

# Bipolar Network News

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Updates from the 2011 NCDEU Conference

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## Lithium More Effective than Valproate for Bipolar Disorder

According to two studies in 2011, **lithium is more effective in treating episodes of bipolar disorder than valproate**, while the drugs may be equally effective in reducing suicidality among bipolar patients.

The first study, of more than 4000 Danish patients with bipolar disorder, found that **patients taking lithium had fewer hospital visits and were less likely to need new medications than those taking valproate**. Patients taking lithium had fewer admissions to a hospital for any type of episode. In addition, patients taking valproate had a higher rate of switching to or adding on treatment with antidepressants, antipsychotics, or anticonvulsants than those taking lithium. The study included up to **12 years of follow-up** with the patients and is the largest study with the longest period of follow-up of patients taking valproate or lithium to date. Results were published by Lars Kessing et al. in the *British Journal of Psychiatry* in July 2011.

In the other study, a randomized controlled trial of 100 patients with bipolar disorder who had attempted suicide at least once in the past, Maria Oquendo of Columbia University found that **there were no significant differences in number of suicide attempts, hospitalizations for suicide attempts, or time to a new attempt between patients taking lithium and those taking valproate** over a follow-up period of 2.5 years.

Forty-five suicide events, which included attempts, hospitalizations, and changes to medication in response to suicide plans, were experienced by 35

patients (16 who were taking lithium and 19 who were taking valproate). Eighteen suicide attempts were made by 6 patients taking lithium and 8 taking valproate. There were no suicide completions during this study, which was published in Volume 168 of the *American Journal of Psychiatry* in 2011.

*Editor's Note: Suicide attempts are much more common than completed suicides. It appears that the second study was not large enough or long enough to detect differences in the rate of completed suicides. Older naturalistic studies suggest that treatment results in low suicide rates and that in patients who stop treatment with lithium, the rate of suicide attempts and completion increases dramatically. This is another reason for good responders to treatment regimens that include lithium to continue taking their medications.*

## Aripiprazole Makes Lamotrigine More Effective

In a poster at the 9th International Conference on Bipolar Disorder (ICBD) held in Pittsburgh in 2011, Rahman and colleagues reported that **in patients being treated for bipolar disorder, the addition of atypical antipsychotic aripiprazole to maintenance treatment with lamotrigine was more effective than the addition of placebo to the same maintenance treatment with lamotrigine**. Improvements in Young Mania Rating Scores (YMRS) with the combination of aripiprazole plus lamotrigine were significantly greater than that of lamotrigine plus placebo.

*Editor's note: These data add to a growing literature that shows that an atypical antipsychotic added to a mood stabilizer is associated with better*

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*prophylactic effects than use of the mood stabilizer alone. Previously, most of the studies of this type of combination used lithium or valproate as the mood stabilizer and, to our knowledge, this is the first to demonstrate that long-term prevention with lamotrigine is enhanced by the addition of an atypical antipsychotic.*

*Many of the atypical antipsychotics are FDA-approved as adjunctive treatments to mood stabilizers in the long-term treatment of bipolar disorder. The controlled clinical trial data that led to this FDA approval support the practice of many clinicians who prescribe combination treatment rather than monotherapy in order to achieve a more rapid onset of anti-manic stabilization and longer-term*

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## Aripiprazole Makes Lamotrigine More Effective

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*maintenance effects. The use of aripiprazole and quetiapine as adjuncts to lithium and valproate is particularly common in bipolar disorder since the same atypical antipsychotics are FDA-approved as adjunctive treatments in unipolar depression, and clinicians are familiar with prescribing them to improve ineffective acute antidepressant treatment.*

### Bipolar Network News

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

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

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The opinions expressed in the BNN are solely those of the editors, and do not represent the views of any scientific entity or foundation.

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## Antidepressants Prevent Suicide in Depression

Researcher A. Kahn reported at the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in Boca Raton in 2011 that **severely depressed and suicidal unipolar patients taking citalopram (Celexa) or a combination of citalopram and low dose lithium experienced improvements in depression and suicidal thoughts.** This study was unusual because most clinical trials exclude actively suicidal patients. In the group of subjects receiving citalopram plus lithium (300 mg/day and achieving 0.5 mEq/l or higher), there were several indications of better anti-suicide effects than in those on citalopram alone. The authors concluded that with appropriate doses, antidepressants plus lithium may prospectively reduce suicidal thoughts, and that it is possible to conduct clinical trials in severely depressed and suicidal patients if adequate safety measures are included.

Surprisingly, improvement in suicidal ideation preceded improvement in depressed mood per se. *Editor's note: The study reported here suggests that in those with high suicidal ideation scores at baseline, antidepressants with or without lithium may quickly bring about anti-suicidal effects on thoughts, desires, and behaviors. Whether these effects occur reliably in studies in other groups of patients and in younger individuals remains to be established.*

These data are an interesting contrast to data on antidepressant use in patients

*with unipolar depression who have low levels of suicidality at baseline. A number of studies have suggested that in children and adolescents who were exposed to an antidepressant, a small percentage experienced increases in suicidal ideation in the first two months of treatment compared to patients taking placebo. This led to a Federal Drug Administration (FDA) warning (directed at all patients taking antidepressants) that increases in suicidal ideation and action may occur upon starting antidepressants.*

