

# Bipolar Network News

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## New Data Affirm Continuity of Childhood and Adult Bipolar Disorder

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In the last issue of the BNN (Vol. 12, Issue 2, 2008), we highlighted new findings in the presentation and treatment of childhood onset bipolar illness. A major diagnostic controversy about the syndrome in young children remained: whether it was part of a bipolar illness spectrum and would have continuity with episodes of mania and depression as they appear in adults.

The data of Barbara Geller et al (*Archives of General Psychiatry*, Vol. 65, Oct 2008, pp. 1125-1133) now provide clear answers in the affirmative.

The researchers followed children (mean age=11.1 years) with a diagnosis of BP-I mania for an average of 8 years. Of those who reached age 18 or older by the study's conclusion, a large portion did exhibit typical adult manic episodes.

Subjects were ill in an episode 60.2% of the weeks in the 8 years of followup, indicating very considerable continuing morbidity and dysfunction despite treatment as usual in the community. While 87.8% recovered (for 2 months) from their mania, 73.3% again relapsed into mania.

Of the subjects reaching age 18 or older during followup, 44.4% had manic episodes, which was 13- to 44- fold higher incidence than expected in the general population. None of these patients had engaged in substance abuse at the time of study entry, but substance abuse increased to 35.2% in those 18 and older. Thus not only were the children severely affected by their affective disorder, but more than a third acquired a second difficult-to-treat chronic illness, i.e. a substance disorder.

Early onset bipolar illness and the presence of substance abuse comorbidity are both currently associated with a more severe and difficult-to-treat course of bipolar disorder in adults. The need

for earlier and more effective treatment strategies is obvious, and now Geller and associates (and Ellen Leibenluft in an editorial about the findings in the same publication) add their names to a long list of other investigators calling for more treatment-related research in this underserved and under-investigated area. Given the now clear long-term adverse implications of this diagnosis in children (i.e. three-fifths of their life so far spent ill), the need is now even more pressing.

## Ultra-Ultra Rapid Cycling Also Shows Continuity Into Adulthood

A second area of controversy in childhood-onset bipolar disorder had been whether the high incidence of ultra-ultra rapid (or ultradian) cycling, meaning distinct mood shifts from manic to depressive within a single day, rendered the illness different from the adult variety. Geller et al found 78.3% showed ultradian cycling at entry and 87% showed this pattern during followup. Subjects averaged 3.7 +/- 2.1 cycles/day.

In addition, 60.9% were psychotic (hallucinations or delusions) at baseline and 73.0% were so during followup.

Thus, in addition to this study establishing continuity of childhood-onset mania into adulthood, the study also indicated persistence of ultra-ultra fast cycling frequencies and of psychotic elements.

While there are still some elements of diagnostic controversy to be clarified (such as whether those with pure irritability belong in the bipolar spectrum), the Geller et al 2008 article, along with many other prospective studies in the literature, should completely silence those who claim childhood-onset mania does not exist.

It is time to move away from the diagnostic controversy and toward the critical questions of which individuals

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and which subtypes of children within the bipolar spectrum respond best to which treatments. This should include those with BP-NOS (not otherwise specified), who experience episodes lasting less than the 4 days duration required for a diagnosis of BP-II, as these children are extremely difficult to stabilize. Treatments for those who may fall outside of the spectrum of formal bipolar diagnoses (i.e. those with severe mood dysregulation (SMD)) also require rapid definition.

It is not clear how the children in the Geller et al (2008) follow-up cohort were treated in the community, but one could hope that with greater application of consensus and guideline-based treatment, the illness would follow a more benign course than it did for these individuals. While we know the general outlines of such recommended treatment, i.e. mood stabilizers and atypical antipsychotics (prior to psychomotor stimulants or antidepressants), the details, appropriate sequencing of treatments, and optimal use of drugs in combination is virtually unstudied. This shameful situation, based only on allocation of resources (rather than a dearth of scientific discoveries), should be corrected immediately.

# The Atypical Antipsychotic Quetiapine (Seroquel)

## Quetiapine Effective in Acute Mania & Depression and Now in Prophylaxis of Both Types of Episodes

At the Society of Biological Psychiatry meeting in Washington, DC in May, Martin Brecher and others reported on the prophylactic effects of quetiapine compared with placebo as an adjunctive treatment to either lithium or valproate therapy. Both 400 and 800 mg of quetiapine were

superior to placebo in preventing manic and depressive episodes.

*Editor's Note: As noted above, quetiapine is effective in monotherapy of both acute mania and acute depression. Now that it shows robust effects in prophylaxis as augmentation therapy, quetiapine emerges as the atypical with the best record for mood stabilization*

*with both acute and prophylactic efficacy in manic and depressive phases of the illness. In addition, quetiapine (150 mg/day) is effective in unipolar depression, and other data support the efficacy of quetiapine monotherapy in generalized anxiety disorder, indicating a very broad spectrum of antidepressant and anti-anxiety effects of this agent.*

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### 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.

