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Bipolar Network News

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Anti-Alzheimer's Drug Memantine (Namenda) Has High Sustained Success Rate As Adjunct in Treatment-Resistant Bipolar Disorder

Koukopoulos et al. published a study of the anti-Alzheimer's drug memantine in the *Journal of Affective Disorders* in 2012. The study of memantine (10-30mg/day) as an add-on to patients' regular treatment for highly treatment-resistant bipolar disorder was open (i.e. not blind, randomized or placebo-controlled), but it deserves careful attention for its noteworthy results. **Of the 40 patients in the study, who had been severely ill for long periods of time, 72.5% showed a rating of much or very much improved on the Clinical Global Impressions Scale for Bipolar Disorders (CGI-BP)** after both 6 months and 12 months. Among rapid cyclers, 68.4% stabilized and remitted on memantine.

Editor's Note: Memantine is an antagonist of glutamate NMDA receptors and is approved by the Federal Drug Administration (FDA) for the treatment of Alzheimer's dementia, but not for other indications. Nonetheless, few (if any) drugs have this high a response rate in such a difficult-to-treat population, and the researchers suggest that even based on these preliminary data (which replicate their previous observations), careful clinical trials of memantine in individual patients would be worthy of consideration.

The data are so promising that fast-track development of this drug for FDA approval would be warranted. More formal randomized controlled clinical trials are needed.

We have written before about a few treatments that have rapid-onset antidepressant effects, including intravenous (IV) ketamine (at a dose of 0.5mg over 40 minutes). Ketamine works by blocking glutamate NMDA receptors, but the rapid antidepressant effects it produces (within 2 hours of treatment) last only 3 to 4 days. Given the similar mechanisms of action of ketamine and memantine and memantine's high success rate in this study by Koukopoulos, it is plausible that treatment with memantine could extend the rapid onset effects of IV ketamine. However, this speculation has not yet been tested. At the very least, the similarity between the mechanisms of memantine and ketamine in blocking the glutamate NMDA receptor lends additional support to the clinical rationale for using adjunctive memantine in bipolar disorder.

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Memantine (Namenda) Efficacious for Cognitive Dysfunction In Patients With Bipolar Disorder

Many patients with bipolar disorder experience cognitive dysfunction, but few treatments are available for this aspect of the illness. In an abstract presented at the 67th Annual Meeting of the Society of Biological Psychiatry in 2012, Dan V. Iosifescu reported that in a randomized 12-week study in which the anti-Alzheimer's drug memantine was given to 72 euthymic bipolar subjects experiencing cognitive deficits, **the drug was associated with improvement in spatial and working memory, verbal and episodic memory, and other indices that included measurements of attention and language skills**. A subgroup of subjects showed increases in left hippocampal NAA (a measure of neuronal viability) and increases in choline in the right hippocampus. The initial improvements in these neuropsychological test results remained over 12 weeks of open follow-up.

Editor's Note: These data are of considerable importance. Many studies indicate that the severity of the cognitive dysfunction patients experience while euthymic varies directly as a function of the number of prior episodes of mania or depression they have experienced. The degree of cognitive dysfunction in patients with bipolar disorder is also correlated with disability in social and economic functioning. Thus, the data that memantine can lead to improvement in several types of memory tests suggest that the drug could be useful in treating these deficits in some patients with bipolar disorder.

Memantine acts in part by blocking glutamate NMDA receptors and provides a different mechanism of action compared to the other drugs used to

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When Added to Valproate, Memantine Increased HDLs ("Good" Cholesterol) But Did Not Enhance Effectiveness of Treatment

R.B. Lu and S.Y. Lee reported in a poster at the 5th Biennial Conference of the International Society for Bipolar Disorders in 2012 that **adding memantine (Namenda) to treatment with valproate (Depakote) was associated with increases in high-density lipoproteins (HDLs) or "good" cholesterol in bipolar II depressed patients**. However, the combination was no more clinically effective than valproate alone in treating the patients' bipolar illness, as had been hoped.

