dry mouth and constipation, nor for the histamine H_1 receptor, which has been associated with sedation and weight gain.

Long-Term Treatment with Lithium, Valproate, or Carbamazepine: Lithium Best in Most Cases

Shannon Stepan, Eric Peselow and Nunzio Pomara from Maimonides Medical Center in Brooklyn, NY, have analyzed naturalistic observations of long-term maintenance treatment of bipolar disorder with valproic acid, lithium, and carbamazepine. The team followed 225 outpatients for up to 124 months, or until they had a manic or depressive episode or dropped out of the study during a well phase. Ninety-eight patients took lithium, 78 took valproate, and 50 took carbamazepine. Fifty-two percent of the participants dropped out of the study during a well phase.

One hundred three patients (45.8%) had either a manic or depressive episode during the study. This included 36.7% of the patients taking lithium, 55% of patients taking valproate, and 50% of patients taking carbamazepine. Median time until a first episode was 45 months for the entire sample, 36 months for those patients on valproate, 42 months for those on carbamazepine, and 81 months for those on lithium. A statistical analysis known as a Cox regression model indicated that patients taking valproate had a significantly higher risk of having a manic or depressive episode than those taking lithium.

Editor's note: These naturalistic data are highly consistent with a number of more controlled clinical studies. In particular, the BALANCE study by Geddes et al. (2010) reported that lithium was superior to valproate on most outcome measures in a two-year randomized study, and that the combination of lithium and valproate was significantly better than valproate alone.

These data are particularly noteworthy because valproate is used much more often than lithium in the US (while lithium remains the main mood stabilizer in most European countries).

There is even more evidence that lithium is a more successful treatment in most patients with bipolar disorder. In the Bipolar Collaborative Network, in which I am an investigator, we found that a treatment regimen that included lithium was associated with long-term stabilization for at least six months in a higher percentage of patients than a treatment regimen that included valproate. Lithium also was associated with greater long-term success than valproate in a study comparing US patients with those from the Netherlands and Germany.

Lithium repeatedly emerges as superior to valproate in long-term prevention of bipolar disorder.

Clinicians should consider prescribing lithium first rather than valproate in many patients with classical presentations of bipolar illness. Lithium is also FDA-approved for long-term prophylaxis of bipolar illness, while valproate is not.

The data from all of these sources is in agreement. It suggests that clinicians in the US should return to lithium as the first-choice mood stabilizer for patients with bipolar illness, since valproate has now been shown to be less successful in long-term prophylaxis in several naturalistic and controlled studies.

The shift toward greater use of valproate was based in part on the randomized placebo-controlled data of Bowden and colleagues, which showed that valproate had better antidepressant effects than lithium, although neither lithium nor valproate response exceeded that of placebo on the main outcome measure of time to relapse into a manic episode. Patients in that study had fairly inactive illnesses, and only 25% of the patients on placebo relapsed during the study. Inexplicably, lithium was inferior to placebo in preventing depressive relapse. The conclusions from that study differ greatly from meta-analyses that indicate lithium is highly effective in preventing both manic and depressive episodes when compared with placebo. The study by Bowden et al. appears to be an outlier that likely resulted from the stringent selection criteria, which required long periods of wellness prior to entering the trial, making relapse on any agent, including placebo, highly unlikely.

I should note that valproate is, in fact, helpful for some subgroups of patients who are not responsive to lithium, and it has a better profile of efficacy than lithium in those with dysphoric as opposed to euphoric mania, and possibly in those with higher levels of comorbid anxiety as well.

Similarly, carbamazepine appears to be effective in many of the subgroups that are less responsive to lithium, including those with more rapidly recurrent or continuously recurrent episodes, comorbid substance use, mood-incongruent delusions (consistent with a schizoaffective presentation) and those with a negative family history of mood disorders in first-degree relatives.

Lithium in combination with these drugs may be useful for difficult-to-stabilize bipolar illness. Lithium in combination with lamotrigine would also be useful in those with predominantly depressive recurrences. In the absence of a good prophylactic response to these combinations, the addition of a well-tolerated atypical antipsychotic is often the next option.

Ketamine Infusions May Help in Suicidal Emergencies

Intravenous ketamine has consistently been found to bring about almost immediate antidepressant effects (usually within two or three hours), which can last three to five days in duration. Typical doses are 0.5 mg/kg IV infusion over 40 minutes. A new abstract presented at the meeting of the American College of Emergency Physicians last year indicated that 0.2 mg/kg ketamine infused over a period of 1-2 minutes resulted in decreased suicidal ideation within 40 minutes. Fourteen of 15 subjects were no longer suicidal after the infusion, and in 13 of those 14 the improvement was sustained at follow-up ten days later.