Although the editors of the BNN have made every effort to report accurate information, much of the work detailed here is in summary 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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Send any comments or suggestions to: To be placed on the mailing list, please contact us at:

**BNN**  
5415 W. Cedar Lane  
Suite 201B  
Bethesda, MD 20814

**BNN**  
PO Box 18  
Beltsville, MD 20704-0018

**Website:** www.bipolarnews.org  
**Email:** info@bipolarnews.org

## Efficacy in Unipolar Depression and Generalized Anxiety Disorder

As noted in a previous BNN, quetiapine appears to have a very broad clinical spectrum of action. This now includes unequivocal evidence (double blind, placebo controlled results replicated across at least two studies) of efficacy in mania in adults and in children and adolescents (in addition to efficacy in the acute and maintenance treatment of schizophrenia). Quetiapine monotherapy is also effective in acute bipolar depression.

As noted above, when used in combination with lithium or valproate, quetiapine is significantly more effective than placebo in preventing both manias and depressions. **Now, in addition to this broad spectrum of action in bipolar illness, the drug has been reported effective in both unipolar depression and generalized anxiety disorder.**

The two most prominent side effects of quetiapine are: 1) sedation and somnolence, and 2) weight gain and the potential for diabetes mellitus. Sedation can often be assessed with a 25 mg test dose administered in the evening to see if a high functioning patient has trouble getting out of bed the next morning, as suggested by Joe

Calabrese of Case Western Reserve University. (This can be done on a Friday or Saturday evening when a patient may have fewer work or academic commitments the following day.) If sedation is not problematic, the dose can be escalated rapidly. Weight gain and the possible induction of other elements of the metabolic syndrome deserve close monitoring. The metabolic syndrome is considered present if three of the following five factors occur: increased waist circumference, increased triglycerides, increased low-density lipoproteins (cholesterol), high blood pressure, and glucose intolerance (or outright diabetes mellitus).

Allen Young of the University of British Columbia in Vancouver reported another placebo-controlled trial of quetiapine compared with lithium and placebo in adults with bipolar depression. **Not only was quetiapine, in doses of 300 and 600 mg/day, more effective than placebo, but was also more effective than lithium, which was not significantly better than placebo.** Quetiapine was effective in both bipolar I and bipolar II depressive disorder in this and other studies.

## Mechanisms of Action and Dose-Response Effects

New data suggest possible biochemical mechanisms of quetiapine and its active metabolite, which could explain the range of antidepressant and antianxiety effects of the drug in addition to its known effects in mania and schizophrenia.

It is likely that the antimanic and antipsychotic effects of quetiapine reside in its ability to weakly inhibit dopamine D<sub>2</sub> receptors, as many other typical and atypical antipsychotic drugs do. However, the side-effects profile does not include prolactin increases or major problems with extrapyramidal side effects, which affect the smooth modulation of motor movements, because the drug rapidly dissociates from dopamine receptors and does not produce a full blockade.

Quetiapine also blocks serotonin 5HT<sub>2A</sub> receptors, like many other atypical antipsychotics and like drugs trazodone (Desyrel) and nefazodone (Serzone), where this effect

is thought to account for increasing slow-wave or deep phases of sleep. The blockade of serotonin 5HT<sub>2A</sub> receptors is also thought to contribute to antidepressant effects of the compound.

A desalkyl metabolite called norquetiapine has been discovered, which is potent in blocking the reuptake of norepinephrine, similar to other antidepressants such as desipramine (DMI) or (Norpramin) and nortriptyline (Pamelor), which are quite potent and selective in blocking norepinephrine reuptake.

The norquetiapine metabolite is also a partial agonist at serotonin 5HT<sub>1A</sub> receptors, which are thought to mediate the antidepressant and antianxiety effects of buspirone (Buspar) and other compounds. The metabolite is quite potent in blocking 5HT<sub>2C</sub> receptors, too. This is of particular interest since blocking this system increases release of forebrain norepinephrine and dopamine, which are thought to be

deficient in depression. Since activation of 5HT<sub>2C</sub> receptors normally inhibits the release of norepinephrine and dopamine, the fact that norquetiapine is an antagonist at 5HT<sub>2C</sub> receptors results in disinhibition and increased release of these important amine compounds.

There are some dose-response relationships that appear to differ in quetiapine's clinical spectrum of action. In studies of its efficacy **in generalized anxiety disorder, both 150 and 300 mg were more effective than placebo. The antidepressant dose ranges have typically been 300 and 600 mg/day**, with single nighttime dosing, although 600 mg was not significantly superior to 300 mg, suggesting that antidepressant dosing at or below the 300 mg range may be optimal. **Antimanic and antipsychotic effects of the drug are thought to occur at even higher dose ranges of 600 to 800 mg/day.**

## Quetiapine's Likely Mechanisms of Action in Different Syndromes

### Efficacy in Mania & Schizophrenia

Dopamine D<sub>2</sub> blockade (weak, no prolactin increase)

### Efficacy in Depression & Anxiety

\*Blockade of Norepinephrine reuptake via potent antagonism of the NE transporter (NET)

\*Partial Agonism of Serotonin 5HT<sub>1A</sub> receptors

\*Blockade of 5HT<sub>2C</sub> receptors (increasing release of NE & DA in forebrain)

Blockade of 5HT<sub>2A</sub> receptors (increasing slow wave sleep)

\* = effects of Norquetiapine



# Updates on Potential New Treatments

## Ziprasidone (Geodon) in Pediatric Bipolar

Melissa P. DelBello reported at the Society of Biological Psychiatry meeting in May in Washington, DC that children aged 10 to 17 with bipolar I disorder responded significantly better to ziprasidone (80-160 mg/day) than placebo.