Editor's Note: These data on memantine's failure to improve patients' bipolar illness when used as an adjunct to valproate contrast with data on the combination of memantine and lamotrigine. Amit Anand et al. reported in 2012 that memantine was a partially successful adjunctive treatment when added to ongoing treatment with lamotrigine. This combination was associated with faster onset of antidepressant effects than the combination of lamotrigine plus placebo in patients with bipolar depression. This effect was significant in the first four weeks of the study as the dose of memantine was slowly increased from 5mg/day to 20mg/day, but not over the last four weeks of treatment at 20 mg/day.

It makes theoretical sense that memantine and lamotrigine would be more successful. Since lamotrigine inhibits the release of glutamate and memantine inhibits the actions of glutamate at the NMDA receptor, the two together might produce additive decrements in glutamatergic actions through two different mechanisms. In contrast, valproate is more closely associated with increases in GABAergic mechanisms, and this may explain why its effects on bipolar disorder were not improved by the addition of memantine.

Bipolar Network News

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Comments on Treatment Conundrums

Clinical medicine is an art, and as medical pioneer Sir William Osler declared, often involves "skillful use of combinations." As the risks of inadequately treated illness increase, use of drugs with inadequately delineated benefit-to-risk ratios may be increasingly justified, such as in the case of memantine as recommended by Koukopoulos (see page one of this *BNN*).

Early, effective, preventive pharmacological treatment of the recurrent unipolar and bipolar disorders is essential. When this is not accomplished, an increasing number of unknowns enter the treatment equation, and as these illnesses enter more serious stages of recurrence, progression, and treatment resistance, the path to remission and wellness becomes increasingly complicated and relies on skillful management, guesswork, and good data from patients.

Given the multiple unknowns, patients can play an important role. They can be intimately involved in the decision-making and provide precise feedback in the formal or informal longitudinal monitoring of mood, sleep, other symptoms, and side effects so that whatever is tried can be accurately assessed.

A treatment with known efficacy is only worthwhile if it is effective in a given patient. When evidence of efficacy in the literature is unclear, the evidence of effectiveness of a given treatment regimen in a given individual becomes all the more important to discern. We recommend that patients chart their mood and medications using the National Institute of Mental Health's Life Charting Method (NIMH-LCM) or another type of personal calendar (we offer several on our website http://bipolarnews.org). This type of careful longitudinal monitoring method can help in the quest for an optimal treatment result.

Our old recommendation would appear particularly appropriate for this discussion. When things are going well (in the treatment of recurrent mood disorders), be conservative and stay the course. Conversely, when mood is not stabilized, be more radical and continue to explore new options until stability is achieved.

The Unfolding Story of Poor Response to Antidepressants in Bipolar Depression

The role of the traditional antidepressants in the treatment of depression in bipolar illness remains controversial. Despite mounting evidence that they are not efficacious in the treatment of bipolar depression, they are still among the most widely used treatments for that condition. At the first biennial conference of the International Society for Bipolar Disorders held in Istanbul this past March, Mark A. Frye and Shigenobu Kanba chaired a symposium on antidepressant-induced mania and individualized treatment for bipolar depression.

This editor (Robert M. Post) discussed factors influencing antidepressants' effects on patients with bipolar depression. In a recent meta-analysis, researchers Sidor and MacQueen reviewed data from studies encompassing 2373 patients with bipolar depression and found that antidepressants had no significant benefits over placebo on measures of response or remission. Pooled estimates for a thousand patients showed no increase in patients' risk of switching into mania after treatment with antidepressants. However, in a smaller sub-analysis, the risks of switching into mania following treatment with the older tricyclic antidepressants (43%) and venlafaxine (15%) was greater than the risk of switching after being treated with SSRIs (7%) or bupropion (5%).

