

# Bipolar Network News

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*The following articles are based on reports from the Eighth International Conference on Bipolar Disorder in Pittsburgh, PA in June. It was well-attended, with about 800 participants including investigators, clinicians, advocacy members, and patients. New data from several large, randomized clinical trials were presented that are likely to have an important impact on clinical practice.*

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## Lithium and Valproate Most Highly Effective in Combination

### Prophylactic Efficacy of Lithium vs. Valproate vs. the Combination: BALANCE Study Finds the Combination is Slightly Superior to Lithium Alone, and Both are Superior to Valproate

John Geddes of Oxford University presented the results of the BALANCE study, a practical, randomized, open clinical trial of lithium and valproate at 41 sites across four countries in Europe.

The design included 459 patients (129 of whom dropped out either due to lack of tolerance of the lithium/valproate combination or withdrawal of consent). 330 patients who tolerated the combination during the 8-week preliminary phase were then randomized to lithium (0.4 – 1.0 mEq/L), valproate (target daily dose of 1250 mg/day) or the combination of the two drugs. The

patients averaged 43 years of age and had a mean of two prior hospitalizations.

The trial ran for 33 months, and the main outcome measure was the length of time well before requiring an intervention with a new drug or hospitalization. The study resulted in the finding that the combination of lithium and valproate was most effective, followed by lithium, which was non-significantly different from the combination. Valproate monotherapy was least effective, being both inferior to lithium ( $p < .05$ ) and to the combination ( $p < .002$ ).

Essentially the same results were found whether one observed the two

outcome measures (the need for an alteration in medication and incidence of hospitalization) separately or together. In addition, on a measure of time to first-needed intervention for emerging depression, the combination of the two drugs and lithium monotherapy again led to better outcomes than valproate.

Geddes reported that the two-year risk for relapse from the literature was estimated to be 34% in this type of population. Lithium reduced this down to 21%, valproate to 21%, and the combination down to 13%.

## Very Low Response Rates to Lithium or Valproate Monotherapy in Rapid Cyclers

After observing several studies of rapid cyclers at Case Western Reserve in the laboratory of Joseph Calabrese and colleagues, Dr. Keming Gao investigated reasons why so few patients stabilized on the combination of lithium and valproate over four consecutive weeks, such that they could be randomized to either monotherapy. At the Eighth International Conference on Bipolar Disorder, Gao presented an abstract on predictors of poor response to the combination treatment.

In a 2005 study by Calabrese et al. of those with rapid cycling bipolar illness (i.e., more than four episodes per year), 60 of 254 patients, or only 24%, met the initial criteria for four weeks of stability. In another cohort of rapid cycling patients who had comorbid substance abuse (Kemp et al., 2008), 31 of 149 or 21% of the patients stabilized sufficiently in order to be randomized to either drug.

Together, these two data suggest that in rapid cycling patients (with or without

substance abuse) there is some 75-80% likelihood of their not responding acutely to the combination of lithium and valproate.

In the Calabrese et al. study of those who were randomized to either drug, about 50% relapsed during the year-and-a-half on either lithium or valproate monotherapy. These data suggest that in a group of **patients with rapid cycling bipolar disorder, the vast minority (only some 12.5%) might do reasonably well in the long term on either monotherapy.**

Gao reported the reasons the 311 patients in the two studies combined did not meet criteria for randomization—42.2% did not comply; 21.2% had depression that was not responsive to the valproate/lithium combination; 20.3% had side effects that made the combination intolerable, and 11.3% had non-responsiveness due to manic symptomatology.

Predictors of those who would not achieve randomization status included: a recent history of substance abuse

disorder; female gender; a history of verbal abuse; and a late onset of the first depression. Surprisingly, a history of psychosis and older age at the time of randomization predicted stability on the combination of lithium and valproate.

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# Clinical Implications of the Lithium/Valproate Combination Data

In the BALANCE study mentioned on the front page, the lithium/valproate combination was superior to lithium monotherapy and vastly superior to valproate monotherapy. It would appear that **initiating prophylactic treatment with the combination might be the most optimal and conservative treatment strategy in the large majority of patients considering long-term prophylaxis for their bipolar illness** (average age 42 and after an average of two prior hospitalizations).