In 150 subjects randomized to ziprasidone, the change from baseline in the Young Mania Rating Scale score was -13.83; in the 88 subjects randomized to placebo, it was -8.61 ( $p = 0.0005$ ). Side effects included sedation in 22%, somnolence in 25%, nausea in 13%, fatigue in 13%, and dizziness in 11%, although no changes in BMI, lipids, liver enzymes, or glucose levels were observed. **QTc prolongation on the EKG, which at some durations is considered a sign of increased risk for cardiac arrhythmias, was not a significant problem and occurred only in one subject.**

*Editor's Note: These data are particularly important because ziprasidone is one of the best-tolerated atypical antipsychotics for adults and children, and*

*is now unequivocally effective in childhood-onset mania. Its mild side-effects profile is particularly notable and more benign than that of olanzapine, which also shows efficacy in pediatric mania.*

Leslie Citrome at New York University School of Medicine reported that in schizophrenia **higher doses of ziprasidone (120-160 mg/day) were associated with significantly lower all-cause medication discontinuation than placebo and lower doses (40-80 mg/day).**

*Editor's Note: These data continue to suggest the dose-related efficacy of ziprasidone in mania and acute schizophrenia, with better tolerability of higher than lower doses. One possible explanation for this is that ziprasidone works on 5HT<sub>2C</sub> receptors, which release dopamine and norepinephrine into the prefrontal cortex. At low doses of ziprasidone, this might be associated with some degree of activation. At higher doses, ziprasidone would block the dopamine receptor and counter the tendency for agitation or activation.*

## Extending the Rapid-Onset Antidepressant Effects of Ketamine

Many researchers have found a rapid onset of antidepressant effect in unipolar depressed patients within several hours of administering intravenous ketamine, a glutamate antagonist, with improvement often lasting some five days. Researchers are eager to determine how this effect might be sustained.

Marijeann het Rot from Dennis Charney's group at Mount Sinai School of Medicine reported the latest exploration at the Society of Biological Psychiatry meeting held in May in Washington, DC. **After an initial dose of ketamine was shown to produce antidepressant effects, five additional doses (0.5 mg/kg i.v.) were administered on days 1, 5, 8,**

**10, and 12. Subjects maintained improvement throughout the two-week period of infusions and for another 14 days thereafter.** Adverse effects occurring after each infusion diminished with each successive infusion and were generally mild in severity.

*Editor's Note: This group and that from the NIMH are also exploring the ability to maintain acute onset of ketamine effects with another glutamate-active drug, riluzole, and double-blind, placebo controlled studies are currently being conducted. Ketamine is being explored in bipolar depression, and may have potential to induce rapid onset antidepressant effects in those with treatment-refractory depression.*

## Cytidine in Bipolar Depression

At the Biological Psychiatry annual meeting this past May in Washington, DC, Sujung J. Yoon and others from Bruce Cohen and Perry Renshaw's group at Harvard reported a potential new treatment for bipolar depression with the pyrimidine cytidine, used as an adjunct to valproate.

Mitochondria are the energy factories of cells, and there is evidence of mitochondrial dysfunction in bipolar patients, leading to an energy imbalance. One of mitochondria's functions is to synthesize pyrimidines. The researchers postulated that administering pyrimidine orally would reduce energy requirements of the mitochondria and fix the energy imbalance in bipolar patients.

They randomized 65 bipolar depressed adults to valproate with either placebo or oral cytidine (a pyrimidine known to have antidepressant effects in animals) for 12 weeks, and found that **cytidine supplementation significantly improved depressive symptoms over placebo, with an early onset of action, and cytidine also reduced elevated levels of glutamine/glutamate in the brain measured by MR spectroscopy.**

*Editors Note: If replicated, these findings would represent a completely new treatment based on new understandings of the pathophysiology of bipolar illness. Such a rationally-based drug development is highly unusual compared to the typical serendipitous discovery of effective therapeutic agents for bipolar illness.*

*Neurobiology Update***BDNF as a Biomarker and Potential Treatment**

In previous BNNs, we have reviewed the important role of brain-derived neurotrophic factor (BDNF) in bipolar disorder. There is much evidence that levels of the factor in blood decrease during manic or depressive episodes in proportion to their severity. Since BDNF is important for the survival of neurons and the development and maintenance of long-term memory,

*BDNF in blood decreases during depressive and manic episodes in proportion to the severity of the episodes.*

these findings suggest a mechanism whereby repeated episodes could endanger neurons and glia (or support cells) in the brain and increase the risk of cognitive impairment.

Because BDNF tends to normalize with effective treatment and euthymia, BDNF levels may be a useful tool and biomarker of active bipolar illness.

BDNF levels in blood correlate with those in the brain, and new data also suggest that those with lower BDNF in the blood have smaller hippocampi. The hippocampus plays a role in short term memory and spatial navigation.