*It is important to note that the warning does not refer to completed suicides; the data set that led to the FDA warning included no completed suicides. More than 70% of those with suicidal ideation do not make an attempt, and the vast majority of attempts do not result in*

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*Despite the FDA warning that suicidal ideation can increase when starting antidepressants, new data show that the drugs decrease suicides and suicide attempts.*

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*a completed suicide.*

*Acutely suicidal patients were excluded from most of the studies that found the slight increase in suicidal ideation in some patients after beginning antidepressant treatment. Since the study of citalopram and lithium used a population of severely depressed and suicidal patients and found that antidepressants improved suicidality, it appears important to consider a patient's baseline state when considering psychiatric interventions. In another example, there is an interesting difference between the way depressed patients and non-depressed normal volunteers respond to one night's sleep deprivation: depressed patients often show dramatic improvement, while normal volunteers tend to feel worse.*

## More Evidence that ADs Prevent Suicide in Unipolar Depression

A new study by DeLeon published in the Journal of Clinical Psychiatry in 2011 found that **during periods of life when unipolar patients were taking antidepressants (compared to times when they were not taking them) the patients experienced 20% fewer suicidal acts or completed suicides.**

Using a large cohort of patients whose health reports were collected over a period of 37 years, the study examined specific suicidal acts in individual patients and determined whether each patient was being treated with antidepressants at the time of the act. Since patients tended to go on antidepressants at times of more severe depression, the researchers adjusted the analysis to control for clinical differences in depression severity. This analysis (a propensity-based

correction) is powerful because it uses each patient as his or her own control.

*Editor's Note: This study used real-world patients who are more representative of the general population of depressed patients than the highly selective cohort of patients who are enrolled in randomized placebo-controlled clinical trials of antidepressants. In clinical trials, patients tend to be excluded if they have active suicidal ideation, medical comorbidities, or substance abuse problems, complications that are common in the general population of depressed subjects.*

*DeLeon's data do not detract from the FDA warning to exert particular care in the first several months after beginning antidepressants, but clarify that in the long term, antidepressants not only do not cause suicidal behavior, but they actually help prevent it.*

*Together the data from the study of citalopram with lithium above and the study by DeLeon help to clarify the relationship between antidepressants and suicide. Despite the rare occurrence of suicidal ideation at the beginning of antidepressant treatment as warned about by the FDA, antidepressants with or without lithium rapidly improve suicidal ideation in those who were suicidal at baseline, and in the long term, treatment with antidepressants reduces suicidal actions.*

*See below for more reasons to consider long-term use of antidepressants in recurrent unipolar depression. However, it should be emphasized that the above findings do not apply to bipolar depression where, instead of antidepressants, long-term use of lithium, mood stabilizing anti-convulsants, and atypical antipsychotics are typically endorsed.*

## The Risk-Benefit Ratio Encourages the Use of Antidepressants to Treat Unipolar Depression

Above we reviewed new data that shows that despite the FDA warning that antidepressants can increase suicidal ideation among young people in the first few months they are taken, antidepressants actually reduce acute suicidal ideation and decrease suicidal acts. As we described in our article on five myths about antidepressants in BNN Volume 14, Issue 3 from 2010, **antidepressant treatment in recurrent unipolar depression is important to patients' long-term wellbeing, cognitive functioning, and even life expectancy.**

Untreated depression, and particularly untreated recurrent depression, carries high risks not only for lethality by suicide, but also for increases in medical mortality, particularly from cardiovascular disease. In addition to these medical risks, data from many studies suggest that a higher number of prior depressions is associated with increased cognitive dysfunction, and

recent large data sets from a case registry in Denmark indicate that patients with four or more prior unipolar or bipolar depressive episodes have double the risk of receiving a diagnosis of dementia in old age. Thus, depressions are dangerous for a patient's psychological, medical, and cognitive health.

### Antidepressants Are Highly Effective in Depression Prevention

In 1992 researcher John Davis completed a meta-analysis of all antidepressant data available at the time in unipolar depression studies and not only found that antidepressant continuation was more effective than placebo in reducing the likelihood of later depressions, but also calculated that the statistical likelihood that this finding was due to chance was minuscule, i.e.,  $p < 10^{-34}$ . John Geddes and colleagues in a meta-

analysis in 2003 indicated that there was an approximate 70% reduction in the risk of depressive recurrences with antidepressant continuation compared with discontinuation.

Treatment of a first or second episode of unipolar depression is recommended for six to nine months following achievement of remission. After a third episode, all treatment guidelines of which this editor is aware recommend long-term preventive treatment with antidepressants, particularly if episodes have been severe or close together temporally. This long-term antidepressant continuation for prophylaxis is much like long-term treatment of high blood pressure or high cholesterol recommended for those with or at high risk for cardiovascular disease.

There is some evidence that cognitive behavior therapy reduces the

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## Long-Term Antidepressant Use Encouraged in Unipolar Depression

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risk for depressive recurrence in those discontinuing antidepressant treatment, but it appears maximally beneficial to engage both psychotherapeutic and pharmacological treatment to prevent future episodes.

In most longitudinal studies, about 20-25% of patients who remain on antidepressants for several years still relapse. However, this is considerably less than the more than 50% who relapse within the first year after discontinuing an antidepressant that had been acutely effective. The rate of relapse following antidepressant discontinuation increases to about 85% by the third year off treatment in those with prior recurrent depressive episodes.