**This recommendation appears to be even more important in patients with risk factors for a difficult treatment course, including rapid cycling with or without substance abuse.** In these instances, 75-80% of the patients in the two studies at Case Western Reserve never even stabilized adequately enough on the lithium/valproate combination to be randomized to either monotherapy. When they were, half relapsed on either drug, suggesting that very few in these high-risk populations might ultimately do well for a year-and-a-half on monotherapy.

**Many investigators have long speculated that initiating prophylactic treatment with the combination from the outset was, in fact, the best approach for a substantial group of patients,** but this had not reached strong enough consensus to appear in general treatment guidelines. The new data reviewed here suggest that this threshold has now been reached, and clinicians and patients should definitely consider more aggressive treatment from the outset in order to attempt to forestall the likely relapses with either monotherapy.

It is also of interest that this large practical clinical trial (BALANCE) achieved results dissimilar from those of the randomized clinical trial of Bowden et al. (2000) comparing lithium, valproate, and placebo in a group of patients who had to show a high degree of mood stabilization prior to study entry, and thus were not at high risk for relapse. In that study, both lithium and valproate, widely known to be effective agents, were not more effective than placebo on the primary outcome measure of time to manic relapse. The results were even stranger for time to relapse in a depressive episode, wherein valproate was superior to lithium or placebo, and, surprisingly, lithium was significantly worse than placebo in preventing depressive relapses.

This editor would argue that the results of a randomized, non-blind, practical clinical trial (BALANCE) are more reliable and

provide more evidence consistent with both literature and with clinical experience than a more tightly controlled, double-blind, randomized, placebo-controlled clinical trial in a highly selected but perhaps non-representative population (Bowden et al. 2000). As John Marsh (2002), this editor, and many others have repeatedly argued, these data suggest the great clinical import and informativeness of "practical clinical trials" (trials that are easier to perform and less expensive) compared to formal placebo-controlled parallel group randomized clinical trials (RCT).

Even when RCTs are done well, they are not particularly informative about which patients are likely to respond, and what to do next in those not adequately responsive. There is a great need for clinical trial designs that are more clinically informative, and help patients and physicians make the difficult treatment choices that are encountered in virtually every phase of the longitudinal course of bipolar disorder, but rarely studied.

Moreover, as in other fields of medicine such as cancer chemotherapy, clinical trials in bipolar illness should include systematic comparative evaluation of different combinations of treatments and aim to develop practical methods for evaluating the comparative efficacy of complex treatment regimens.

## Bipolar Network News

**Editor-in-Chief:** Robert M. Post, MD  
**Managing Editor:** Moira McCauley

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.

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Dr. Post has consulted to or spoken for the following pharmaceutical companies: Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

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[mccauleybcn@gmail.com](mailto:mccauleybcn@gmail.com)  
BNN  
5415 W. Cedar Lane  
Suite 201B  
Bethesda, MD 20814

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## A Comparison of Lithium, Quetiapine, and Placebo in Long-Term Prophylaxis: The SPARKLE Study

Rick Weisler and Willem Nolen headed a clinical trial dubbed SPARKLE, which included randomizing 546 patients who had been partially stabilized on quetiapine to either lithium, quetiapine monotherapy, or placebo. In this study, **quetiapine monotherapy was marginally more effective than lithium on the primary outcome measure of time to any relapse, but both were extraordinarily more effective than those randomized to placebo, on which**

80% of the patients relapsed prior to the end of the study, which lasted 2 years.

Lithium and quetiapine monotherapy were not significantly different in time to relapse for either depression or mania. However, while the blood level range of lithium was targeted at 0.6 to 1.2 mEq/L, the average lithium level was only 0.63. **In those with lithium levels below 0.6 (n = 137), rates of relapse were significantly higher than in the 209 patients with higher lithium levels.**

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# Clinical Implications of the SPARKLE and BALANCE Data

As reviewed in previous *BNNs*, quetiapine is now approved for monotherapy in the acute treatment of both manic and depressive episodes. It has also been shown to be highly effective as an adjunct to lithium or valproate in the prevention of both manic and depressive episodes, and is FDA-indicated for that use as well.