Heath D. Schmidt and Ronald S. Duman from Yale University School of Medicine reported a striking new finding at the Biological Psychiatry annual meeting in Washington, DC in May. They found that **intravenous administration of BDNF increases the production of hippocampal neurons in animals and produces**

**antidepressant-like behavioral effects** (including reduced immobility in a forced swim test and shorter latencies to drink water in a novel environment). Compared to mice treated with saline, mice treated with intravenous BDNF displayed more new neurons in a part of the hippocampus called the dentate gyrus. The authors concluded that, in addition to BDNF being a biomarker of major depression and bipolar disorder, peripheral administration of BDNF has behavioral and cellular effects similar to antidepressants.

*Editor's Note: These findings are particularly remarkable in two different ways. One suggests the possibility of peripheral treatment with BDNF itself as a potential antidepressant and inducer of neurogenesis. This remains to be further explored in clinical studies.*

*The second perspective is that not only are BDNF levels a biomarker for the occurrence and severity of both manic and depressive episodes, but the low levels in serum of affectively ill patients could actually be contributing to affective dysfunction. If high levels of BDNF induce neurogenesis and antidepressant-like behaviors in animals, it is possible that low levels consistently observed during affective episodes could be physiologically problematic.*

*These data provide strong mechanistic rationales for continuous treatment with mood stabilizers in patients with bipolar illness. Not only do lithium, carbamazepine, and valproate prevent affective episodes, they have also been shown to directly increase BDNF. Whether these increases in BDNF contribute to their clinical profile of effectiveness or not remains to be determined.*

*Neurobiology Update***Immune Alterations In Children And Adults With Bipolar Disorder**

There is now considerable evidence that patients with affective disorder suffer from increased immune abnormalities, oxidative stress (which produces free radicals and other toxins in the brain) and an increased ratio of pro-inflammatory cytokines to anti-inflammatory cytokines. These three factors put some cellular elements of the brain and body at extra risk for dysfunction or atrophy, especially since BDNF and other neuroprotective factors also decrease with affective episodes.

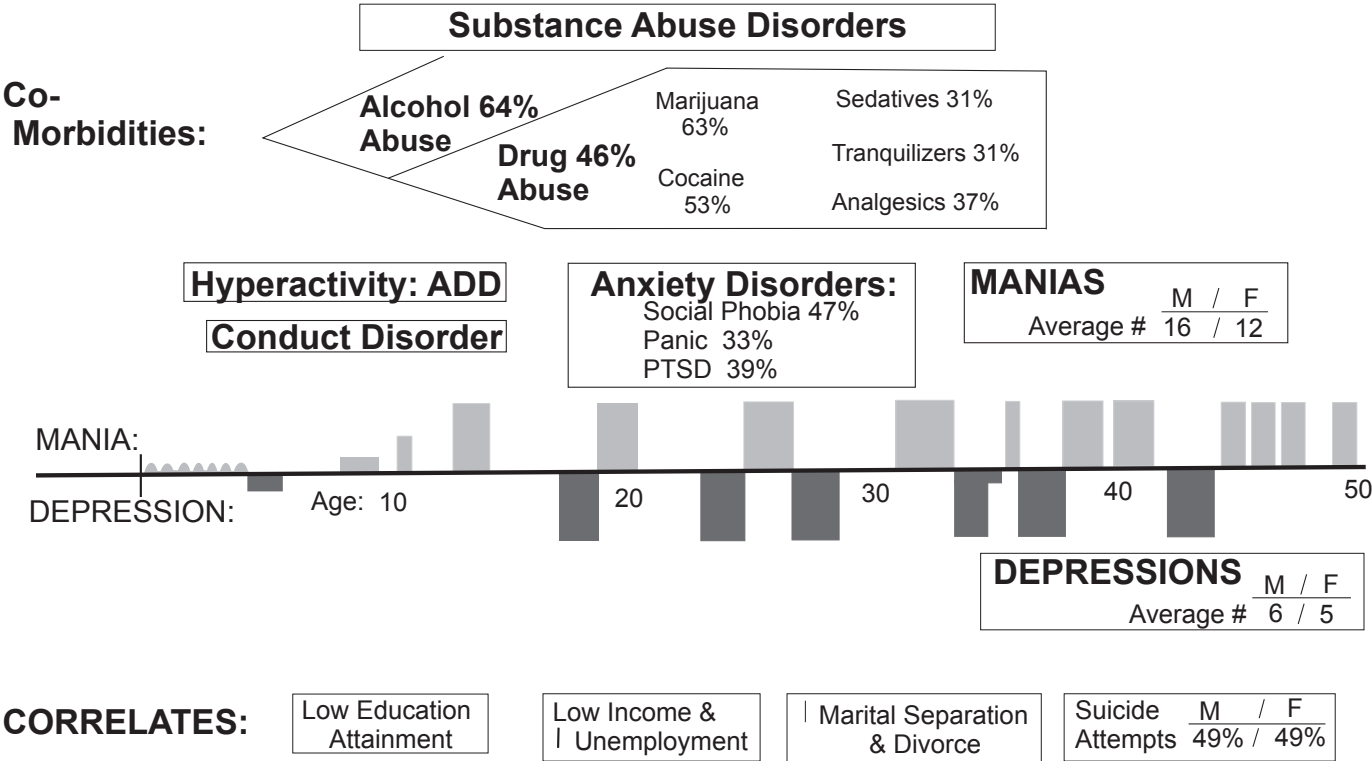
At the Biological Psychiatry annual meeting in Washington, DC in May, Marlon P. Quinones

reported on his study of 71 bipolar adults and children, 48 adults with major depressive disorder, and 69 demographically-matched healthy controls. **The bipolar adults and children were found to have multiple immune abnormalities.** In adult subjects, a panel of markers including RANTES, MDC, BDNF, and Fatty Acid Binding Protein discriminated bipolar patients from unipolar and controls in 83% of instances. In children, a panel including CD40 and Insulin Growth Factor-1 discriminated bipolar patients from unipolar patients and controls in 65% of instances.