**In addition to preventing relapse, antidepressants may also have positive effects on the brain.** They increase brain-derived neurotrophic factor (BDNF), a protective factor important for long-term learning and memory that decreases when stressors and episodes of depression occur. In addition to these increases, Yvette Sheline has demonstrated that **patients with unipolar depression who were on antidepressants more of the time experienced less hippocampal atrophy** with aging compared with those treated with antidepressants less of the time.

It is important to put the risk/benefit ratio of antidepressant treatment for unipolar depression in perspective, particularly since some articles in the mainstream press, including one on the cover of *Newsweek* last year, suggest that acute treatment with antidepressants may not be much more effective than placebo. Antidepressants sometimes fail to show efficacy acutely compared with placebo, but this is not unexpected given the relapsing and remitting nature of the illness and difficulties of research design. While some of these articles are narrowly factual about the small magnitude of acute antidepressant efficacy

compared to that of placebo, they fail to communicate the breadth of data noted above about the large effects of antidepressants in prevention.

In blind studies, when patients improve on antidepressants and then are randomized to either a group that continues preventive antidepressants or a group in which the antidepressant treatment is replaced by a placebo, the group that continues antidepressant treatment is more successful in

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*Antidepressants are extraordinarily effective in preventing recurrent unipolar depressions, which in turn prevents suicides and multiple medical problems.*

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avoiding future episodes at a level that is statistically astronomical. Since greater numbers of depressions are associated with increased dysfunction, disability, cognitive dysfunction, suicide risk, and premature loss of life from excess medical mortality, antidepressants are extremely important in helping prevent these risks.

### Limited Risks of Long-Term Antidepressants

There are some real risks associated with antidepressants in addition to the FDA warning about suicidal ideation. Some are medical risks and some relate to the fact that antidepressants are not equally effective in all patients.

Medical risks that come with antidepressant treatment include 20% increased risk of cataracts, but this readily correctable medical problem

pales in comparison to the enormous risks associated with depression recurrences. There is some evidence of more serious medical risks. Recent studies have suggested that antidepressants are associated with cardiovascular problems and cancer. However, these studies do not always control for the fact that depression itself increases the risks of these medical illnesses, and those with more severe depression are more often treated with antidepressants.

Antidepressants may not be effective in some individuals. Antidepressants can lose their effectiveness over time or fail to adequately prevent recurrence, and other strategies may be needed. One or more antidepressant augmentation strategies may be necessary to achieve a full remission from depression. As discussed in previous BNNs, these could include folate, lithium, T3, N-acetylcysteine, and many others.

### Antidepressants Not Recommended for Bipolar Depression

Antidepressants are not usually effective in bipolar depression. A recent meta-analysis published by Sidor and MacQueen in the *Journal of Clinical Psychiatry* in 2011 indicates that antidepressants, even when used as augmentation to mood stabilizers, are not more effective than placebo as acute treatments for bipolar depression. They may even increase the switch rate of cycling into the next episode of mania or depression in some individuals. This occurs particularly in those with more rapid cycling presentations (i.e., those with four or more episodes of bipolar depression or mania per year).

Recent data by Ghaemi showed that antidepressant continuation in bipolar depressed patients who had a period of remission of several months was associated with a lower and delayed recurrence of the next depressive episode, but **in those with a prior**

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## New Atypical Antipsychotic Lurasidone Has a Good Metabolic Profile

Andre Pikalov and colleagues from Sunovion Pharmaceuticals Inc. reported at the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in 2011 on the [weight and metabolic effects seen in short- and long-term trials of the atypical antipsychotic lurasidone \(Latuda\) in schizophrenia](#). The studies compared lurasidone to olanzapine (Zyprexa, at 15mg), haloperidol (Haldol, at 10mg), and placebo. Doses of lurasidone ranged from 20-120mg administered once daily. Short-term treatment for six weeks was associated with changes in weight and metabolic indices similar to those of placebo, while participants taking

olanzapine gained substantial amounts of weight and had increases in triglycerides and cholesterol. Changes in glucose and hemoglobin A1C were similar on lurasidone, haloperidol, and placebo, but higher on olanzapine. In the long-term sample, mean weight gain on lurasidone at 12 months was 0.71 kg and metabolic parameters remained relatively unchanged.

*Editor's note: Multiple posters at the meeting composed a substantial body of evidence concerning acute and long-term studies of lurasidone, which shows that [the drug has a weight and metabolic profile relatively similar to placebo and more favorable than that of olanzapine](#).*

*Although lurasidone has not been studied acutely or in the long term in patients with bipolar disorder, the safety profile of this drug in schizophrenia indicates that it may eventually be useful for acute and long-term treatment strategies in bipolar disorder. All typical and atypical antipsychotic drugs that have been approved for treatment of schizophrenia have subsequently been shown to have efficacy in acute mania, and given lurasidone's similar actions in blocking dopamine receptors, there is little reason to expect that this drug will be any different. The results of actual studies of this drug in mania and depression are eagerly awaited.*

## Antidepressants

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[history of rapid cycling, antidepressant continuation was associated with an increased frequency and rapidity of recurrent depressive episodes](#). A few studies suggest that antidepressants can be effective in patients with bipolar II depression who have isolated, intermittent episodes and are not highly recurrent.