The SPARKLE data now suggest that quetiapine monotherapy equals lithium for prevention of any mood episode, and both are more effective than placebo, on which 80% relapsed during the course of the trial.

As noted on page 2, this is essentially opposite to what happened in the placebo-controlled trial of Bowden and colleagues (2000), where long-term stabilization was required prior to randomization and only about 25% of the patients relapsed even when treated with placebo. This suggests that the general failure to enroll relatively ill or rapidly recurrent patients into the Bowden et al. study led to results that were largely uninterpretable.

One obvious implication of the SPARKLE study is that **lithium levels of 0.6 mEq/L or higher, if tolerated, are superior to lower levels**. To some extent these prospective controlled data are at variance with retrospective findings by Kleindienst and colleagues that higher doses of lithium were better for preventing manic episodes, but relatively lower doses were more effective for preventing depressions. Several other recent studies have not replicated the findings that lower doses/blood levels are more effective for depression prophylaxis. The SPARKLE study suggests the importance of trying to reach therapeutic levels.

However, as this writer has argued elsewhere, there is sufficient reason to consider maintaining lithium prophylaxis even when adequate blood levels cannot be achieved because of side-effects intolerance. In these instances, **one could hope, as revealed in animal studies, that lower doses would still achieve lithium's neurotrophic and neuroprotective effects and, potentially, even exert some of its anti-suicide effects as well**.

A recent study in Japan presented remarkable epidemiological data suggesting that suicide rates in 18 different municipalities of one prefecture varied inversely

with the degree of even trace amounts of lithium in the water supply (Ohgami et al., *British Journal of Psychiatry* 2009). Populations exposed to higher (although still trace) levels of lithium had the lowest rates of suicide, while other municipalities where trace amounts were lower had a higher incidence of suicide. It had previously been estimated in some U.S. states with higher trace levels of lithium that one would have to drink a tank car full of water in order to achieve therapeutic

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*Both lithium and quetiapine (Seroquel) are superior to placebo in preventing relapse in a two-year study.*

*Higher lithium levels (over 0.6 mEq/L) were better than lower levels.*

*Quetiapine is also FDA approved as an adjunct to lithium or valproate for prophylaxis.*

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lithium levels. This new study, if it proves valid, suggests that normal intake of **trace amounts of lithium may still have clinically relevant effects in preventing suicide in the general population**. Terao et al. (2009) also summarized the potential implications of naturally occurring trace levels of lithium reducing suicide.

These data from Japan provide further indirect support for the general recommendation of this investigator that patients be maintained on essentially any level of lithium that they are able to tolerate without uncomfortable or disconcerting side effects. This is further supported by the positive lithium data in the BALANCE study on the front page of this *BNN*, indicating that lithium is significantly better than valproate in long-term prophylaxis, and

the combination (although in that instance, targeted to achieve therapeutic levels) was vastly better than valproate monotherapy.

Quetiapine monotherapy now appears to be a potential appropriate choice of treatment for some patients because it is associated with a 70% reduction in risk of relapse compared with placebo, and is able to maintain a relatively large number of patients without relapse over a period of 2 years. These new SPARKLE data taken in conjunction with the previous FDA approval of quetiapine as an adjunct to lithium and valproate clearly support its efficacy in prevention of both manic and depressive episodes.

Based on the BALANCE data, **Geddes recommends starting most moderate-risk patients on the combination of lithium and valproate**.

However, he recommends considering lithium monotherapy in a 21-year-old woman with other predictors of a positive response to lithium, because one would want to **avoid valproate in women of child-bearing age**. This is because there is a risk of malformations such as *spina bifida* and other major problems in some 20% of the fetuses delivered from mothers who were pregnant on valproate. This also now includes average drop in I.Q. of nine points on valproate compared to other anticonvulsants, indicating that infants exposed to valproate may be at high risk for substantial developmental delay. Thus, if a young woman who was treated with lithium began to experience breakthrough manic episodes and had a profile of comorbid anxiety and insomnia, quetiapine might be an ideal adjunct.