There is a conundrum in the literature. While antidepressants don't work very well in bipolar depression, there is a small subgroup of patients who, having responded well to antidepressants for two months, benefit more from continuing the antidepressant treatment than from discontinuing the drug. Continued treatment with adjunctive antidepressants (added to regular treatment with a mood stabilizer or an atypical antipsychotic) was associated with fewer relapses into depression over the next year when the antidepressants were continued compared to when they were discontinued. Lori Altshuler et al. have published two uncontrolled studies to this effect, Russell Joffe et al. have published one, and a more recent randomized study of this by Nassir Ghaemi replicated some of the results in patients who had non-rapid-cycling bipolar disorder. **At the same time, the literature shows that there are a number of risk factors for switching into hypomania during antidepressant treatment in bipolar depression.**

Risk factors for switching into mania upon treatment with an antidepressant include: younger age, bipolar I compared to bipolar II, rapid cycling in the past year, mixed depression, use of older tricyclic antidepressants compared to newer second-generation antidepressants, use of noradrenergic active antidepressants compared to those that act on serotonin or dopamine, and a history of substance abuse. Another potentially confounding set of studies comes from J. Amsterdam at the University of Pennsylvania. Amsterdam found that in non-rapid-cycling patients with bipolar II disorder, long-term treatment with the antidepressant fluoxetine as monotherapy was more effective than either lithium or placebo in the treatment of bipolar depression and in preventing relapse.

One way of making sense of all the data is to consider that antidepressant response may be related to where a patient with depression falls on the spectrum of unipolar to bipolar disorder and what their rate of episode recurrence is. That is, in unipolar major depression, the antidepressants work well acutely and prophylactically with minimal risk of switching into mania. In non-rapid cycling bipolar II disorder, antidepressants may still be effective. However in rapid cycling and bipolar I disorder, antidepressants may not only be ineffective but may increase the risk of switching into mania.

Two studies (one by Mark Frye and one by Joe Goldberg) indicate that classically depressed patients with bipolar disorder who have even one or two symptoms typical of hypomania, such as racing thoughts or increased energy, are more likely to switch on antidepressants compared to those without this symptomatology. In addition, depressed patients with more typical mixed episodes, i.e. episodes that would meet the criteria for both a mania and depression, are also much more likely to experience switching on antidepressants.

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Memantine for Cognitive Dysfunction in Bipolar

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treat Alzheimer's, which increase acetylcholine by blocking acetylcholinesterase.

Memantine has also shown promising effects in enhancing the antidepressant effects of lamotrigine, a drug that inhibits glutamate release. Thus, the similar target of action by which lamotrigine (blocking glutamate release) and memantine (blocking glutamate receptors) operate suggest that the two drugs used in conjunction might produce additive effects in decreasing glutamate function. The current data suggest that memantine compared to placebo as an add-on to other agents in euthymic bipolar patients improves several measures of cognition as well.

New data published by Koukopoulos in the *Journal of Affective Disorders* in 2012 suggest that memantine (10-30mg/day) is an effective add-on treatment in severely ill patients with treatment-resistant bipolar disorder. Among those in Koukopoulos' study, 72.5% were much or very much improved, thus there is a strong rationale for considering this drug.

Antidepressants in Bipolar Depression: Risky but Sometimes Beneficial

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Studies by Vieta et al. and this editor Post and colleagues have shown that venlafaxine (which is active in blocking both serotonin and norepinephrine reuptake sites) is more likely to switch patients into mania then serotonin selective antidepressants (SSRIs) such as paroxetine (Paxil) or sertraline (Zoloft) as well as the dopamine active antidepressant bupropion (Wellbutrin). Rapid cycling patients were particularly likely to switch on venlafaxine (43% of rapid cyclers compared to 28% of non-rapid cyclers), and these rates of switching were much higher than those seen on bupropion or sertraline, which ranged from 8% to 17% in both rapid and non-rapid cycling patients.

A study called Emboldened II by Sue McElroy and colleagues compared acute response in bipolar depression among patients who were given monotherapy with either of two doses of the atypical antipsychotic quetiapine, the antidepressant paroxetine, or placebo. In this study both 300mg/day and 600mg/day doses of quetiapine were more effective than placebo, while paroxetine was not better than placebo. These data are consistent with those of Gary Sachs and colleagues in the treatment network STEP-BD, who found that adding the antidepressants bupropion or paroxetine to mood stabilizers in patients with bipolar depression was no more effective than adding placebo.

