

# Bipolar Network News

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Updates from the 2014 Meeting of the International College of Neuropsychopharmacology (CINP)

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## CRP, A Marker of Inflammation, Predicts Response To Two Different Antidepressants

C-reactive protein, or CRP, is a protein found in blood plasma. Levels of CRP rise in response to inflammation. In a recent study, levels of CRP were able to predict which of two antidepressants a patient was more likely to respond to.

The 2014 article by Rudolph Uher et al. in the *American Journal of Psychiatry* reported that **low levels of CRP** (<1 mg/L) predicted a good response to the selective serotonin reuptake inhibitor (SSRI) **escitalopram (Lexapro)** while **higher levels of CRP** predicted a good response to the tricyclic antidepressant **nortriptyline**, a blocker of norepinephrine reuptake.

The research was part of the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, a multi-center open-label randomized clinical trial. CRP was measured in the blood of 241 adult men and women with major depressive disorder. In the article the researchers say that CRP and its interaction with medication explained more than 10% of the individual variance in response to the two antidepressants.

If these findings can be replicated with these and similarly acting drugs, it would be a large step in the direction of personalized medicine and the ability to predict individual response to medications.

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## Levels of Inflammation Predict Depression Persistence

Links between inflammation and depression continue to be identified. Researcher N. Vogelzangs et al. reported in a 2014 article in *Neuropsychopharmacology* that inflammatory and metabolic dysregulation in antidepressant users predicted an outcome of depression two years later. **Elevated levels of the marker of inflammation IL-6, low HDL (or “good”) cholesterol, high triglycerides, and high blood sugar were associated with poor response to medication and chronicity of depression.** Of 315 people treated with antidepressants (average age 43), 138 (43.8%) were in remission after two years, while 177 (56.2%) were still depressed. People with four or more types of inflammatory or metabolic dysregulations had a 90% chance of still being depressed after two years.

Among inflammatory markers including CRP and TNF-alpha, IL-6 alone was associated with chronic depression. IL-6 can cross the blood-brain barrier. We have previously reported that researcher Scott Russo found that in rats in a depression-like state known as defeat stress (brought about through repeated defeat by a larger rodent), blocking IL-6 can prevent depressive behaviors such as social avoidance or loss of preference for sucrose.

Like inflammation, metabolic abnormalities also complicate depression. Lipid dysregulation and hyperglycemia are associated not only with depression persistence, but also with new onset of depression.

Vogelzangs et al. conclude that these data “suggest that inflammation and metabolic dysregulation

worsens depression course owing to reduced [antidepressant] response and that alternative intervention treatments may be needed for depressed persons with inflammatory and metabolic dysregulation.”

It is noteworthy that a 2014 meta-analysis of the anti-inflammatory drug celecoxib (Celebrex) published by Farhad Faridhosseini et al. in *Human Psychopharmacology* showed that the drug, often prescribed for arthritis, is effective for unipolar depression when added to patients’ regular treatment.

It remains to be ascertained whether celecoxib’s effects are seen in depression in general, or if they pertain only to the 30% of depressed patients who show inflammation at baseline.

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## Inflammation

*Continued from Page 1*

Statins, prescribed to lower cholesterol, also have anti-inflammatory effects, and may also be effective in preventing depression.

Determining treatment approaches for those patients showing signs of inflammation or metabolic irregularities remains a high priority for study. The preliminary data noted here suggest that treating these dysregulations in those with depression may be useful.

### Bipolar Network News

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

Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in abstract or pre-publication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact or 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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## In Rodents, Thalamus Implicated in Depression-Like Behavior and Resilience to It

At the 2014 meeting of the International College of Neuropsychopharmacology (CINP), researcher Scott Russo described characteristics of rodents who showed depression-like behavior after 10 days of exposure to a larger, more aggressive animal (a phenomenon known as defeat stress). These animals exhibited many behaviors that resembled human depression, including anxiety-like behaviors while navigating a maze; activation of the hypothalamic-pituitary-adrenal axis; circadian rhythm abnormalities; metabolic changes such as glucose intolerance; susceptibility to addiction; anhedonia, a lack of interest in sucrose, sex or intracranial self-stimulation; and profound and permanent social avoidance.