Editor's note: Such rapidly occurring, robust antidepressant/antisuicidal effects from IV ketamine continue to suggest that it is useful for emergency room therapeutic maneuvers.

An article by L.I. Lee et al. published in Science *in 2010 suggested that an intracellular pathway involving the enzyme mTOR is critical to the acute antidepressant actions of ketamine in animal system models. If this pathway is blocked with drugs acting at ERK, PI3K or AKT (enzymes and kinases that form part of a signal transduction pathway leading from neurotrophic receptors to the nucleus), the effects of ketamine do not occur (L.I. Lee et al.,* Science, *2010).*

In an animal model of chronic unpredictable stress, a variety of biochemical and micro-anatomical changes are observed when animals demonstrate depressive-like behavior. Chronic unpredictable stress is associated with reductions in all of the following: numbers of synapses, amounts of post-synaptic density 95 protein, gluR1 subunits in the glutamate receptor, and dendritic spine density in glutamate-containing pyramidal cells. This atrophy could result in decreased synaptic function and could also affect memory and behavior. Ketamine not only reverses these deficits in pyramidal cell dendritic spine density (particularly in layer 1 of the cortex), but it also increases synthesis of brain-derived neurotrophic factor (BDNF).

The data by Lee et al. are particularly remarkable because they demonstrate that an acute ketamine infusion can actually reverse some of the micro-structural changes associated with an animal model of depression (i.e. chronic unpredictable stress). It is not known whether the same positive effects on dendritic spines occur in humans, but it is likely given the remarkable acute onset of antidepressant and antisuicidal effects when people receive ketamine infusions. Now a key objective is to determine the best methods for sustaining the acute onset effects achieved with IV ketamine for a longer term.

Ketamine blocks the glutamate N-methyl-D-aspartate (NMDA) receptor, through which calcium flows, and which is necessary for many different types of long-term synaptic plasticity, including long-term potentiation, a molecular model of long-term memory. Ketamine's ability to block NMDA receptors is probably at least partially responsible for its acute onset antidepressant effects, because two pharmaceutical companies have found that compounds that block the NR2B subunit of the NMDA receptor are also associated with acute onset antidepressant effects. In addition, the anti-Alzheimer's drug memantine (Namenda), which blocks the NMDA receptor, has been reported to augment and accelerate the acute antidepressant effects of lamotrigine. It appears that blocking the NMDA receptor is a new target of therapeutics that may yield new antidepressant treatments with rapid onset of action.

Methylene Blue in the Treatment of Bipolar Disorder

In a double-blind, placebo-controlled trial of methylene blue for patients with bipolar disorder, Martin Alda and colleagues from Dalhousie University in Halifax, Nova Scotia found that the compound was an effective augmentation for mood stablizers. Methylene blue inhibits nitric oxide synthetase and guanylate cyclase, the overproduction of which might be associated with neuronal damage. Since bipolar disorder has consistently been associated with neuronal and glial cell dysfunction and loss, methylene blue could be a promising treatment.

Methylene blue turns urine blue, so in place of a placebo the researchers used very low doses (15 mg daily) of methylene blue compared with the active dose of 195 mgs daily.

Thirty-seven patients were enrolled in the randomized 26-week trial, and all patients were treated with lamotrigine as their primary mood stabilizer and with any additional medications they were already taking. Patients entered in a well or euthymic state (n =20), mildly depressed (n=14), or while minimally cycling (n = 3).

Methylene blue was well tolerated, with only transient and mild side effects observed. Scores on both the Montgomery-Asberg Depression Rating Scale and the Hamilton Rating Scale for Depression improved significantly, with an effect size of 0.47 and 0.42, respectively. Hamilton Anxiety Rating Scale scores also improved significantly with an effect size of 0.46.

The researchers concluded that methylene blue used as an adjunctive medication to lamotrigine and other previously inadequately effective agents significantly improved depression and anxiety in patients with bipolar disorder. They proposed further exploration of the mechanisms involved in this change, with the possibility that other drugs with similar actions could also be effective in this disorder.