In an article published in the *Journal of Clinical Psychiatry* in 2012, this editor Post and associates from the Bipolar Collaborative Network assessed the number and duration of prior antidepressant trials in patients who were to enter treatment and follow-up studies in the network. (The average age at entry in these studies was 41.) These patients then received naturalistic treatment in the network, and many of them eventually experienced a good or excellent response for a period of at least 6 months. However, a substantial subgroup failed to respond when treated with the same number and intensity of medications. Analysis showed that **those patients who had previously had more antidepressant trials were less likely to achieve good long-term response to this prospective naturalistic treatment.** Patients' number of prior antidepressant trials remained an independent predictor of nonresponse whether or not the antidepressant had been used with a mood stabilizer, and even when other course-of-illness characteristics were considered. Other correlates of poor prospective long-term response were having had more than 20 prior episodes and having had a comorbid anxiety disorder.

Thus, the bulk of the data suggest that antidepressants may be no more acutely effective than placebo on average and may induce switching into mania in certain subgroups of patients even when used as adjuncts to mood stabilizers or antipsychotic drugs.

A new randomized study by Nassir Ghaemi may help explain why antidepressants remain a common treatment for bipolar depression among clinicians despite the poor results seen in published studies in the literature. Ghaemi found that in patients with bipolar disorder who had been stable for 2 months after the addition of antidepressants to their treatment regimen, continuing those antidepressants was associated with a delay in the duration of time until the next depressive episode compared to discontinuing the antidepressant. These results are similar to the non-randomized, observational findings of Altshuler et al. and Joffe et al. However, **in the subgroup of patients who were rapid cyclers, i.e. those who had had 4 or more episodes in the prior year, those patients randomized to antidepressant continuation experienced an exacerbation of their illness and an increased number of depressive recurrences compared to those who discontinued antidepressants.**

Thus the take-home message would be to use mood stabilizers and atypical antipsychotics before anti-depressants for the treatment of bipolar depression. If patients continue to be nonresponsive to these mood stabilizers or atypical antipsychotics alone and in combination and after trying different options within these drug categories, then it would seem reasonable to add an antidepressant to a mood stabilizer. For patients with non-rapid cycling illness, a physician might consider earlier use of antidepressants as adjuncts to mood stabilizers, but for those with rapid cycling bipolar disorder presenting in the depressed phase, antidepressants should clearly be deferred to later in the sequence or avoided altogether.

Meta-Analysis: Antidepressants For Bipolar Depression Not More Effective Than Placebo

In the next formal presentation of the symposium, Glenda MacQueen of the Department of Psychiatry at the University of Calgary also discussed her meta-analysis and the efficacy of antidepressants in patients with bipolar depression and the risk of switching into mania following treatment. Her conclusion was that the overall benefit-risk ratio for antidepressants in the treatment of bipolar depression is too low.

MacQueen listed other agents that do show statistical superiority over placebo in the treatment of bipolar depression. The list included the only monotherapy approved by the Federal Drug Administration (FDA) for bipolar depression, quetiapine (Seroquel). The combination of olanzapine and fluoxetine is also FDA-approved for bipolar depression. Lamotrigine is approved for prevention of depressive episodes in bipolar disorder, but not

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Using Genetic Data to Predict Response to Antidepressants

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for their acute treatment. However, some data support the efficacy of lamotrigine in acute depression. One study was positive, then a series of four additional industry-sponsored studies each found that lamotrigine was not significantly superior to placebo, but the meta-analysis of all the studies did show a significant improvement on the drug over placebo. A study undertaken at the National Institute of Mental Health by Mark Frye et al. also indicated that lamotrigine was superior to both gabapentin and placebo in treatment-resistant depressed patients.

Pharmacogenetics of Antidepressant Response and Switch

In the third presentation of the symposium, Mark Frye, Chairman of the Department of Psychiatry at the Mayo Clinic, discussed antidepressant-induced mania and the future possibilities of pharmacogenetics (using a profile of gene markers to predict the effectiveness and side effects of a drug for a given individual).