Like searching for a needle in a haystack, Russo attempted to identify the neurons responsible for this type of behavior among the billions of neurons and the 100 to 500 trillion synapses in the brain, and thinks he found it.

In susceptible animals, Russo found anatomical changes in the GABAergic

neurons of the nucleus accumbens, including increased numbers of synapses and a greater number of stubby spines on dendrites (the branched projections of neurons where electrical signals are passed from one cell to the next), as well as greater excitability of glutamatergic input, observed as excitatory post-synaptic potentials.

The medium spiny neurons of the nucleus accumbens contain GABA and receive synapses from the prefrontal cortex, amygdala, and intralaminar nucleus of the thalamus (ILT), in addition to dopamine inputs from the VTA, and cholinergic, somatostatin, and orexin inputs. **Russo found that it was the ILT inputs that conveyed susceptibility to defeat stress, and their presynaptic endings showed increased levels of glutamate transporters (VGLUT-2).** Driving the ILT was sufficient to cause the rodents to display the depression-like behaviors, and silencing the ILT during defeat stress prevented the susceptible behaviors (like social avoidance) and promoted resilience.

## Depression and Cardiovascular Risk in Women

In a 2013 article in the journal *European Psychiatry*, in which researcher Valery V. Gafarov examined depression's influence on cardiovascular health in Russia, **an astonishing 55.2% of women aged 25–64 years in the study were diagnosed with depression.** The study, in which 870 women in the city of Novosibirsk were surveyed over 16 years from 1995 to 2010, was part of a World Health Organization program called MONICA-psychosocial.

The researchers collected information on the incidence of heart attack, arterial hypertension, and stroke

among the women. Over the 16 years of the study, 2.2% of the women had heart attacks and 5.1% had strokes. Women with depression were 2.53 times more likely to have a heart attack and 4.63 times more likely to have a stroke than women without depression.

Among women with average education levels, married women with depression were more likely to have heart attacks, hypertension, and strokes. Hypertension was more likely among women who worked as managers or light manual laborers.

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## FDA Warning About Antidepressants Followed by Drop in Use and Increase in Suicide Attempts

A decade ago the Federal Drug Administration (FDA) released several warnings that children, adolescents (ages 10-17), and young adults (ages 18-29) taking antidepressants were at increased risk for suicidal ideation and behavior. A recent study found that following these warnings, antidepressant use among adolescents, young adults, and adults dropped, and psychotropic drug poisonings (a validated measure of suicide attempts) increased among adolescents and young adults. Numbers of completed suicides did not change for any age group.

The decision to place the warnings on antidepressant packaging was somewhat controversial because it was based on studies that were not necessarily designed to measure suicide risk. The relationship between depression, medication, and suicide is complicated. Medication can improve mood, but patients may seek out medication because of pre-existing suicidal thoughts, and the medication may not reduce these in young people.

The reduction in antidepressant use that occurred after the warnings was accompanied by a drop in depression diagnoses in children and adults. Studies have suggested that the decrease in antidepressant prescriptions was not accompanied by increases in other treatments, such as psychotherapy or atypical antipsychotics, among young people. Increased monitoring of patients was called for in the FDA's box warning, but did not take place.

The study of the aftermath of the FDA warnings, published by Christine Y. Lu et al. in a 2014 article in the journal *BMJ*, used data from 11 insurance networks throughout the US. The researchers used an interrupted time series study design, which is used to show whether a policy causes an abrupt change in the expected slope of study outcomes. Data covered the pre-warning period (first quarter of 2000 to third quarter of

2003), the warning "phase-in" period (last quarter of 2003 to last quarter of 2004) and the post-warning period (first quarter of 2005 to last quarter of 2010). The study cohorts included around 1.1 million adolescents, 1.4 million young adults, and 5 millions adults per quarter.