In patients with predominance of low energy and hypersomnic depressive breakthroughs on lithium, adjunctive lamotrigine might, in those instances, be considered instead.

In considering long-term prophylaxis, obviously issues of tolerability must be integrated with those of efficacy and relative effectiveness. This is all the more the case in light of data reported in previous *BNNs* of a catastrophically large loss of years of life expectancy to medical mortality in patients with serious mental illness.



## Treatment with More Drugs Can Produce Fewer Side Effects

This editor has emphasized that avoiding side effects is one rationale for the use of complex combination therapy in the treatment of patients with bipolar disorder. There are some claims that treatment with more medications in combination leads to greater numbers of side effects. However, this claim is generally not supported by careful clinical observations when doses of the combinations of drugs are carefully titrated so that the side

effects of each new drug in the entire regimen are carefully monitored and minimized. If conventional doses of two drugs are administered without such individual titration against side effects, the side-effects burden may exceed that of either drug alone.

It is easy to visualize that pushing the dose of lithium monotherapy to higher and higher levels in hopes of achieving more complete therapeutic responsiveness would normally engender greater

numbers of side effects (tremor, G.I. upset, diarrhea, etc.) than if the lithium dose titration is stopped when side effects begin to emerge, and the rest of the required therapeutic efficacy is achieved by adding another agent, also below its side-effects threshold. There is now systematic evidence in support of this clinical viewpoint as reported in the pink insert below.

### Polytherapy May Result in Better Cognitive Function than Monotherapy

Bilik and collaborators from Turkey presented poster 21 in *Bipolar Disorders*, vol. 11 (supplement 1), "Neurocognitive functions in euthymic bipolar patients on mono- versus poly-therapy in comparison to healthy controls." These researchers found that euthymic bipolar patients had greater neurocognitive performance deficits compared with normal volunteer controls, as has been reported by many other groups, and performance was positively correlated with the amount of prior education and negatively correlated with the duration of illness.

When these latter two variables were controlled in a multiple regression analysis, it was revealed that, counter to the investigators' hypothesis, patients on monotherapy did worse than patients on polypharmacy on a test in which they were asked to remember a series of numbers and repeat it backwards.

This is one of the first studies to directly support our clinical management suggestions that more drugs may be associated with equal or better efficacy and fewer side effects when carefully administered and individually titrated. Utilizing more drugs with different mechanisms of action is

widely practiced in most areas of therapeutics of multiple illnesses, including treatment of rheumatoid arthritis (wherein polytherapy is directly recommended), cancer chemotherapy, tuberculosis, AIDs, hypertension, and coronary artery disease.

Thus, it is this editor's belief that **patients should not be concerned about the number of medicines they are taking, but instead with how well a treatment regimen is working for them and whether or not it conveys an acceptable side-effects burden.** A large number of drugs in combination is often required to stabilize individual patients, and if there is an absence of side effects, one should not reduce number of medications willy-nilly without a very cogent rationale. Too often we have seen patients deteriorate when one of the medications in a complex regime was withdrawn, simply for medication regimen "simplification." In general, and in the relative absence of side effects, our rule of thumb (in the absence of contradictory data otherwise) is to continue to use the regimen that was required to achieve acute mood stabilization into long-term continuation therapy and prophylaxis.

### Carbamazepine and Oxcarbazepine Effective Adjuncts to Lithium for BP I and II

Juruena presented Poster 105, "Residual symptoms in bipolar I and II: oxcarbazepine and carbamazepine as add-on treatment to lithium in a double-blind, randomized trial lasting eight weeks." Mean final dose for oxcarbazepine (OXC) was 637 mg/day and for carbamazepine (CBZ) was 673.5 mg/day.

Both OXC and CBZ were effective in reducing scores from baseline to endpoint, although OXC was more effective than CBZ at weeks 4 and 8, and resulted in significantly greater reduction in measures of symptom severity including YMRS, HDRS-21, MADRAS, CGI-S, and CGI-I scores from baseline to week four and week eight. The authors conclude that this pilot study suggests that OXC as adjunctive therapy to lithium may be effective in both the acute and long-term treatment of bipolar I and II disorder.