L-Methylfolate Augments the Antidepressant Effects of SSRIs in Treatment-Resistant Major Depression

The B vitamin folate has been shown to be a useful augmentation treatment for patients who are nonresponsive or only partially responsive to selective serotonin reuptake inhibitor (SSRI) antidepressants. Treatment with folate works even in those who are not folate-deficient at baseline.

When folate is broken down in the body by reductase enzymes, it turns into the active form L-methylfolate, and crosses the blood-brain barrier. Giovanni Fava and colleagues at Massachusetts General Hospital (MGH) performed two placebo-controlled, randomized studies of L-methylfolate for depression, and found significantly greater improvement when SSRIs were augmented with L-methylfolate than when they were augmented with placebo. The results were significant with the use of 15mg of L-methylfolate, but not with 7.5mg, suggesting dose-related effects.

Editor's note: These data add to the literature suggesting the importance of using folate or L-methylfolate as adjunctive treatments to antidepressants in unipolar depressed patients. Alec Coppen and colleagues have reviewed the literature, mostly from Europe, that shows that regular folate (usually in the 400 to 800ug/day range) is a significant augmenting agent for patients with inadequate responses to antidepressants. Based on this literature, it is generally recommended that in those with difficult-to-treat depression, women should take 1mg/day of folate and men should take 2mg/day (as per the suggestion of Andy Stoll from MGH).

L-methylfolate may have additional advantages, since it is four times more potent than folate when taken directly. There is a proprietary preparation of L-methylfolate (Deplin, available by prescription only at 7.5mg or 15mg). L-methylfolate is also available from some health food stores in a generic version containing 1mg of the compound. Given the findings by Fava that 15mg (but not 7.5mg) of adjunctive L-methylfolate was an effective augmentation for SSRIs, relatively higher doses of L-methylfolate may be more effective than the 1-2mg of regular folate often used in European studies.

However, multiple studies have shown folate is more effective than placebo for augmenting antidepressants, and it remains to be studied directly whether L-methylfolate would be more effective in those without the reductase deficiency.

Taking L-methylfolate instead of folate is necessary for the 15% of the general population who have a common gene defect that interferes with the ability of their tetrahydrofolate reductase enzyme to function at full capacity.

In those with this deficiency, folate is unable to be converted to L-methylfolate and thus facilitate the metabolic pathway by which homocysteine, which has negative effects on central nervous system function and cognition, is turned into to s-adenosyl methionine (SAMe), which has positive antidepressant effects in unipolar depression as shown in multiple placebo-controlled clinical trials.

Thyroid for Women with Treatment-Resistant BP Depression

We have previously written about a study of supra-physiological doses of levothyroxine (a synthetic version of the hormone T_4 sold under the brand name Synthroid) performed by Mike Bauer and colleagues in Dresden, Germany and at UCLA. Sixty-three patients were initially treated with an antidepressant and/or a mood stabilizer for one week during a single-blind phase. Then the six-week double-blind phase of the study began, in which patients were given either adjunctive T_4 (in the form of levothyroxine) or placebo, and this was followed by an additional six weeks of open treatment with T_4. Patients were started at 100mcg and increased on a weekly basis to 200 and then 300mcg/day.

Overall, T_4 had no statistically significant effect that differentiated it from placebo, but among women, there was a significantly greater degree of improvement in the Hamilton Rating Scale for Depression scores for those on T_4 (-42.4%) than for those on placebo (-16.6%), p= .018.

Editor's note: This study is the first randomized, placebo-controlled trial of supra-physiological doses of T_4. A small series of reports in the literature from several different investigative groups had previously suggested efficacy of this compound in rapid cycling and treatment-resistant patients.

The supra-physiological doses of T_4 used in this study are different from typical replacement doses of T_3 or T_4, which have often been used in adjunctive treatment of patients with unipolar and bipolar depression. T_3 has been studied more than T_4, and a meta-analysis of T_3 augmentation (usually 25-50mcg/day) has shown positive effects over placebo. Those results suggest the potential utility of a trial with usual-dose T_3 augmentation prior to treatment with supra-physiological doses of T_4.

Even with the low or replacement doses of T_3, it appeared that women were more likely to respond to the treatment than men were, so the potential gender differences in response to thyroid augmentation (both replacement T_3 and supra-physiological T_4 doses) deserve further investigation. However, what is clear in both instances is that baseline thyroid function is not related to therapeutic response, i.e. antidepressant augmentation with thyroid does not depend upon a patient being hypothyroid at baseline. Some endocrinologists may not be aware that thyroid has antidepressant effects independent of its thyroid hormone effects, and may think thyroid hormone supplementation is unnecessary if a patient exhibits normal baseline thyroid indices.