Among [adolescents](#), the previously upward trend in antidepressant use declined by 31.0% in the second year after the warnings, and psychotropic drug poisonings increased by 21.7% (a figure that was statistically significant for males). Poisonings by any drug increased by 13.9% in the second year after the warnings. After 2008, the downward trend in antidepressant use reversed, indicating that either the initial effects of the warning had worn off or that modifications to the warnings in May 2007, which encouraged patients and doctors to consider the risk of antidepressants alongside the risk of leaving mood disorders untreated, led to increased use.

Among [young adults](#), the upward trend in antidepressant use declined by 24.3% in the second year after the warnings, and psychotropic drug poisonings increased by 33.7%, a statistically significant change for both male and female patients.

Among [adults](#), to whom the warnings were not directed, antidepressant use decreased by 14.5% in the second year after the warnings.

**The study by Yu et al. is the first to show that suicide attempts actually increased after the FDA warnings. The authors suggest that the increase in suicide attempts might be a consequence of undertreating mood disorders, since antidepressant use dropped simultaneously.** The warnings and related media attention may have led to these unintended consequences, since media reports can sometimes be oversimplified.

*Editor's Note: As reviewed in previous issues of the BNN, considerable evidence supports the view that long-term antidepressants decrease suicide risk.*

## Folate Supplements May Delay Onset of Depression in Young People at High Risk

Low levels of folate, also known as folic acid or vitamin B9, have been associated with depressive symptoms in the general population. A 2014 article by A.L. Sharpley et al. in the *Journal of Affective Disorders* explored whether folate has protective effects. Teens and young adults (ages 14-24) at high risk for mood disorders due to a family history of these illnesses were randomly assigned to receive either folate supplements (2.5 mg daily) or placebo for up to three months. While there were no significant differences in the percentage of young people in each group who went on to be diagnosed with a mood disorder, [in the folate group there was a delayed onset of illness in those who went on to become unwell.](#)

## High Risk of Suicide Attempts in Bipolar Disorder with Substance Abuse

At the 2014 meeting of the International College of Neuropsychopharmacology, researcher Rieva et al. reported that 60% of bipolar patients with comorbid alcohol abuse have attempted suicide, and 48% of bipolar patients with cocaine abuse have attempted suicide. Thus, both of these comorbidities deserve specific attention and treatment. Unfortunately there are currently no Federal Drug Administration-approved drugs for bipolar patients with these comorbidities. The most promising treatments, based on data in patients with primary addictions, are the nutritional supplement N-acetylcysteine and topiramate, which have both performed better than placebo in studies of alcohol and cocaine abuse disorders.



## Diabetes May Contribute to Low Hippocampal Volume in Bipolar Disorder

Type 2 diabetes can damage the brain, particularly by reducing volume of the hippocampus, and frequently occurs in patients with bipolar disorder. A recent study of patients with bipolar disorder and abnormal glucose metabolism showed that **patients with bipolar disorder who also had insulin resistance, glucose intolerance, or type 2 diabetes had smaller hippocampi than both patients with bipolar disorder and normal glucose function and normal control participants without a psychiatric disorder**. In those with bipolar disorder and glucose abnormalities, age was associated with lower hippocampal volume to a greater extent than in bipolar patients with normal glucose function.

In the study, published by Tomas Hajek et al. in the journal *Neuropsychopharmacology*, not only did diabetes or prediabetes reduce the size of the hippocampus, but also reduced gray matter in the cerebral cortex, including the insula.

The researchers hope that treating diabetes, or possibly initial symptoms of bipolar disorder, more effectively may prevent these gray matter losses and slow brain aging in patients with bipolar disorder.