Editor's Note: *These data are somewhat surprising because CBZ is more potent than OXC, and one-and-a-half times the dose of CBZ is required for OXC to have equal effectiveness. Despite relatively similar doses (i.e. relatively low doses of OXC compared to CBZ), OXC was superior to CBZ as an adjunct to lithium. This interesting study deserves further exploration and replication, because prior monotherapy studies would have suggested the superiority of CBZ over OXC, particularly in patients with more severe manic presentations.*

## Atypical Antipsychotics

### Ziprasidone effective with mood stabilizers without causing weight gain

Bowden and collaborators presented poster 27, "A six-month randomized placebo-controlled, double-blind trial of a mood stabilizer with or without ziprasidone in subjects with bipolar I disorder." Patients who were on lithium and divalproex who had been stabilized for eight consecutive weeks with open label ziprasidone (80-160 mg/day) were randomized to ziprasidone continuation or placebo substitution.

Time to intervention was significantly different in favor of ziprasidone, and time to discontinuation for any reason also favored ziprasidone. In the first open label period, sedation (22.9%) and somnolence (17%) were the most common side effects, while in the double-blind period, only tremor occurred more frequently in the ziprasidone group (6.3%) than in the placebo group (3.6%).

Notably, in this six-month clinical trial, weight gain was not significantly different, and laboratory values related to the metabolic syndrome also did not change significantly. These data continue to support the excellent tolerability of ziprasidone compared with some of the other atypicals which are associated with weight gain and several aspects of the metabolic syndrome, including increases in cholesterol, triglycerides, and glucose (or insulin insensitivity).

### Ziprasidone monotherapy useful in pediatric bipolar with no weight gain

Correll et al. reported in poster 49 that ziprasidone monotherapy when compared with placebo was not only more effective than placebo in the treatment of pediatric bipolar patients between the ages of 10 and 17, but it was also not associated with increases in body weight or other cardio-metabolic alterations.

### Risperidone injections better than oral atypical antipsychotics for bipolar disorder

Chengappa of Pittsburgh presented poster 44, "Fifteen month random assignment effectiveness trial of long-acting risperidone injections versus oral atypical antipsychotic agents in persons with bipolar disorder." Long-acting risperidone injections were associated with patients remaining longer in treatment and experiencing significantly fewer clinical events.

### Atypicals better than mood stabilizers for manic youth and adults, but may increase side effects

In poster 48, Correll et al. gave a literature review of the relative efficacy and tolerability of antipsychotics and mood stabilizers in adult and pediatric patients with bipolar I mania in a comparative analysis of acute, randomized, placebo-controlled trials.

The findings show that in manic youth and adults, second-generation atypical antipsychotics appeared more efficacious than mood stabilizers (lithium, divalproex, or topiramate). However, many would argue that topiramate should not be included as a mood stabilizer because it has been repeatedly shown not to have acute antimanic efficacy in adults.

Nonetheless, Correll et al. reported that the effect sizes were larger and the number needed to treat (NNT) (a measure of effect size that calculates the number of patients needed to be treated in order to get one more patient better than would be achieved with placebo) were lower in youth treated with second-generation antipsychotics compared with adults. However, second-generation antipsychotics had greater adverse effects in youth compared with adults, and compared to placebo led to more side effects than did mood stabilizers.

### Aripiprazole better than placebo for BP depression in selected subgroups

Two sub-analyses were conducted of studies in which aripiprazole monotherapy failed to show a significant separation from placebo in the treatment of bipolar I depression. The first analysis, poster 141, suggested that those with **more severe core depressive symptoms at baseline showed a positive separation** of aripiprazole compared with placebo. In the other secondary analysis, **those treated with lower doses of aripiprazole (5 & 10 mg/day)** also significantly showed separation from placebo.