# A Clinical Update on Possible Treatments for Co-occurring Substance Abuse in Bipolar Disorder

## CO-MORBIDITIES AND THEIR CORRELATES IN BPI ILLNESS\* IN EPIDEMIOLOGICAL SURVEY IN THE US

(KESSLER ET AL 1995, 1997)



\* Only 45% of BPI Patients Were In Any Form of Active Treatment ! ? !



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## Treatment Of Alcohol Abuse In Patients With Bipolar Disorder

There is a considerable incidence of alcohol and stimulant abuse in patients with bipolar disorder. Often, these are notably improved upon successful mood stabilization. However, in instances in which the alcohol and stimulant abuse remain problematic despite improvement in mood, there are now several clinical approaches to be considered.

*Editor's Note: All of these approaches are off-label (not FDA-approved for use in bipolar illness) in that most of the studies have been conducted in those with the primary substance abuse disorders and not in those with comorbid bipolar illness. The following statements are highly preliminary and based on indirect inferences only.*

It is of primary importance that the patient has a consistent treatment setting with a supportive focus on management of both their bipolar illness and substance abuse issues. Alcoholics Anonymous (AA) and other related support groups are often helpful adjuncts, except in those now-rare instances in which the groups are not sensitive to the need for pharmacotherapy of the bipolar illness and endorse abstinence from all medications.

**FDA-approved treatments for primary alcohol abuse in the context of ongoing psychotherapy include the opiate antagonist naltrexone (Revia), the glutamate NMDA receptor-active acamprosate (Campral), and disulfiram (Antabuse), which**

**causes sickness should the patient drink alcohol while on that treatment.**

Topiramate is one option not yet approved by the FDA for this use. Data from two large randomized, controlled clinical trials by Bankole A. Johnson and colleagues at the University of Texas Health Science Center indicate that **topiramate is more effective than placebo on most measures of alcohol**

*Women with bipolar disorder are 7 times more likely to abuse alcohol than women in the general population.*

M. Frye et al (2002, *Am J Psychiatry*)

**avoidance**, including number of days of heavy drinking, number of days with clean urine, and degree of craving.

It is noteworthy that topiramate itself does not have acute antimanic efficacy and in this instance, topiramate might be considered for use as an adjunct specifically targeting the co-occurring alcohol abuse disorder and, as noted below, it has shown some efficacy in placebo-controlled trials for decreasing cocaine intake as well.

A major part of treating those with co-occurring alcohol disorders is addressing any underlying anxiety disorder that may drive the desire

for alcohol's initial anxiolytic effects. While lithium does not treat anxious components of the illness, **valproate (Depakote, Depakene), carbamazepine (Tegretol, Equetro), and even lamotrigine (Lamictal) are mood stabilizers that do have anti-anxiety effects.** In addition, the **atypical antipsychotics usually have a substantial anxiolytic and pro-sleep effects** in addition to their antimanic and, in some cases, antidepressant efficacy.

Short-acting benzodiazepines are to be avoided, and the long-acting ones should be used exceedingly sparingly in those with an alcohol and substance abuse history.

Carbamazepine, valproate, and gabapentin (Neurontin) have some evidence of efficacy with acute alcohol withdrawal symptomatology and anxiety. In some European countries, carbamazepine is widely used for long-term treatment for the anxiety and dysphoria of those with alcohol abuse disorders. There is some preliminary evidence that carbamazepine has particularly good antidepressant effects in those with a history of prior alcohol abuse problems.

One study by Ihsan M. Salloum and colleagues at the University of Miami suggested that valproate, which in this single instance was studied in bipolar patients with a history of alcohol abuse problems, was helpful in the further avoidance of alcohol intake.

## NEUROANATOMY of ALCOHOL DEPENDENCE

(after G. Koob 11/9/04)