## Another Promising Open Study of Minocycline in Bipolar Depression

Researcher Joanna Soczynska of the University of Toronto presented a poster at the 2014 meeting of the International College of Neuropsychopharmacology (CINP) on the anti-inflammatory and neuroprotective antibiotic minocycline.

Twenty-seven patients with a major depression received minocycline in addition to the medications they were already being prescribed. Dosage was 100mg twice a day. Treatment with adjunctive minocycline was associated with significant improvement on several scales that measure depression severity.

*Editor's Note: What was particularly interesting was that a subset of patients achieved complete remission, raising the question whether these patients might have markers of inflammation that would predict this excellent response.*

*The authors concluded that the "results provide a rationale for testing minocycline's efficacy in a larger randomized, placebo-controlled trial."*

*Exactly this type of study has been proposed by researcher Andy Nierenberg, but not yet funded.*

## Lithium Combined with Atypical Antipsychotic More Effective Than Valproate Combined with Atypical Antipsychotic In One Study, But Not Another

Spanish researcher Evaristo Nieto et al. presented a poster about the naturalistic study of the efficacy of acute treatment of manic inpatients with lithium and valproate at the 2014 meeting of the International College of Neuropsychopharmacology (CINP). In the lithium group, all patients were treated with lithium and oral antipsychotics (N=85). In the valproate group, all were treated with valproate and oral antipsychotics (N=92). Outcome was measured using scores on scales for mania and for general functioning (the YMRS and the CGI-S). The atypical antipsychotic was typically olanzepine or risperidone.

**Nieto et al. found that the mean change in CGI scores from baseline to the day of discharge was significantly higher in the lithium group (-2.84 versus -2.6), and concluded that, "Although it is used in more severe cases, treatment of manic inpatients with lithium associated with antipsychotics is more effective than treatment with valproate associated with antipsychotics."**

However, W.M. Bank et al. came to the opposite conclusion in a Korean study. Bank et al. "compared the 1-year rehospitalization rates of first-episode bipolar manic patients who were discharged while being treated with lithium or valproate in combination with an atypical antipsychotic.... The rehospitalization rate was 17.3% during the 1-year follow-up period."

**Bank et al. found significantly higher rates of rehospitalization in the lithium (23.1%) compared to the valproate (13.3%) group** using the Kaplan-Meier formula for estimations.

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## Cariprazine for Mania Appears Safe and Well-Tolerated

At the 2014 meeting of the International College of Neuropsychopharmacology (CINP), researcher Lakshmi Latham presented a poster on three studies of the atypical antipsychotic cariprazine, a treatment that has not yet been approved by the Federal Drug Administration. **We call it an atypical antipsychotic because it is a partial agonist at dopamine D2 and D3 receptors, meaning it stimulates the receptors a little, but in the presence of high levels of dopamine, it blocks excess activity by sitting on the receptor and preventing the actions of the excess dopamine.** Aripiprazole is also a partial agonist at dopamine and serotonin 5HT1a receptors, but cariprazine differs in that it has a particular affinity for the D3 receptor.

Previous analyses had revealed that cariprazine has good acute antimanic efficacy. All three studies described by Latham were randomized, double-blind, placebo-controlled three-week studies in patients with bipolar mania.

In total the studies included 1065 patients, 442 of whom received placebo and 623 of whom received cariprazine.

For the analyses, cariprazine doses from the three studies were pooled, and ranged from 3-12 mg/day. Additional analyses evaluated the 3-6 and 9-12 mg/day groups specifically.

Approximately 70% of patients completed the study. The most common side effects included akathisia or restless legs (placebo, 5%; cariprazine, 20%), extrapyramidal disorder characterized by abnormal motor symptoms (5%, 13%), restlessness (2%, 6%) and vomiting (4%, 9%). The incidence of serious side effects was similar across the placebo and the treatment groups. Side effects that led to discontinuation of participation in the study occurred in 7% of placebo patients and 12% of cariprazine patients. Suicidal ideation was an infrequent side effect (placebo, 4; cariprazine, 2), and there were no suicide attempts.