Thus, the endorsement of antidepressant prophylaxis applies only to those with unipolar recurrent depressions. For those with bipolar depression an entirely different set of treatment approaches and guidelines must be considered.

### Benefit-to-Risk Ratio Positive for Antidepressants in Unipolar Depression

Since recent findings show that antidepressants do not cause suicide, but actually prevent it, the benefit-to-risk ratio for long-term antidepressant prophylaxis (instead of antidepressant discontinuation) is enormously positive. The benefits are large and important and the risks are relatively small. Patients need this full picture about antidepressant efficacy so that they can make informed decisions about long-term prevention of recurrent unipolar depressions.

## Citicoline May Boost Cognition in Healthy Women

Citicoline is a natural substance found in the brain and the liver that is also available as a nutritional supplement. At the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit in 2011, Erin McGlade and other researchers from the University of Utah Brain Institute presented research showing that [citicoline enhanced cognition among healthy women, particularly bringing about improvement in attention](#). Citicoline has few side effects.

The participants in this study were 60 women aged 40 to 60 years who had neither a psychiatric disorder nor any abnormal cognitive decline. The women were divided into groups in which, over the course of a month, they received either 250mg of citicoline, 500mg of citicoline, or a placebo. [Both groups who received citicoline performed better on a test of attention at the end of the month than the women who had received placebo](#).

*Editor's Note: Given that citicoline helps with cognition in healthy women, it may be effective in preventing the cognitive deficits that accompany both the normal aging process and some psychiatric illnesses, although this has not yet been directly demonstrated.*

## Possible Sequential Ways to Protect Memory in the Recurrent Affective Disorders

1. Prevent depressions
2. Decrease sedating medications
3. Treat depression to remission
4. Use [folate](#) to decrease homocysteine
5. Use [bupropion](#) for residual depression and ADHD
6. Use [modafinil](#) for depression or ADHD
7. Try stimulants for ADHD
8. Treat mild cognitive impairment with [citicoline](#)
9. Use [lithium](#) (150mg/day) for mild cognitive impairment
10. Try [pramipexole](#) for residual depression
11. Try [minocycline](#) for inflammation and mitochondrial dysfunction
12. Use [memantine](#) plus acetylcholine esterase inhibitor for early aggressive treatment of Alzheimer's



## Small Daily Doses Of Lithium May Slow Progression of Mild Cognitive Impairment

**A very small dose of lithium, 150 mg/day, has been reported to lessen the progression of mild cognitive impairment over a period of one year compared to placebo.** In a 2011 article by Orestes Forlenza and colleagues published in the *British Journal of Psychiatry*, the researchers reported the findings from their prospective randomized study of lithium versus placebo in 45 patients.

*Editor's Note: While these findings must still be replicated, there are several reasons to suggest that they may be reliable and valid.*

*A preliminary epidemiological study by Lars Kessing et al. published in the Archives of General Psychiatry in 2008 indicated that risk of dementia was lower in patients taking lithium chronically, who were identified by having renewed their prescriptions at least once.*

*Lithium exerts a number of neuroprotective effects in animals. These effects include increases in cell survival factors BDNF and BCL-2 and decreases in cell death factors BAX and P53. Lithium can also decrease the size of a brain lesion and its associated functional deficits in many animal models of neuropsychiatric disorders, including stroke, Huntington's chorea, Alzheimer's disease, and AIDS (according to the work of DeMaw Chuang and colleagues who formerly worked in this editor Robert Post's laboratory at the National Institute of Mental Health).*

*In humans lithium increases neuronal integrity, as observed via magnetic resonance spectroscopy (MRS) measuring increases in N-acetylaspartate (NAA). Lithium also increases gray matter volume and hippocampal volume measured via magnetic resonance imaging (MRI).*

*Miniscule amounts of lithium may exert positive effects in humans. Three studies (carried out in Texas and in regions of Japan and Austria) have found that higher trace levels of lithium in the water supply, which are still approximately 1000-fold lower than those considered necessary for therapeutic effects in bipolar disorder, are associated with a reduced suicide rate in the general population compared to nearby areas with lower trace levels of lithium in the water.*

*While it will take time to establish the possible effects of lithium on long-term cognition, this editor suggests that quicker action be*

*considered for patients with bipolar illness and mild cognitive impairment who are not currently taking lithium. Perhaps they should talk to their physicians about adding lithium in low to moderate doses to their therapeutic regimen.*

### Rationales for Considering Lithium:

1. Even euthymic patients have been shown to have some cognitive deficits compared to volunteer controls. These deficits increase in likelihood with the number of affective episodes experienced.

2. Depression is a risk factor for the progression of mild cognitive impairment to full-blown cognitive dysfunction, and lithium can help treat and prevent depressions.

3. The experience of four depressive episodes (unipolar or bipolar) doubles the risk for the diagnosis of dementia late in life.

4. Given that depression is the most difficult phase of bipolar disorder to treat and prevent, patients with the disorder are at high risk for further episodes and the subsequent increased risk for cognitive dysfunction.

5. Although very low-dose lithium has never been studied in patients with bipolar disorder, it is possible that treatment with moderate doses could decrease risk of suicide, given the data from the three studies showing positive effects on suicide in the general population based on trace levels of lithium in the water supply. Parenthetically, people living in areas with higher trace levels also lived longer than those living in areas with lower trace levels.