Editor's Note: *These data help confirm the initial suggestion that the reason why aripiprazole failed to sustain positive effects over placebo in the original large industry-sponsored trials in bipolar depression was because of higher initial dosing and higher targeted final doses than those used in the aripiprazole augmentation studies in unipolar depression.*

*In unipolar depression, patients were started on 2 or 5 mg with a target of 5 to 10 mg, and about 90% of patients completed the clinical trial. In contrast, in the two bipolar I depression aripiprazole monotherapy studies that failed to separate from placebo at end-point, initial doses were 10 to 15 mg/day with a target of 25-30 mg, and 50% of the patients dropped out of the trial by the end of the eight-week study.*

*Taken together, the adjunctive studies in unipolar depression and these secondary analyses of aripiprazole monotherapy in bipolar depression suggest that starting depressed patients on lower doses of drug than the 15-20 mg/day manic and schizophrenic patients are started on, and moving towards higher targeted levels of 20-40 mg/day may produce better tolerability and less akathisia (restless legs). This is likely the case because depressed patients, with their hypothetical low brain dopamine levels, may secondarily engender dopaminergic*

*Continued on Page 7*



## Antidepressants

### Pregabalin (Lyrica) promising for treatment-resistant BP and helpful for anxiety and pain

In an uncontrolled clinical trial, Schaffer et al. reported on the potentially promising effects of pregabalin (Lyrica) as adjunctive treatment for outpatients with treatment-resistant bipolar disorder. Of the 58 patients so treated, 41 were rated as responders.

Fifteen (or 44%) of the nonresponders discontinued the trial because of overactivation; ten (29%) because of increased appetite and weight gain; and five (15%) due to lack of efficacy. Although patients were taking an average of 3.3 other psychiatric medications, no adverse drug-drug reactions were reported.

Editor's Note: To some extent these results appear to parallel those with gabapentin (Neurontin). Gabapentin monotherapy does not appear to have acute antimanic efficacy, and it was no more effective than placebo in treatment-refractory patients in a study in which this editor participated, as reported by Frye et al. (2000) and Obrocea et al. (2002). We also saw a tendency for some

patients to have increased dysphoric activation of their mania during treatment with gabapentin. However, Vieta and colleagues (2006) reported in an adjunctive study of gabapentin vs. placebo that gabapentin was significantly more efficacious on several outcome measures, and it remains to be seen whether either gabapentin or pregabalin will have a prominent role in the treatment of bipolar depression.

Both gabapentin and pregabalin have notable anti-anxiety and antinociceptive (anti-pain) effects, and they may be particularly useful for bipolar patients with these types of comorbidities. Both increase levels of the major inhibitory neurotransmitter in brain, gamma-aminobutyric acid (GABA), and both drugs are also potent on the alpha-2-delta subunit of the L-type calcium channel, which is potentially related to these drugs' anti-anxiety and antinociceptive effects. Further study of both of these compounds is warranted in order to better place their role in the therapeutic armamentarium for the treatment of bipolar disorder.

### Intravenous administration of fish oil may have a rapid onset of antidepressant effects in bipolar depression

Severus et al. presented poster 180, "Intravenous omega-3 fatty acids in the acute treatment of inpatients with bipolar depression – a pilot study." They found that administration of a fish oil emulsion with a high content of long-chain omega-3 fatty acids (Omegavent™) resulted in rapid onset (within three days) of clinical improvement on most measures. They suggested that randomized controlled studies were indicated.

Editor's Note: Controlled trials are clearly needed, because even with oral administration of omega-3 fatty acids, both positive and negative trials exist in the literature. Overall, the preponderance of

trials using 1-2 g of the active ingredient (either EPA or the combination of EPA and DHA) are generally positive, while a study in which this editor participated of 6 gms EPA was one of the largest studies to date but did not show statistically significant improvement on active EPA compared with placebo (Keck et al. 2003). There was an interaction with age, in that patients older than 45 actually were worse on EPA compared with placebo, while those younger than 45 did, in fact, improve more on 6 gms of EPA compared to placebo. Thus, age of the subject population as well as dose and now oral vs. intravenous formulations all deserve further study in the treatment of bipolar depression.