Serotonin is a neurotransmitter thought to be deficient in depression. After serotonin is released from a presynaptic neuron, it is taken back up by a transporter for storage and re-release the next time the neuron fires. Serotonin-selective antidepressants block the transporter, increasing levels of serotonin in the synapse. The serotonin reuptake transporter comes in 2 common forms—a short form, which is less effective as a transporter, and a long form that is more effective. In patients with unipolar depression, those who have the short form of the serotonin transporter are at greater risk of becoming depressed after stresses in childhood and adulthood. Some data suggest that those with the short form are also less likely to respond to antidepressants.

Frye and colleagues reviewed a series of studies that considered whether the short form of the serotonin transporter would similarly be associated with antidepressant nonresponse and/or switching into mania in patients with bipolar depression, but the literature is not yet sufficiently robust to come to strong conclusions. Nonetheless it is hoped that this kind of pharmacogenetic marker, along with the examination of clinical factors, neurobiological factors, and other common variations in genes, may ultimately be able to usher in an era of personalized medicine where predictions about the best medicine for a given individual can be made with greater confidence than is now currently possible.

NTRK2 May Be a Genetic Marker of Response to Lithium

At the 5th Biennial Conference of the International Society for Bipolar Disorders and the 67th Annual Meeting of the Society of Biological Psychiatry, John Kelsoe presented his research on personalized pharmacotherapy for bipolar disorder, describing genetic predictors of response to lithium.

Kelsoe found that a variant of the gene that codes for neurotrophic receptor type II (NTRK2), the receptor for brain-derived neurotrophic factor (BDNF), was associated with good response to lithium in patients with a family history of bipolar disorder or a history of euphoric mania. The "T" allele of rs1387923 was associated with better response to lithium retrospectively, and these results were replicated in a prospective study.

Editors Note: These data are among the first to indicate that genetic information could be used to make treatment decisions. Lithium increases BDNF and neurogenesis, thus it makes some sense that a variation in the BDNF receptor would affect clinical responsiveness to lithium.

In a similar vein, Janusz K. Rybakowski reported at the Society of Biological Psychiatry meeting on another possible predictor of long-term excellent response to lithium in bipolar disorder. Due to normal genetic variation, different people have different versions of BDNF. Rybakowski found that the patients with a version known as Val66Val who had bipolar disorder performed significantly better on the Wisconsin Card Sorting Test, which evaluates abstract reasoning. However, he found that patients with a methionine amino acid in the place of one of the valine amino acids (resulting in a Val66Met allele, which is associated with minor cognitive difficulties) showed significantly better response to preventative treatment with lithium. It is noteworthy that these excellent lithium responders also performed better on a complex neuropsychological battery than those who were less good responders to lithium. The good responders' performance on these tests was not different from healthy controls.

Editor's Note: These data add to the possibility that prediction of lithium response is linked to common gene variations in neuroprotective factors or their receptors. It is interesting that the patients with the Val66Met allele, which works less efficiently, show the best long-term response to lithium. This is consistent with the view that lithium, which increases BDNF, is most effective in those who have a sluggish functioning of their BDNF due to having the Met allele. As we have written before, those with the Met allele have slight decrements in working memory, and in animal models, those with the Met allele show deficits in long-term potentiation (LTP), which suggest problems with long-term memory. Thus, using lithium to increase BDNF function in those with a "sluggish" variation in their BDNF makes sense and may ultimately be clinically useful.

Genetic and Other Risk Factors for Onset of Bipolar Disorder

A Genetic Risk Factor For Bipolar Disorder: The CACNA1C Gene

In an abstract presented at the 5th Biennial Conference of the International Society for Bipolar Disorders, Sophia Frangou reported on the CACNA1C polymorphism, a genetic variation that has been associated with the risk of developing bipolar disorder in several genome-wide association studies that search for links between genes and illnesses. Frangou found that those people with the genetic variation had increased volume in some parts of the brain, including the right hypothalamus and the right amygdala, and decreased volume in others, including the putamen, as well as alterations in the functional connectivity of different cortical areas.

These data may be related to findings that calcium influx may play a role in bipolar disorder. In people with the genetic variation, the risk allele binds to a subunit of the voltage-dependent calcium channel, which modulates the influx of calcium from the outside to the inside the neuron.