6. The side effects of 150mg lithium in the study by Forlenza did not differ from that of placebo.

*Thus, there might be some rationale for a patient with bipolar disorder who has neither kidney dysfunction nor an allergy or intolerance to lithium to be prescribed a small dose of lithium even if it has not proven to be an effective treatment for that patient's mood disorder.*

## Low Doses of Levetiracetam May Improve Mild Cognitive Impairment Within Two Weeks

**Levetiracetam, an anticonvulsant often used to prevent seizures in epilepsy, may improve memory by decreasing hippocampal hyperactivity.** Hippocampal hyperactivity in amnesic mild cognitive impairment (aMCI) was once thought to be beneficial, but results from a recent study suggest that increased activity in this structure may contribute to memory impairment. Levetiracetam was effective for memory when given in much lower doses than those used to treat epilepsy.

In a study by Michela Gallagher and colleagues presented at the Alzheimer's Association International Conference in 2011, a placebo-controlled, randomized crossover design was used to study 17 aMCI patients and a similar number of healthy controls. Both groups went through two distinct treatment periods. People in the control group received placebos in both periods, while patients with aMCI received placebo during one period and low-dose levetiracetam (125mg twice daily) in the other period. After 2 weeks of taking the drug, hippocampal hyperactivity among aMCI patients decreased into the normal range, and memory was improved to the level of the healthy controls.

*Editor's Note: The findings from this small study are preliminary and need to be replicated in larger and longer studies before they are applied clinically. As we noted at left, very low doses of lithium (150mg/day) prevented the progression of mild cognitive impairment compared to placebo in a one-year study. Whether these effects of levetiracetam or lithium are reliable, are of large effect, and occur by similar or different mechanisms remains to be determined.*

## Exercise May Improve Cognitive Function in Depression

Tracy L. Greer of the University of Texas Southwestern in Dallas presented an abstract at the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in 2011 that suggested that **exercise improved the cognitive function of patients being treated with selective serotonin reuptake inhibitors (SSRIs) for major depressive disorder.**

Thirty-nine participants reported cognitive impairment at baseline. Subjects were randomized to receive antidepressant treatment in the form of an SSRI augmented by either an exercise regimen designed to burn 16 kilocalorie/kg per week (kkw) or one designed to burn 4 kkw. Both exercise regimens resulted in improved response time on a measure of attention, and for the higher intensity (16 kkw) exercise group, there were improvements in

response time for visual memory tasks as well as decreased errors on an executive function task.

*Editor's note: There is a somewhat mixed literature on the efficacy of exercise in potentiating antidepressant effects of other treatments. Recent data by Fred Gage and colleagues showed that in animals, exercise increased not only brain-derived neurotrophic factor (BDNF), which seems to be necessary for long-term learning and memory, but also the formation of new neurons (neurogenesis). Gage found that new neurons that migrated to the dentate gyrus of the hippocampus were more excitable than older neurons and were important in a variety of cognitive tasks.*

*The newer neurons could more precisely distinguish between closely related stimuli, while the older neurons were sufficient only for discriminating stimuli that were widely and obviously different from each other.*

*Thus, the increase in new neurons and BDNF that may follow exercise and antidepressant use may be associated with some cognitive improvement in depression, particularly in the realm of response speed and perhaps also in making relatively fine discriminations among relatively similar objects.*

*While not much evidence for the effect of exercise on cognition has been collected in humans, exercise has many other benefits. Since it is good for cardiovascular fitness and wellbeing, as well as potentially generating new neurons that could play an important role in fine cognitive discriminations, **encouraging exercise in depressed patients (especially as their depression improves and they have renewed motivation to engage in exercise regimens) could be of value, even if exercise is not a guaranteed enhancer of antidepressant effects per se.***

## BDNF Related to Cognition and Fitness in Men with Coronary Artery Disease

At the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in 2011, Walter Swardfager and colleagues from Toronto, Ontario presented a study indicating that **brain-derived neurotrophic factor (BDNF) concentrations in blood are associated with cognitive performance and cardiopulmonary fitness in people with coronary artery disease.**

In 88 mostly male subjects with a mean age of 63 years, cardiopulmonary fitness was directly correlated with BDNF in blood as well as higher scores of cognition on two tests, the mini mental status exam and the digit symbol coding task.

The investigators concluded that better fitness, psychomotor processing speed, and overall cognition were consistent with a hypothesis that BDNF protects midbrain dopaminergic neurons against inflammatory neurodegenerative processes.

Low blood levels of interleukin 6, a measure of inflammatory cytokines, were associated with better mini mental status scores in a multivariate analysis that controlled for BDNF levels.

*Editor's note: BDNF appears to be necessary for long-term learning and memory. Meta-analyses indicate that BDNF levels are low in depression and improve with euthymia. Many mood stabilizers including lithium, valproate,*

*carbamazepine, and lamotrigine and most types of antidepressants are able to increase BDNF. The current findings linking BDNF with better cardiopulmonary fitness and cognition continue to emphasize the potential importance of BDNF beyond its role as a marker for depression.*

*In BNN Volume 12, Issue 3 from 2008, we reported on the data of Schmidt and Duman, which indicated that BDNF administered in a subcutaneous minipump is able to reverse many depressive-like behaviors in an animal model of depression, suggesting that even peripheral BDNF may have a role in the central nervous system.*



## IV Scopolamine Brings About Rapid Onset Of Antidepressant Effects

Frankel and colleagues from the National Institute of Mental Health presented a randomized, placebo-controlled clinical trial of intravenous (IV) **scopolamine for bipolar depression** at the 9th International Conference on Bipolar Disorder (ICBD) in 2011. The same group of investigators previously showed that IV scopolamine was able to induce fast-acting antidepressant responses in those with unipolar major depression. This represents a new and independent study exclusively among patients with bipolar depression.