Dopamine D_2 and D_3 Agonist Pramipexole May Enhance Cognitive Function in Bipolar I Disorder

Anil Malhotra from the Zucker Hillside Hospital found that pramipexole (Mirapex), a dopamine D_2 and D_3 agonist used in the treatment of Parkinson's disease, improved measures of processing speed and working memory in euthymic bipolar patients (whose average age was 42) when compared with placebo in an adjunctive clinical trial.

Editor's Note: Bipolar patients in a euthymic phase have consistently been shown to have some degree of cognitive dysfunction that is typically correlated with the number of prior depressive and/or manic episodesthey have experienced. This is one of the first studies to directly target this cognitive dysfunction with a pharmacotherapeutic agent.

Pramipexole may be of additional value among depressed patients, because in two small, placebo-controlled studies, one led by Carlos Zarate at the National Institute of Mental Health and one led by Joseph F. Goldberg in New York, pramipexole has been shown to exert acute antidepressant effects in bipolar patients in the depressive phase of the illness. The new data from Malhotra raise the possibility that there could be a two-for-one benefit when pramipexole is used in the depressive phase of bipolar illness – improvement in both depression and cognition.

Other approaches to improving cognition in patients with bipolar disorder

There are other interventions that can improve cognitive function in bipolar patients. These include: optimizing pharmacotherapy in order to eliminate residual manic or depressive symptoms and achieve a complete remission; removing potentially sedating or cognition-impairing agents; adding folic acid, thereby reducing levels of homocysteine, which are directly correlated with degree of cognitive dysfunction in euthymic bipolar patients; using the indirect dopamine agonist bupropion (Wellbutrin), which has been shown to have some positive effect in those with ADHD; using modafanil (Provigil) to treat residual depressive symptoms and attention and concentration dysfunction; reserving use of psychomotor stimulants for later stages of the treatment algorithm, since these may be associated with the development of tolerance when used to treat residual depressive symptoms; and, finally, considering the use of anti-Alzheimer's drugs such as the acetylcholinomimetic agents, including donezepil (Aricept) and the NMDA inhibitor memantine (Namenda). Cognitive improvement can also occur with the dihydropyridine l-type calcium channel blocker nimodipine (Nimotop), which has been shown to increase somatostatin in cerebrospinal fluid. Somatostatin is often low in those with depression and Alzheimer's disease. Now pramipexole is an option, particularly in instances of mild residual depression and/or an inability to tolerate the indirect dopamine agonist bupropion (Wellbutrin).

Since in multiple studies the degree of cognitive dysfunction has appeared to be related to the number of prior episodes, it is important to institute effective long-term preventive treatment as early in the course of bipolar disorder as possible in order to limit the number of manic and depressive episodes and thus prevent cognitive decline. Preventive treatment with mood stabilizers not only helps patients avoid episode-related cognitive deficits directly, it also increases levels of brain-derived neurotrophic factor (BDNF). BDNF has neuroprotective effects and is necessary for learning and long-term memory. For example, animals whose brain BDNF was reduced 50% also lost their ability to perform easy tasks, such as learning to navigate a maze.

Since each episode of mania or depression is associated with decreases in BDNF, using agents that both prevent episodes (and thus prevent episode-related decreases in BDNF) and increase BDNF directly may be of particular clinical importance. Lithium, valproate, carbamazepine and lamotrigine all increase BDNF, and additionally several of these agents have been shown to increase the production of new neurons (neurogenesis) in the hippocampus as well. The atypical antipsychotic quetiapine also increases BDNF in the hippocampus and prevents stress from reducing BDNF, as do many other antidepressant modalities. Ziprasidone (Geodon) prevents stress from decreasing BDNF in the hippocampus, although the drug does not increase BDNF in the hippocampus.

It is important to prevent affective episodes because more episodes are associated with more cognitive dysfunction.

It is noteworthy that in the ziprasidone studies, the typical antipsychotic haloperidol not only did not prevent stress-induced decreases in BDNF, but it actually exacerbated them.

The best defense against cognitive deficits may be lithium. Preliminary studies by Lars Kessing and colleagues suggest that long-term use of lithium may actually reduce the incidence of dementia in late life; the risk of late-life dementia also appears to be associated with an increasing number of prior depressive episodes. Lithium could thus reduce the risk of dementia by: 1) preventing episodes; 2) increasing BDNF, BCl-2, and neurogenesis; and 3) increasing hippocampal volume.