Mean changes in weight were small (averaging 0.17kg in patients taking placebo and 0.54kg in those taking cariprazine), and the proportion of patients with 7% or higher increase in weight were similar across the two groups (both 2%). Mean changes in blood pressure and pulse were slightly greater with cariprazine and were related to dosage. Cariprazine was not associated with mean increases in electrocardiogram (EKG) parameters except for a slight increase in ventricular heart rate versus placebo (5.0 and 0.9 bpm, respectively). Mean changes in lipids and glucose were generally small and similar between groups. Levels of the hormone prolactin decreased in both groups.

Latham concluded that cariprazine treatment for three weeks was safe and well-tolerated.

Stay tuned: the efficacy of cariprazine in bipolar depression will be covered in the next issue of the BNN.

## Memory Tips for Bipolar Disorder

Like cancer patients undergoing chemotherapy, patients with bipolar disorder often have memory problems, particularly if they have had many prior episodes. Some memory tips from CancerCare's Chemobrain Information Series may also help patients with bipolar disorder remember things better and keep their memory sharp. Here are some of their tips:

**Make lists.** Carry a notepad with you, or use a smartphone to keep track of errands, shopping lists, daily tasks, and when you should take your medications.

**Use a paper or electronic day planner** or a personal organizer to keep track of appointments and special days like birthdays or anniversaries.

**Use a wall calendar** and hang it in a place that you will see it multiple times per day.

**Carry a notebook** and record everything you need to remember, including to-do lists; the dates, times, and addresses of appointments; important

telephone numbers; and the names of people you meet and a brief description of them. You can also use the notebook to keep track of medical information: your medication schedule, any symptoms or side effects you are having, or questions to ask your doctor. You can also do this using an app like What's My M3 or by downloading a personal mood charting calendar from our website, bipolarnews.org.

**Leave yourself a voice-mail message** to remember something important. When you listen to it later, write down the information.

**Organize your home or office.** Keep things in familiar places so you always know where to find them.

**Avoid distractions.** Find a quiet, uncluttered place to work or think where you can focus your attention for longer.

**Have conversations in quiet places.** This will help you concentrate better on what the other person is saying.

**Repeat information aloud, and write down important points.** If someone

gives you information about an appointment, you might repeat the time, date, and location of the appointment out loud while righting it down.

**Keep your mind active.** You can use crossword puzzles, word or math games, or attend events about topics that interest you.

**When writing, proofread.** Double-check whether you've used the correct words and spellings.

**Train yourself to focus** through mindfulness. For example, if you keep misplacing your keys, pay extra attention each time you set down your keys. You may say aloud, "I'm putting my keys down on the counter." Hearing the auditory cue can boost your memory.

**Exercise, eat well, and get plenty of rest and sleep.** These habits will help your memory work best.

**Tell your loved ones that you are having memory problems,** so that they'll understand that you may forget things you may normally be able to remember. They can help you or encourage you.

## Korean Study of Mental Disorders in Children of Bipolar Parents

Korea, like the US, has a moderate incidence of childhood-onset bipolar disorder among children who are at high risk because they have a parent with bipolar disorder. In a recent study by Young-Sun Cho et al. presented at the 2014 meeting of the International College of Neuropsychopharmacology (CINP), **59 out of 100 children with a parent who had been diagnosed with bipolar disorder met the criteria for a mental disorder themselves.**

Mood disorders were most common. Of the 59 children with mental disorders, 22 were diagnosed with bipolar disorder, and 16 were diagnosed with a depressive disorder. Others included four with attention deficit hyperactivity disorder (ADHD), four with an anxiety disorder, two with disruptive behavior disorders, one with a tic disorder, one with an autistic disorder, and one with schizophrenia and an anxiety disorder.