In the first phase of the study, three sessions of either IV scopolamine at 4 mcg/kg or a sham treatment were scheduled three to five days apart. In the second phase of the study, the patients were switched to the other treatment for three sessions. **The results showed a rapid improvement in depression following the first session with scopolamine**, more than occurred with the sham treatment. Hamilton Anxiety Rating scale (HAMA) scores also improved more on scopolamine than with the sham treatment, while Young Mania Rating Scores (YMRS) did not differ.

*Editor's note: As previously discussed in the BNN, scopolamine, an antagonist of acetylcholine muscarinic receptors, appears to exert rapid onset*

*antidepressant effects in both unipolar and bipolar depression. When administered intravenously it takes its place with other rapidly acting antidepressant treatments, including IV ketamine, IV thyrotropin releasing hormone (TRH), and one night of sleep deprivation. The new data indicate that both unipolar and bipolar depression can respond rapidly (i.e. within a matter of hours) to certain treatments, even though most conventionally acting antidepressant modalities can take weeks to achieve maximum antidepressant effects.*

*We've suggested before (in BNN Volume 15, Issue 1 from 2011) that ketamine would be ideal for use in emergency rooms during suicidal crises. Scopolamine's potential role in clinical therapeutic strategies remains to be established, although the possibility exists that like ketamine, scopolamine could be used acutely and then followed up with a slower acting antidepressant modality for longer-term results.*

*Some clinicians (mostly in Europe) have tried to extend the antidepressant effects of one night's sleep deprivation using lithium, antidepressants, or a circadian phase manipulation. In a circadian phase manipulation, a patient goes to sleep at 6pm and awakens at 2am on the first night after sleep deprivation, then sleeps from 7pm to 3am the second night, 8pm to 4am the third, and so on until a normal sleep cycle is achieved.*

*Because response to scopolamine can be measured after just one administration, it would be relatively easy to eventually identify neurobiological predictors that particular patients may or may not be likely to respond to this treatment. However, a successful follow-up treatment to sustain the response still remains to be identified with further research.*

### Scopolamine Produces Larger Antidepressant and Antianxiety Effects in Women Than in Men

In a study by Furey et al. published in *Neuropsychopharmacology* in 2010, **three sessions of intravenous scopolamine (4µg/kg over 15 minutes) led to rapid antidepressant response in both men and women, but the magnitude of response was larger in women.** Women also experienced significant reduction in anxiety.

*Editor's Note: Scopolamine is a potent blocker of acetylcholine receptors of the muscarinic type. This can cause side effects such as dry mouth and constipation. However, when given intravenously, scopolamine produces rapid onset of antidepressant effects in both bipolar and unipolar depressed patients. This study suggests that the drug may be more effective in women than in men.*

## New Experimental Brain Stimulation Method Uses Ultrasound Pulsations

Alexander Bystritsky of UCLA and colleagues at McLean Hospital and Harvard Medical School reported at the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in 2011 that **low intensity focused ultrasound pulsation could eventually be used as a noninvasive intervention for diagnosing and treating brain disease.**

In animal studies, the researchers used low intensity 100 Hz stimulation,

which could produce a focused activation or inhibition of specific brain areas. Researchers were able to produce acute and long-term anticonvulsant effects in the animals, and when targeting the hypothalamus they could increase the animals' heart rate and blood pressure.

*Editors note: These preliminary pre-clinical data raise the possibility that in the future this new mode of non-invasive and relatively precise brain stimulation may be used to treat neuropsychiatric disorders. Existing non-invasive brain stimulation*

*methods include repeated transcranial magnetic stimulation (rTMS), low level magnetic fields, and transcranial direct current (tDCS). The new data suggest that deep brain structures could be stimulated without electrodes. Vagal nerve stimulation (VNS), which requires an implant in the chest, is more invasive. The most invasive and the most precisely targeted method of brain stimulation is deep brain stimulation (DBS). In this type of treatment electrodes are inserted in the brain of the patient.*



## Clinical and Laboratory Evidence May Explain the Mechanisms of Ketamine's Rapid Acting Antidepressant Effects

At the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in 2011, C.G. Abdallah from SUNY Downstate Medical Center reported on a study of intravenous ketamine for treatment-resistant depression. Twelve medication-free participants aged 18-65 received 0.5mg/kg ketamine over 40 minutes. **There was a rapid-onset antidepressant effect, as there has been in other studies of unipolar and bipolar depressed patients.** In a subgroup of 4 patients examined with magnetic resonance spectroscopy (MRS), **there were rapid increases in brain GABA followed shortly thereafter by increases in brain glutamate concentrations.**

*Editor's note: The rapid increases in GABA and glutamate that occur after the administration of intravenous ketamine may help account for its therapeutic*

*effects. Other studies have shown that brain GABA is low in depressed patients, so the rapid increase in GABA with ketamine administration could partly explain the antidepressant effects of the drug. The role of the glutamate increases remains to be further explored.*