**BRAIN AREA - CORRELATE (Drug Effect)**

**BNST – Context Memory**

**Amygdala – Cue, Emotional M.**

**Hippocampus – Place Memory**

**N. Accumbens – Motivation & Reward**  
(Glutamate from ctx and Dopamine (DA) from VTA)

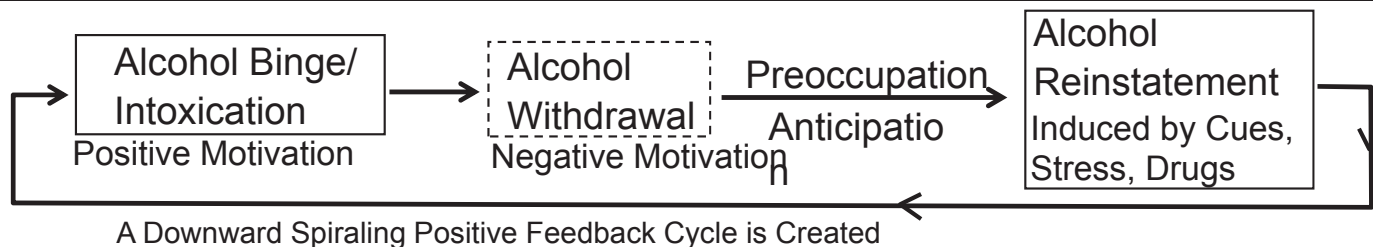
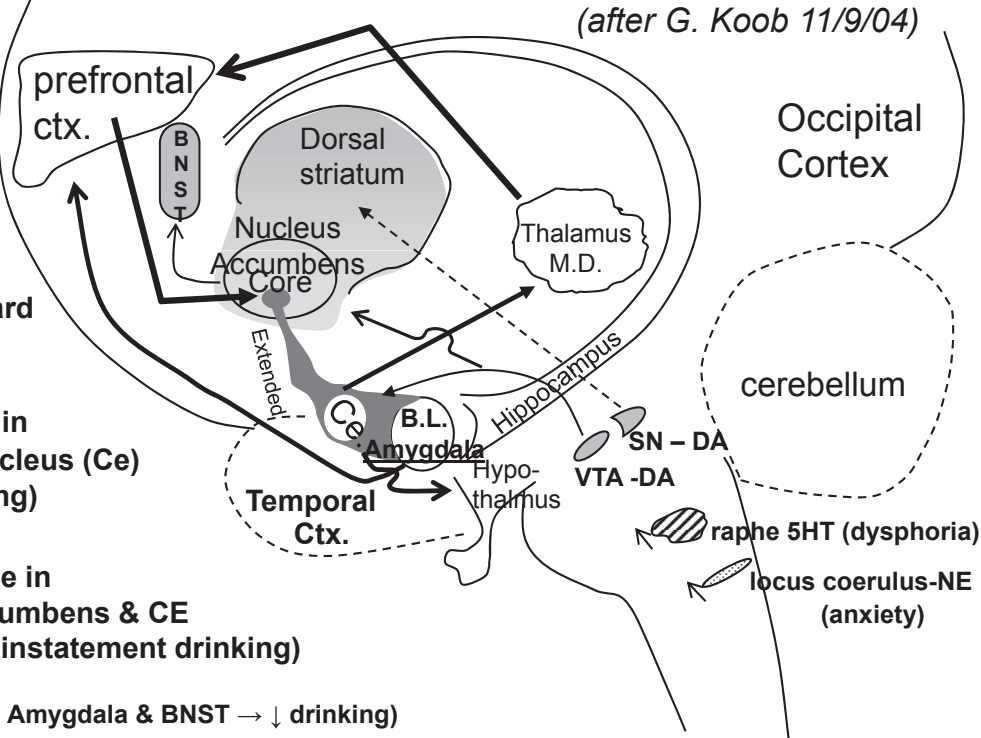
**↑CRF<sub>Amygdala</sub> – Stress – (Antagonist in Central Nucleus (Ce) → ↓drinking)**

**↑Ne – Stress**  
Locus Coeruleus

**↑Dynorphin – Dysphoria (Naloxone in Dorsal Striatum N. Accumbens & CE → ↓ reinstatement drinking)**

**↓ GABA<sub>A</sub> - Anxiety, Pain – (Musimol in Amygdala & BNST → ↓ drinking)**

**NPY- Anti-stress – (↑NPY → ↓ drinking)**





## Possible Approaches to Stimulant Abuse in Patients with Bipolar Illness

As described in the previous article, there are no FDA-approved treatments for patients with primary stimulant abuse, and virtually no data about treatment for bipolar patients with co-occurring stimulant abuse disorders. However, there are emerging data about possible treatment approaches for those who are struggling with these issues.

Just as anxiety is a key long-term target of therapeutics in alcohol avoidance, adequate mood stabilization of both manic and depressive phases of the illness is an ideal place to start in approaching the bipolar patient with comorbid stimulant abuse. If stimulant abuse persists after mood stabilization, there are still several treatments that might be considered.

There are placebo-controlled data (in primary stimulant abusers only) that **modafinil (Provigil) helps in the avoidance of cocaine**. This makes the drug attractive for consideration in the treatment of bipolar patients. Mark A. Frye and colleagues (*American Journal of Psychiatry*, 2007) also reported that modafinil showed superiority to placebo in adjunctive treatment of residual bipolar depression.

A key issue in treating substance abuse in the context of bipolar illness is the question of how the proposed treatment, studied only in stimulant abusers without bipolar illness, might interact with the mood symptomatology of bipolar disorder.

In this case, modafinil would appear promising because of its potential positive effects in unipolar and bipolar depression. Conversely, the GABA-B agonist baclofen, a muscle relaxant that has shown positive effects over placebo in patients with primary cocaine abuse, would not be recommended for use in bipolar patients because **baclofen has been found to worsen depression in at least one small group of patients**.

Another potential option, is **topiramate (Topamax), which was found to help with cocaine avoidance in a placebo-controlled clinical trial**. It is noteworthy that there is a modicum of data supporting the use of topiramate in those with

posttraumatic stress disorder (PTSD) as well, since many patients with PTSD have substantial substance abuse problems.