*Editor's Note: In contrast to studies in Germany, Switzerland, the Netherlands, and Canada, where few children are diagnosed with bipolar disorders (even among those who are at high risk because of a family history of bipolar disorder), 22% of high-risk children in Korea were diagnosed with bipolar disorder. This is comparable to or higher than rates at which high-risk children in the US are diagnosed with bipolar disorder. Studies from both the Bipolar Collaborative Network (in which this editor Robert Post is an investigator) and researcher Boris Birmaher et al. found that American parents with bipolar disorder often had a variety of other disorders, such as anxiety, alcohol abuse, or substance abuse. These other illnesses also increase the risk of early-onset bipolar disorder in offspring, and this may account for the higher incidence of early-onset bipolar disorder among high-risk children in the US.*

## Childhood Adversity, Epigenetics, and Hippocampal Volume

At the 2014 meeting of the International College of Neuropsychopharmacology, researcher Booij reported that in humans, there is an interaction between adversity experienced during childhood, and an epigenetic variation in the short form of the serotonin transporter (5HT-T ss, or SLC6A4), which can influence hippocampal volume during depression.

Epigenetics refers to environmental influences on the way genes are transcribed. The impact of life experiences such as stress is not registered in DNA sequences, but can influence the structure of DNA or tightness of its packaging. Early life experiences, particularly psychosocial stress, can lead to the accumulation of methyl groups on DNA (a process called methylation), which generally inhibits DNA's ability to start transcription (turning on) of genes and the synthesis of the proteins the genes encode. DNA is tightly wound around proteins called histones, which can also be methylated or acetylated based on events in the environment. When histones are acetylated, meaning that acetyl groups are attached to them, DNA is wound around them more loosely, facilitating gene transcription (i.e.

the reading out of the DNA code into messenger RNA, which then arranges amino acids in order to construct proteins). Conversely, histone methylation usually tightens the winding of DNA and represses transcription.

Booij followed 33 children who had experienced some form of adversity at a young age until they were 15 or 16, examining methylation of the serotonin transporter in their T cells and monocytes compared to 36 children who had not experienced adversity during childhood. He found that **in children who had experienced abuse in childhood, the degree of that abuse was correlated with methylation of the serotonin transporter and was inversely related to the volume of the hippocampus**, as measured using magnetic resonance imaging (MRI). Thus, child abuse yields lasting epigenetic effects (methylation of the serotonin transporter) and has anatomical consequences in teenagers, as seen in smaller hippocampi. These data parallel converse findings by Joan Luby et al. published in the journal *PNAS* in 2012, in which increased maternal warmth directed toward a child aged 4-7 was associated with increased volume of the hippocampus several years later.

## N-Acetylcysteine May Improve Preliminary Symptoms of Schizophrenia

At the 2014 meeting of the International College of Neuropsychopharmacology, researcher N. Miyake described the effects of the nutritional supplement n-acetylcysteine (NAC) on clinical symptoms in subjects with subthreshold symptoms of psychosis.

N-acetylcysteine, a glutathione precursor, has diverse neural effects. In this case series, four patients with subthreshold psychosis were given 2000mg/day of NAC for 12 weeks. **The**

**patients' symptoms improved to the point that three of the four were no longer considered at risk for psychosis.**

*Editor's Note: These promising anecdotal observations deserve careful follow up using a control group. Omega-3 fatty acids have been shown to slow conversion to full psychosis and performed better than placebo in a controlled study. Both n-acetylcysteine and omega-3 fatty acids should definitely be studied for those with emerging symptoms of bipolar disorder.*



## Link Between Schizophrenia and Blood Clot-Preventing Protein tPA

Schizophrenia is generally associated with a reduction in volume of the hippocampus. It is thought that the illness results from a predisposition that is triggered by an event such as a trauma or drug use that causes the release of chemicals that damage neurons.