*Neli and associates from Yale had reported that in animals, ketamine was able to rapidly alter synapse structure and function. In an animal model of depression, rodents are exposed to chronic and unpredictable stress and develop depressive-like behavior. The mature, mushroom-shaped spines on their dendrites (the parts of neurons that receive synapses and determine the neuron's excitability) also lose their shape, becoming straighter and spikier like immature spines. Intravenous ketamine not only improves the animals' behavior, but also increases the number of mushroom-shaped spines within a matter of hours, rapidly*

*improving synaptic function. This effect of ketamine was dependent on a novel intracellular pathway involving the enzyme mTOR, which if blocked prevented the re-emergence of the mature spines.*

*In the brains of depressed humans studied at autopsy there is reduced neural volume in the frontal cortex, which could possibly be related to dendritic atrophy and associated changes in spine shape as seen in rodents. The animal data suggest the remarkable possibility that intravenous ketamine's rapid onset of antidepressant effects could also be associated with rapid improvement in the microanatomy of the brain.*

*The data on ketamine's effects in animals and the new clinical data showing that GABA and glutamate increases occurred rapidly in depressed patients administered ketamine provide further insight into the potential mechanisms of ketamine's rapid onset of antidepressant effects.*

## Sleep Apnea Common in Rapid Cyclers

Kellen and colleagues presented a poster at the 9th International Conference on Bipolar Disorder (ICBD) held in Pittsburgh in 2011, in which they reported that **21% of patients with rapid cycling bipolar disorder have confirmed sleep apnea.** Since many patients who screened positive for sleep apnea on the study's sleep questionnaire did not undergo follow-up sleep studies to confirm the diagnosis, it is estimated that up to 40% of rapid cycling patients may, in fact, have sleep apnea.

*Editor's note: Given such a high incidence of sleep apnea among rapid cycling bipolar patients, it would be prudent for patients and clinicians to be alert to the possibility of sleep apnea and follow up with appropriate sleep studies. Sleep apnea can cause daytime fatigue, cognitive dysfunction, and treatment resistance, so its*

*identification and treatment with continuous positive airway pressure (CPAP) may be enormously beneficial to a substantial number of rapid cycling bipolar patients.*

*Clinical hints that a patient may be suffering from sleep apnea include loud snoring, long pauses between breaths, and non-restorative sleep. The likelihood of sleep apnea increases with age and with overweight or obesity.*

*A just-published article by Sukys-Claudino in Sleep Medicine presents findings that compared to placebo, the anti-Alzheimer's drug donepezil (Aricept) started at 5mg/day for 2 weeks and then increased to 10 mg given twice a day (20 mg/day total) helped all measures of sleep apnea including daytime sleepiness in patients with primary sleep apnea. The utility of donepezil in patients with bipolar disorder needs to be further studied.*

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## Antioxidants May Be Deficient in Patients with Bipolar Disorder: Try NAC?

In a poster at the 9th International Conference on Bipolar Disorder (ICBD) held in Pittsburgh in 2011, Guy Goodwin and colleagues reported that relative to controls, **blood from patients with bipolar disorder contained more total glutathione, a potent antioxidant, and a higher ratio of oxidized to reduced glutathione.** Measurements of blood glutathione could eventually serve as a biomarker, suggesting when a diagnosis of bipolar disorder is likely.

*Editor's note: Glutathione is one of the major antioxidants in humans. Oxidized glutathione is a less active form, so the higher levels of oxidized glutathione compared to reduced glutathione in patients with bipolar disorder suggests they may have a relative deficiency of the active form. These data are consistent with reports that patients in manic*

*and depressive phases of bipolar disorder have increased oxidative stress and free radicals that impair cellular functioning.*

*Together, these results highlight the potential utility of treatments that increase antioxidant activity. One option is N-acetylcysteine (NAC), which the body converts into glutathione. As previously noted in the BNN, Michael Berk reported in Biological Psychiatry in 2008 that NAC (1000 mg twice a day) appears to exert greater antidepressant effects over a period of 24 weeks than placebo when added into previously ineffective regimens in patients with bipolar disorder.*

In another poster at the conference, Magalhaes and colleagues reported on NAC treatment for a subgroup of the bipolar patients in the study by Berk who were in a major depressive

episode at the time of the study. They found that NAC had highly significant acute antidepressant effects of large magnitude in this subgroup of patients.

The glutathione data by Goodwin et al. provide a further rationale for consideration of the use of NAC in bipolar disorder, particularly in the acute and longer-term treatment of the depressive phases. As we reported in BNN Issue 1 from 2010, NAC also exerts positive effects in many illnesses that commonly occur comorbidly with bipolar disorder. These include cocaine and heroin addiction, gambling addiction, obsessive compulsive disorder (where NAC is used as an adjunct to selective serotonin reuptake inhibitors (SSRIs)), and trichotillomania (compulsive hair-pulling).