Increased amounts of calcium are consistently found in the white cells and platelets of patients with bipolar disorder compared to controls. Moreover, the drug nimodipine, a dihydropyridine L-type calcium channel blocker, is effective in the prevention of manic and depressive episodes in a subgroup of patients, particularly those with cycling patterns that are ultra-rapid (4+ episodes per month) or ultradian (including a mood switch within a 24-hour period 4+ times per month). A large randomized study of patients with bipolar disorder presented by H.R. Chaudhry at the 2010 meeting of the Society of Biological Psychiatry also found that while lithium was associated with a 50% response rate, the combination of lithium and nimodipine was associated with a 73% response rate, again suggesting the additional efficacy of blocking L-type calcium channels.

Immune Abnormalities May Predict Onset of Bipolar Disorder in Children at High Risk

At the 5th Biennial Conference of the International Society for Bipolar Disorders E. Mesman discussed connections between immunity and bipolar disorder. Mesman and colleagues followed offspring of parents with confirmed bipolar disorder for 12 years and compared them to children in the general population. In the children of bipolar parents the researchers found higher levels of immune markers called cytokines (PTX3 and sCD25) in circulating monocytes, a type of white blood cell. In the children of bipolar parents they also found a high inflammatory setpoint in the monocytes. T-effector and T-regulatory cells were also different in the offspring of bipolar parents.

While these findings were present in children who had already become ill with bipolar disorder, they were also present in those who had yet to experience a mood disorder, suggesting that these immune and inflammatory markers may ultimately be an important risk marker for the onset of bipolar disorder.

Editor's Note: These are among the first studies suggesting that immune and inflammatory abnormalities may precede the onset of bipolar disorder. Many studies have shown that patients with active bipolar disorder show more inflammation, including increases in inflammatory markers interleukin 1 (IL-1), interleukin 6 (IL-6), C reactive protein (CRP), and tumor necrosis factor alpha (TNFa). The new data are of considerable importance not only because inflammation could serve as a marker of illness onset, but also because inflammation could become a potential target for therapeutics (i.e. using anti-inflammatory and immune-suppressing agents to treat bipolar disorder).

Sunlight Could Be a Geographic Risk Factor for Pediatric-Onset Bipolar Disorder

A number of factors appear to be associated with age of onset of bipolar disorder. Several studies have replicated the finding that those who experienced some adversity in childhood and who have a parent or parents with bipolar disorder are at increased risk for earlier onset of the illness. These risk factors are more prevalent in the United States than in many western European countries, and considerable data support the observation that the age of onset of bipolar illness is earlier in the US than in several European countries. However, childhood onsets of the illness are prevalent in Turkey and in Norway.

Researcher Mike Bauer raises another possibility in an abstract presented at the 5th Biennial Conference of the International Society for Bipolar Disorders. He examined the association between age of onset and sunlight in the environment in 24 different sites in 13 different countries. Solar insolation refers to the amount of electromagnetic energy striking the surface of the earth. Bauer found that **larger springtime maximum monthly increases in solar insolation were associated with younger ages of onset of bipolar disorder** ($p = 0.006$). These calculations were derived from NASA Surface Meteorology and Solar Energy databases for each location. The largest maximum monthly increases in solar insolation occurred in varied climates, including in Norway, Chile, and arid parts of California.

Earlier Age of Onset of Bipolar Illness in the US Compared to Europe

As we have previously reported in the *BNN*, the Bipolar Collaborative Network (including this editor Robert M. Post) found that patients from 4 sites in the United States had significantly earlier ages of onset of their bipolar illness compared to 3 sites in the Netherlands and Germany). These findings have been replicated by Frank Bellivier et al., who used a broader sample of European participants.

Bellivier's research group studied two large samples of bipolar I patients from the US (n= 2275) and from 14 countries in Europe (n= 3616). The researchers found 3 different distributions of age of onset, and patients from the US had a greater representation in the early age of onset subgroup. **Sixty-three percent of the sample from the US fell into the early-onset group versus 25% of those from Europe.** The mean age of onset of the early-onset subgroup was significantly lower in the US sample (14.5 +/- 4.9 years) than in the European sample (19 +/- 2.7 years).