Recently, following the finding that **five patients with schizophrenia and recurrent deep vein thrombosis (a blood clotting disorder) achieved remission of their psychosis after being treated with the anticoagulant warfarin** (Coumadin) and have been able to go years with antipsychotic treatment, researchers Silvia Hoirisch-Clapauch and Antonio Egidio Nardi searched the existing literature for any connection between blood clotting and hippocampal neurogenesis, hoping to find a protein that could encourage neuronal growth in the hippocampus.

They found tissue-plasminogen activator (tPA), which facilitates the conversion of plasminogen to plasmin (the major enzyme responsible for breaking down blood clots) and plays a role in the repair of hippocampal neurons after stress. Low tPA activity is associated with clotting disorders

and psychotic events. The drug warfarin reduces blood clotting, and also increases tPA activity, which may explain its effectiveness in treating the five patients who had both schizophrenia and deep vein thrombosis.

Abnormalities in schizophrenia that could be related to low tPA include deficient dopamine transmission at D1 receptors in the prefrontal cortex, impaired cleavage of the precursor to brain-derived neurotrophic factor (pro-BDNF, which can kill cells) to mature BDNF (which helps cells survive), abnormal NMDA receptor-mediated signaling, reduced Akt phosphorylation, and abnormal activation of reelin. The researchers found that all five patients had more than one tPA-related vulnerability to deep vein thrombosis, including high fasting blood insulin, high homocysteine, altered prothrombin activity, and anti-phospho-antibodies.

The same investigators have also examined whether plasmin plays a role in schizophrenia.

Plasmin breaks down proteins in blood plasma, including fibrin clots. In a study of 70 patients with schizophrenia and 98 age-matched normal

control participants, the researchers examined the role of plasmin and substances that activate plasmin. Almost all of the patients with schizophrenia had low plasmin activity, which is associated with prevalence of stroke, severe dysmenorrhea during early adolescence, and stillbirth or preterm birth related to severe placental insufficiency. Study participants who were in the middle of an acute psychotic episode or whose illness had been treatment-resistant showed the most markers of low plasmin activity. The researchers suggest that treatments to normalize plasmin and plasminogenic activators may provide new ways of treating schizophrenia.

*Editor's Note: A key question is whether patients who might have a dramatic antipsychotic effect to warfarin can be identified through biochemical tests without developing deep vein thrombosis. Other key questions are what percentage of patients with schizophrenia might have this kind of dramatic response to warfarin, and would equally positive effects be seen with direct treatment with tPA.*

## Patients with Schizophrenia Have Shorter Telomeres

Telomeres are bits of genetic material that sit at the end of DNA strands and protect it during cell replication. A person's percentage of short telomeres increases with aging. Telomeres also shorten with childhood adversity and as a function of number of depressive episodes.

In a recent study, researcher Kazuya Torimi found that **telomeres in white cells were shorter in 42 patients with schizophrenia compared to 56 healthy control participants.**

Torimi also treated mice with various antipsychotics for two-week periods. Treatment with atypical antipsychotics, such as risperidone,

olanzapine and aripiprazole, but not typical antipsychotics like haloperidol, elongated telomere length in the hippocampus. This probably occurred through effects on serotonin.

Torimi suggests that atypical antipsychotics improve negative symptoms in part through the modulation of telomere length.

*Editor's Note: Lithium has been found to increase telomere length in patients with bipolar disorder, and appears to do this through a direct effect on telomerase, an enzyme responsible for adding to telomere length. Short telomeres are associated with a large number of medical and psychiatric illnesses.*

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## A Paradigm for Treatment of Severe PTSD Developed by Dr. David Bakish

In an earlier BNN we mistakenly attributed the protocol developed by Canadian psychopharmacologist David Bakish to another doctor named Vaishali P. Bakshi. Our apologies to both individuals.