### Uridine effective for patients with 10+ prior episodes

Sachs and colleagues presented poster 167, "Uridine treatment of bipolar I depression: results of a pilot study." Thirty-nine patients were randomized and received 2-4 g twice daily (b.i.d.) of the pyrimidine uridine or placebo (N=44). Better outcomes were seen with uridine from baseline to week six, with significant improvement beginning at week two.

Those with less than ten prior episodes did better on placebo compared with those who had greater than ten episodes. Conversely, **uridine response was greater (-17.85) for subjects with greater than ten prior episodes**, and less (-13.12) for subjects with less than ten prior mood episodes. Thus, uridine was particularly more effective for those with established recurrent disease, and there was a >8 point improvement on the MADRAS ratings in response to uridine compared with placebo. Side effects were mild, and mild G.I. events were the only treatment-associated adverse event.

Editor's Note: These data are particularly striking and of great interest not only in terms of efficacy compared with placebo in bipolar I depression, but also in terms of greater effects of uridine in those with the usual markers of treatment-refractory illness, i.e. more prior episodes. These data deserve rapid replication and such a phase II study is currently in progress.

Another pyrimidine, cytidine, was reported to have acute antidepressant effects by this same group (see BNN 2008, Vol 12, issue #3), and, together, these studies open up a possible novel pathway of treatment of bipolar depression. The results remain to be further established in follow-up clinical trials, but offer promise for a mechanistically new approach to bipolar depressive illness, which is all too often difficult to treat. Better response in highly recurrent patients is very unusual, and opposite to that seen with lamotrigine and naturalistic treatment in general.

## Poor results for Levetiracetam augmentation in BP

In contrast to the promising findings with oxcarbazepine (Trileptal) reported on page 4, Faricicek and associates from Yale University reported in poster 170 that levetiracetam (Keppra) was not effective in the management of bipolar depression in a placebo-controlled study in which add-on levetiracetam (up to 2000 mg/day) was used for six weeks.

This negative study mirrors that of Post et al. (2005) who also did not find highly promising effects of levetiracetam augmentation in open clinical studies in either mania or depression.

## Memantine may improve attention in euthymic patients

Neurocognitive deficits, as we noted on page 4, are sometimes prominent in patients with bipolar disorder who are currently euthymic, but have substantial prior histories of multiple episodes. In an attempt to better treat these disturbances, Segal, as reported in poster 179, examined memantine (Nemenda) titrated to 20 mg/day or placebo for 12 weeks. On most scores, the groups did not differ; however, those who received memantine had greater improvement on an attention index compared with those on placebo.

## Intravenous scopolamine has rapid-onset antidepressant effects in bipolar patients

Wayne Drevets reported on cholinergic alterations in bipolar patients. An excess of cholinergic activity was suggested by many markers, and is correlated with the presence of abnormal genes for the cholinergic system and with illness severity. Furey and Drevets reported in *Archives of General Psychiatry* that the anticholinergic drug scopolamine given intravenously at 4 µg/kg was associated with rapid onset of antidepressant effects.

## Narcolepsy medication Ar-modafinil for use in major depression: more study needed

Joe Calabrese from Case Western Reserve University, Cleveland, presented poster 35, "Adjunctive ar-modafinil for major depression associated with bipolar I disorder: a randomized, double-blind, placebo controlled study." Ar-modafinil is a non-amphetamine wakefulness-producing medication for narcolepsy and is the longer lasting isomer of modafinil (Provigil). Previously, Frye

and collaborators in the Bipolar Collaborative Network had reported in the *American Journal of Psychiatry* (2007) that modafinil significantly improved residual depression, fatigue, and inattention in depressed patients with bipolar disorder. This new study of ar-modafinil provided trends in the same direction, but the results were of marginal statistical significance and larger studies are planned.

## Aripiprazole (cont.)

*Continued from Page 5*

*receptor hypersensitivity, and since aripiprazole is a partial dopamine agonist, this dopaminergic agent may produce the side effects of akathisia and restlessness.*

*In contrast, mania and schizophrenia, with their hypothetical dopamine excesses, would be associated with compensatory dopamine receptor subsensitivity, and even high doses of the partial agonist aripiprazole would then not be associated with prominent restlessness or akathisia.*

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