Editor's Note: It is time for us to take these geographical differences in the frequency of early age of onset of bipolar disorder seriously. While some controversy has surrounded the diagnosis of bipolar illness in children, it becomes increasingly important to recognize that this bona fide, well-diagnosed illness is more common in children from the US than from many other countries.

Affected children should have careful clinical evaluation and, if the diagnosis warrants, definitive treatment. This should include both psychoeducational approaches; focused psychotherapies, including the family-focused therapy pioneered by Dave Miklowitz; and psychopharmacological intervention. When this kind of combined treatment is implemented, young patients who are treated with lithium, another mood stabilizer, or an atypical antipsychotic do much better than those who do not receive these consensus-based treatments.

Treatment algorithms for children of different ages with bipolar disorder are still being developed. However, it appears that in young and very young children, the atypical antipsychotics are often more effective than lithium or valproate monotherapy, as suggested in recent large randomized clinical trials. Initiating appropriate treatment is extremely important, since the duration of the untreated interval (that is, the time from illness onset to first treatment) is directly related to worse outcomes in adulthood. The longer the duration of untreated illness, the greater the severity of depression, the longer the duration of depression, and the greater the number of episodes an adult experiences.

As might be expected from the earlier age of onset of bipolar disorder, US patients also have a higher incidence of the major vulnerability factors for early onset – more genetic vulnerability (parents with bipolar disorder), more childhood stressors, and more stressors in the year prior to illness onset. Patients from the US also had a variety of other poor prognosis factors, including a higher degree of anxiety comorbidity, alcohol and substance abuse problems, a higher incidence of having more than 20 episodes over their lifetime, and a higher incidence of rapid cycling. All of these characteristics combine to produce worse outcomes in adult patients from the US compared to those from Europe. Earlier and more judicious treatment of the illness in the United States is needed to help ward off this more pernicious course of bipolar illness.

N-acetylcysteine (NAC) Also Effective in Unipolar Depression

In 2008, Michael Berk and colleagues showed that N-acetylcysteine (NAC) is effective as an adjunctive treatment for bipolar depression. At the 2012 meeting of the International Congress of Neuropsychopharmacology, **Berk reported that NAC (1000 mg twice a day) was also effective in unipolar depression,** significantly beating placebo in a randomized double-blind 12-week study.

Editor's Note: NAC has a broad spectrum of clinical efficacy in bipolar and unipolar depression, negative symptoms of schizophrenia (such as apathy and withdrawal), irritability in autism, trichotillomania (compulsive hair-pulling), gambling addiction, obsessive-compulsive disorder, and many substance-abuse disorders, such as cocaine, heroin, alcohol, and marijuana.

How can one substance do all this? NAC has antioxidant effects, it turns into glutathione (an antioxidant that is the body's main defense against oxidative stress and free radicals), it has neuroprotective effects (causing neurite sprouting), and it re-regulates glutamate in the reward area of the brain, the nucleus accumbens. Berk believes it is NAC's antioxidant properties that produce its positive effects in such a range of illnesses, while this editor (Robert M. Post) favors the glutamate mechanism (as discussed in BNN *Volume 14, Issue 1 from 2010 and Volume 16, Issue 1 from 2012) as an explanation of NAC's effects.*

Whatever its mechanism turns out to be, NAC is worthy of consideration as an adjunctive treatment. It is readily available from health food stores without a prescription, relatively inexpensive (less than $20 for 100 pills), and relatively well-tolerated. Minor gastrointestinal upsets were the most common reported side effect in the Berk's clinical trial. However, this editor has had one patient experience a worsening of psychosis.

Editor Robert M. Post's Personal Opinion About NAC

With the usual caveat that all treatment strategies discussed in the *BNN* must be evaluated and administered by a physician, it may be useful to consider adding NAC to a treatment regimen for a patient struggling with recurrent unipolar or bipolar depression, and/or a comorbid substance use disorder. Using conventional treatments early in the course of these disorders for acute treatment and for long-term prevention would be the first approach. For less than satisfactory acute responses, conventional adjunctive treatments (as recommended in treatment guidelines elsewhere) might be considered along with NAC, which in some cases can have a delayed onset of action. (Three months may be required to see maximal effects in bipolar disorder.)

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