## In Rare Cases Valproate (Depakote) Can Cause Increases in Blood Ammonia and Associated Neurobiological Symptoms

Researcher C. Lewis reported in two posters presented at the Ninth International Conference on Bipolar Disorder (ICBD) in 2011 that **in a study of patients treated with valproate, some increases in ammonia levels occurred.** This condition, hyperammonaemia, was identified in 31 patients among those treated between 2005 and 2009 at the Cleveland Clinic in Cleveland, Ohio. **High levels of ammonia are associated with a flapping tremor and, in some cases, encephalopathy with confusion, psychiatric symptoms, and motor incoordination.**

The recommended management for hyperammonaemia is

discontinuation of valproate and use of lactulose, a synthetic sugar that can lower ammonia levels. These approaches were not always used. Another option for patients who require valproate treatment is to supplement the drug with carnitine, which is available as a nutritional supplement. Lewis reported success in three such cases.

*Editor's Note: Patients on valproate presenting with a gross flapping tremor of the hands, confusion, or motor imbalance should be tested for hyperammonaemia and treated accordingly.*

## Neurobiological Markers May Eventually Predict Response to Antidepressants

T.L. Lauriat reported at the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in 2011 that **low baseline levels of the neurotransmitter GABA in the brains of depressed patients were associated with greater response to antidepressants.** GABA was measured using magnetic resonance spectroscopy (MRS).

These data raise the possibility that easily observed neurobiological markers, such as levels of GABA or the neurotransmitter glutamate, may ultimately be helpful in predicting clinical response to particular treatments.

## Biomarker Panel May Help Direct Diagnosis and Treatment of Major Depressive Disorder

It is hoped that measuring biochemical substances in blood will help in the early identification of mood disorders and help direct patients to the most effective therapeutic regimens. J.L. Billbielo reported at the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in 2011 that investigators from Ridge Diagnostics in North Carolina were using this type of biomarker panel in an attempt to provide a predictive algorithm for a diagnosis of major depressive disorder. The panel of 10 assays was derived from a larger screening set and included: alpha 1 antitrypsin (Alpha 1AT), brain-derived neurotrophic factor (BDNF), cortisol, epidermal growth factor (EGF), resistin, and soluble tumor necrosis factor receptor II (sTNFR2). The research group found that **this optimized algorithm distinguished depressed subjects from normal controls with a sensitivity of approximately 90% and a specificity of 84%.**

*Editor's note: This assay is available commercially and appears to represent an interesting panel of potential neurobiological markers of depression, including neurotrophic factors, endocrine stress hormones, and inflammatory markers. While its diagnostic utility is somewhat doubtful and must be further demonstrated, this editor hopes that it and similar panels could ultimately help predict individual clinical response to a given treatment. For example,*

*patients with high levels of inflammatory markers might respond better to treatments aimed at suppressing inflammation.*

*So far, it has not been established whether low BDNF or increased inflammatory markers in depression are specifically related to degree of clinical response to treatment. High levels of the stress hormone cortisol and failure to normalize cortisol after dexamethasone (a synthetic steroid that is administered in a dexamethasone suppression test or DST) have repeatedly been shown to be markers for early relapse in those who have remitted clinically.*

*BDNF decreases during episodes of unipolar and bipolar depression, and persistently low BDNF may be another marker of early relapse. This could be a more important use of assay panels than for the diagnosis of depression, which is usually easily made. However, there are likely many varieties of depression, and subtyping them biochemically may be helpful in the future so that clinicians can recommend the appropriate medication for a given type.*

*A combination of clinical and neurobiological markers may be helpful in the early recognition and treatment of bipolar disorder (especially if its development were to render the diagnosis and treatment of children less controversial). Ultimately, it could help in the development of clinical predictors of individual treatment response. This study appears to be a first step toward demonstrating the utility of a broad-based panel of biomarkers that is associated with major depressive disorder.*

## Common Genetic Variation Linked to Response to Antidepressants

Brain-derived neurotrophic factor (BDNF) protects neurons and is important for long-term learning and memory. There are several genetic variations in BDNF depending on which amino acid – valine or methionine – falls at a particular position when the proBDNF protein is being made. Most people have the val-66-val allele, some have the val-66-met, and a few have the met-66-met allele.

Researcher Jessica C. Levenson, working with David Kupfer and Ellen Frank at the University of Pittsburgh, reported at the 51st Annual Meeting of the National Institute of Mental Health's New Clinical Drug Evaluation Unit (NCDEU) in 2011 that **patients with unipolar depression who have the val-66-val allele of proBDNF have better clinical responsiveness to antidepressants than those with the slightly less common variant, val-66-met.**

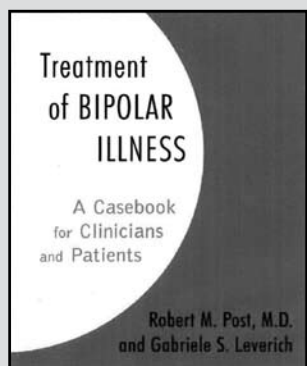
*Editor's note: The val-66-val allele is more effective in enhancing synaptic plasticity and is more easily transported from the nucleus to the dendrites of neurons (where it is necessary for learning and memory) than the val-66-met allele or the least effective met-66-met variant.*

*These findings are intriguing because antidepressant treatments tend to increase BDNF, regardless of their mechanisms of action. Moreover, BDNF levels are low in patients with depression, usually in direct relationship to the severity of depression. Thus, the ability of antidepressants to increase BDNF may lead to a more effective treatment response in those with the better functioning val-66-val allele of BDNF. This remains to be further documented, but the study provides a preliminary example of how genotyping may eventually be able to help predict individual clinical response to a given treatment and thus foster the development of personalized medicine.*

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