Another highly promising approach is that derived from the basic science studies of Peter Kalivas at the University of South Carolina in Charleston. He found that animals whose cocaine habit was extinguished were likely to relapse or resume cocaine intake if they were stressed, if small doses of cocaine were

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### *Modafinil (Provigil) and N-Acetyl-cysteine show promise for use in bipolar disorder with comorbid cocaine abuse.*

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administered, or if cocaine-related cues were available in the environment. This cocaine-reinstatement behavior was associated with a huge increase in glutamate in reward areas of the brain (such as the nucleus accumbens). He found that the introduction of N-acetyl-cysteine (NAC) blocked this excess glutamate secretion upon cocaine reinstatement and also decreased the cocaine-reinstatement behavior.

These data led him to explore the use of NAC in patients with primary cocaine abuse disorders, in whom it decreased cocaine craving. Others have found that n-acetyl-cysteine decreased heroin intake in those with heroin addiction and decreased the urge to gamble in those with pathological gambling problems.

In the instance of N-acetyl-cysteine, as in the case with modafinil, there is reason to expect it might be particularly useful in those with bipolar illness, because NAC, compared with placebo, has shown positive effects in those with residual bipolar symptomatology when added adjunctively to other partially effective treatments. This was observed in a six-month study by Michael Berk and colleagues in Australia (*Biological Psychiatry*, 2008), where **those randomized to NAC felt better than those**

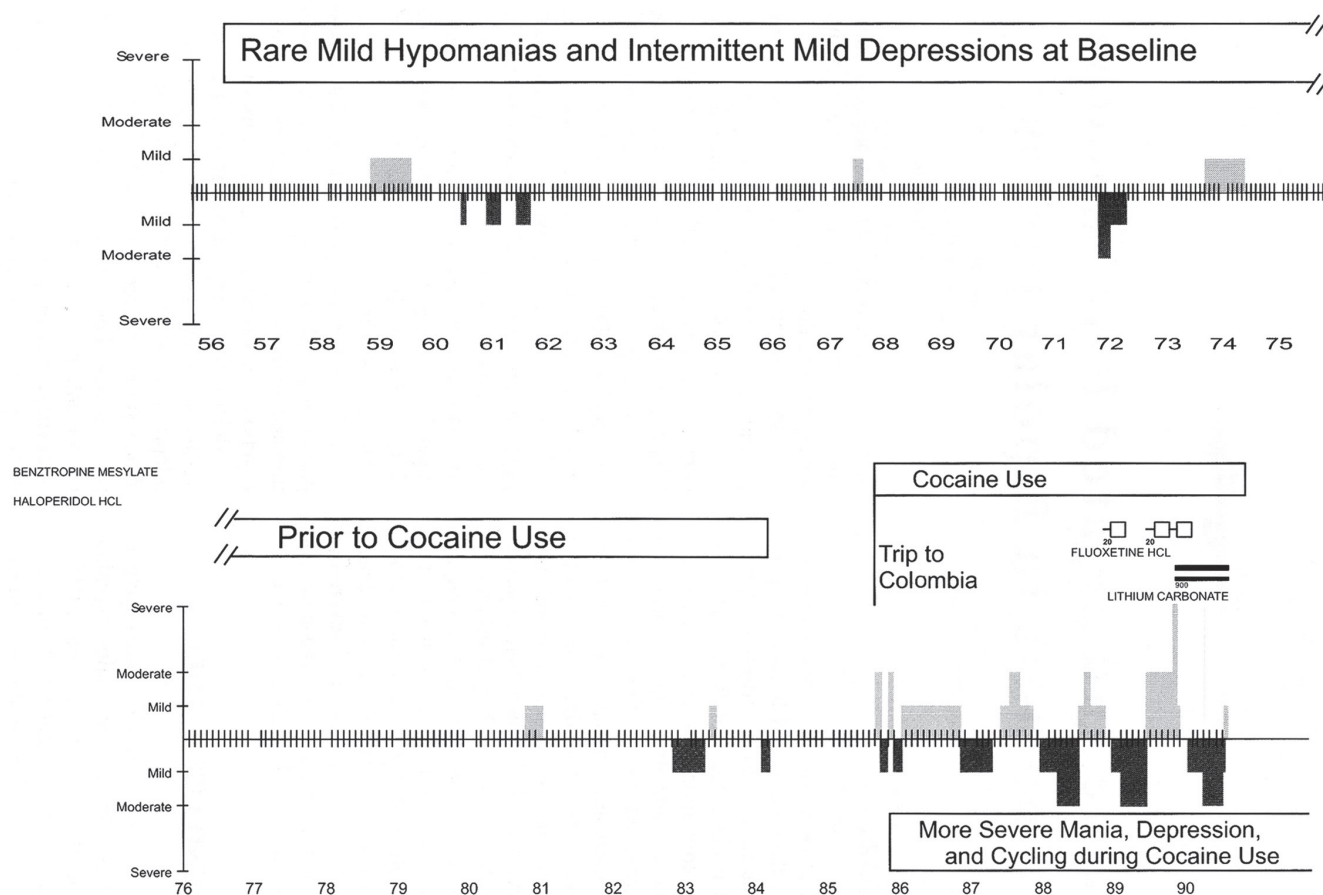
**randomized to placebo**, especially in the third to sixth months of treatment. This was **particularly prominent in the area of improvement in depression**.