The Natural Substance Citicoline May Be Useful in Bipolar Disorder with Comorbid Stimulant Abuse

Sherwood Brown and colleagues from the University of Texas Southwestern Medical Center have completed a successful placebo-controlled trial of citicoline for bipolar and unipolar depression with comorbid methamphetamine dependence. Forty-eight participants with methamphetamine dependence and either unipolar or bipolar depression were randomized to either citicoline (2000 mg/day) or placebo for 12 weeks. Those receiving citicoline had significantly greater improvement in scores on the Inventory of Depressive Symptoms compared with those who received placebo, and patients receiving citicoline stayed in the study significantly longer, with completion rates of 41% on citicoline and 15% on placebo.

In 2007, the same team of investigators reported in the *Journal of Clinical Psychopharmacology* that citicoline had positive effects in bipolar patients with cocaine dependence, who experienced significant decreases in cocaine use and fewer cocaine-positive urine tests while taking citicoline.

Citicoline is a cytosine di-phospholipid that contains choline and is rapidly metabolized to cytidine and choline. Both cytidine and choline have been reported to have positive psychotropic effects. A research group at Massachusetts General Hospital found that cytidine exerted significantly more antidepressant effects than placebo in bipolar depression (as reported in *BNN* Volume 12, Issue 3 from 2008). The dinucleotides, including cytidine and uridine, have been reported to exert antidepressant effects in patients with bipolar depression, further supporting the potential antidepressant utility of these compounds. Interestingly, those with greater numbers of prior episodes were more responsive to uridine (a finding that contrasts with those about most other potential antidepressant compounds in bipolar illness, in which patients who have experienced more episodes are less likely to respond well to treatment).

Editor's note: The studies by Brown and colleagues are rare in that they directly assessed the efficacy of a treatment in patients with mood disorder and comorbid substance abuse. Most studies include only patients with substance abuse without comorbid mood disorder, so doctors are forced to make inferences from these data when determining how to treat patients with a primary unipolar or bipolar disorder. These studies of both cocaine dependence and methamphetamine dependence suggest a potential new treatment approach for these comorbid conditions.

Depression in Perimenopausal Women with Bipolar Disorder

Researchers found that among women with bipolar disorder, those in the menopausal transition period were significantly more likely to be depressed than premenopausal women in the sample, and that the increased proclivity for depression continued in post-menopausal women as well. Wendy Marsh, Terrence Ketter, Sybil Crawford, Julia Johnson and Anthony Rothschild studied 521 women of reproductive age, 107 women in the menopausal transition period, and 145 post-menopausal women in a multisite treatment enhancement program for bipolar disorder (STEP-BD).

The women of reproductive age ranged from 28-38 years old, and the women in the menopausal transition period averaged 42 years old and 365 days past their last menstrual period.

Women in the menopausal transition were less likely to experience a manic episode compared with reproductive aged women, and those who were post-menopausal had the least likelihood of experiencing a manic episode. These data are consistent with others in the literature that suggest that the menopausal transition may be associated with an increased proclivity to depressive episodes.

Estrogen replacement therapy in the early menopausal transition should be studied for its possible antidepressant effects.

These data also raise the question of whether hormone replacement therapy in the late menopausal transition phase may be a useful adjunct for treatment-resistant depression. This idea deserves further study and assessment.

Editor's note: David Rubinow, in a lecture presented at the National Institute of Mental Health's (NIMH) Foundation for Advanced Education in the Sciences (FAES) Psychopharmacology Symposium in November, reported that new analyses of large data sets indicate that among women in the early peri-menopausal years (when it is not yet clear whether a patient is menopausal), the risk of breast cancer was not increased with estrogen-only hormone replacement therapy as it can be after longer-term hormone replacement therapy (i.e. for five years or more) in the post-menopausal period.

These data suggest that randomized controlled studies of adjunctive estrogen for women in the menopausal transition period who have treatment-resistant depression could yield useful results, and might not increase breast cancer risk in this phase of life.

Correction:

In Volume 14, Issue 4 from 2010, in "Smoking Adds to Risks for Patients with Bipolar Disorder," we mentioned that an article about a link between smoking and new onset of depression was published in the *New England Journal of Medicine*. The article was published in the *British Journal of Psychiatry* and stated that nicotine dependence led to depressive symptoms.

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