The researchers used treatment with N-acetyl-cysteine at a dose of 1 gm twice/day and reported that this was associated with relatively few side effects. There is also a positive study of NAC in the treatment of some of the residual symptoms of schizophrenia. Thus, while NAC has not yet been studied directly in bipolar patients with comorbid substance abuse problems, encouraging data in both of these primary illnesses themselves suggest its potential utility and relative absence of side effects.

While NAC is available in some health food stores and apothecaries, we must re-emphasize a caution that we have given about all information conveyed in the BNN. The information is highly preliminary, often based on abstracts, presentations, and unpublished data that has not been peer-reviewed in scientific journals, and thus cannot be relied upon or verified. **The preliminary and speculative data and ideas reported in the BNN must not be acted on without discussion with a treating physician** and independent confirmation that any approach directly or indirectly endorsed in the BNN is appropriate.

Attempting to optimally treat the comorbidities that commonly occur with bipolar illness could be an important component of therapeutics. All evidence suggests that treating patients to remission of their mood symptomatology and effectively approaching and treating the comorbid conditions is not only a primary goal of the patients themselves, but is associated with a lesser likelihood of relapse in the future compared with those who are left with residual symptomatology.

We would encourage patients, with their physicians, to systematically explore their individual responsivity to any potential treatment using careful mood chart ratings of their bipolar illness and any comorbidities, such as anxiety and substance abuse disorders, whether or not the treatments are FDA-approved.



**Figure 64.1** Comorbidity of bipolar illness and cocaine use. The patient showed a dramatic shift to a more severe pattern of manic and cyclic bipolar illness in 2000. He later revealed that this occurred following a trip to Colombia where he was able to acquire a considerable amount of cocaine that he continued to use thereafter. This patient illustrates that abuse of psychomotor stimulants (e.g., cocaine, amphetamine, methylphenidate) can exacerbate and complicate the course of bipolar illness.

## Treatment Update

# SSRIs Relatively Ineffective in Bipolar Depression MAOIs More Effective than Paroxetine (Paxil) in Bipolar Depression

Allen Mallenger of the Intramural Program at NIMH reported at the Society of Biological Psychiatry meeting in May in Washington, DC that a retrospective analysis showed that adjunctive treatment with monoamine oxidase inhibitors (MAOIs) resulted in significantly greater sustained improvement in bipolar patients than the selective serotonin reuptake inhibitor (SSRI) paroxetine. **Fourteen of 21 patients (66.7%) treated with MAOIs achieved long-lasting recovery compared with 5 of 15 patients (33.3%) treated with paroxetine.**

*Editor's Note: These data are retrospective and uncontrolled. However, the low response rate to paroxetine mirrors the findings in a randomized controlled clinical trial by Sacks et al. (2007) that*

*found neither paroxetine nor bupropion augmentation of a mood stabilizer was more effective in bipolar depression than placebo. The findings also mirror findings by Himmelhoch et al. (1991) of excellent antidepressant response in bipolar depression to the MAOI tranylcypromine. Our Bipolar Collaborative Network study in which patients were randomized to either lamotrigine or tranylcypromine also showed good results for the MAOI. Nolen et al. (2008) showed a numerically but not statistically significant greater antidepressant response for the MAOI in a small randomized study.*

*Taken together, these data suggest that MAOIs should not be left off the list for consideration in the treatment algorithm for patients with bipolar depression.*

## Paroxetine Not Effective in Bipolar Depression

As reported at the Society of Biological Psychiatry meeting in May in Washington, DC, Bengt Olausson and others compared quetiapine (300 mg/day and 600 mg/day) with paroxetine (20 mg/day) and placebo for 8 weeks in bipolar depression. They found a highly significant antidepressant effect for both quetiapine doses compared to placebo, and a nonsignificant effect of paroxetine compared with placebo.

*Editor's Note: This new randomized controlled clinical trial (RCT) confirms the acute antidepressant effects of quetiapine in bipolar depression and further brings into question the continued first or second-line use of SSRIs, either in monotherapy or as adjuncts to mood stabilizers in the treatment of bipolar depression, a practice which is still widespread.*

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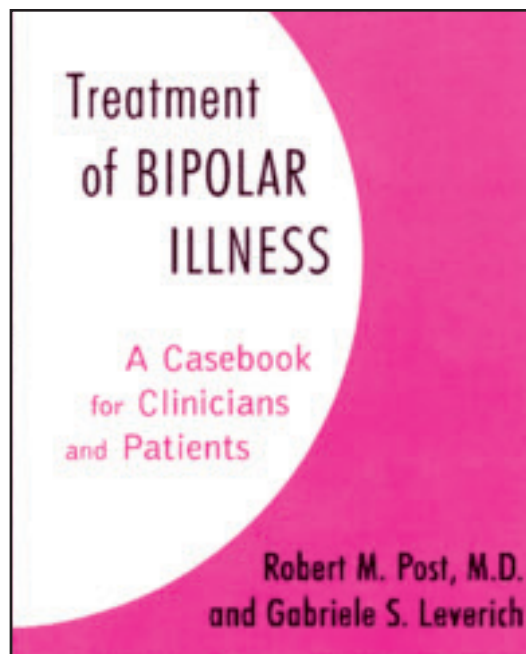
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