Dr. David Bakish is Medical Director at the Ottawa Psychopharmacology Clinic and a former professor of Psychiatry at the University of Ottawa in Ottawa, Ontario. He shared with this editor his novel treatment strategy for patients with exceptionally profound degrees of post-traumatic stress disorder (PTSD), which, particularly among military veterans, can be compounded by traumatic brain injury. He has had a distinguished academic career with an extensive CV and credentials including membership in the International College of Neuropsychopharmacology (CINP), the Royal College of Physicians and Surgeons of Canada, and the Canadian and European Colleges of Neuropsychopharmacology. Most importantly he has had great success in treating large numbers of patients with severe PTSD.

Treatment options based on placebo-controlled clinical trials are sometimes insufficient for the treatment of seriously ill patients. FDA-approved treatment for PTSD consists of serotonin-selective antidepressants, while exposure therapy (in which the patient is gradually exposed to more of the stimuli that triggered symptoms) is the recommended psychotherapy, but these methods often leave patients highly disabled. We relay Dr. Bakish's treatment strategy with several caveats.

**Most of Bakish's suggestions are "off-label" treatments for the treatment of PTSD or traumatic brain injury, i.e. treatments that are not FDA-approved for these purposes.** In some of these instances, there is no controlled research to support the use of these drugs in patients with PTSD. Thus the ideas noted here are anecdotal,

based on his personal experience, and have not been tested in controlled clinical trials. Accordingly, patients with their physicians must make their own decisions about any of the strategies reported in this or other issues of the BNN.

Bakish's typical treatment algorithm goes well beyond the usual treatment guidelines to find solutions for hard-to-treat patients. Bakish first addresses sleep disturbance, which is almost universal in PTSD. He suggests the anticonvulsant **levetiracetam** (Keppra), for the hyperarousal and sleep disorder. He uses starting at doses of 125mg per night and increases by 125mg every three weeks. Once he gets to 500mg, he increases by 250mg increments as tolerated. If he gets to 1g daily, he increases by 500mg increments as needed. This highly sedating anticonvulsant not only improves sleep but may also help cognition, since it is structurally similar to other cognitive enhancers such as piracetam. Levetiracetam also decreases the hippocampal hyperactivity associated with some forms of cognitive dysfunction, as we've noted before.

**Trazodone** (50 to 150mg) can be added for sleep if needed.

Instead of selective serotonin reuptake inhibitor antidepressants (SSRIs), Bakish recommends the selective serotonin and norepinephrine reuptake inhibitors (SNRIs). Among these, he prefers **desvenlafaxine** (Pristiq) over venlafaxine, as desvenlafaxine has fewer interactions with other drugs and with opiates, cannabis, and alcohol, which are often self-administered by patients with PTSD. He finds that duloxetine (Cymbalta) has more interactions with

these other agents. He starts with 25mg Pristiq, as these patients can be sensitive and jumpy, and increases slowly toward the range of 200 to 400mg. Bakish thinks that it makes no sense to start cognitive behavioral therapy until patients' hyperarousal is controlled.

If a PTSD patient smokes or has used cocaine he adds **bupropion** (Wellbutrin). Bupropion is FDA-approved to help with smoking cessation.

Bakish adds **topiramate** (Topamax) up to a maximum dose range of 400mg to 1g/day which helps with avoidance of alcohol and cocaine, as well as anger attacks. If the cognitive side effects of topiramate or levetiracetam are limiting, he uses **lamotrigine** (Lamictal) instead.

In the very small subgroup of patients who have ideas of reference (a psychiatric phenomena in which a person believes innocuous bits of information are significant

messages directed at them alone) and paranoia, he uses an atypical antipsychotic, and prefers **aripiprazole** (Abilify) at doses of 1-2mg.

**"It is important to note that there is no evidence-based medicine on these types of patients. None of these patients would be suitable for a clinical trial because they all have different exclusion criteria. However, they do exist and they are quite ill."**

Bakish cautions, "It is important to note that there is no evidence-based medicine on these types of patients. None of these patients would be suitable for a clinical

trial because they all have different exclusion criteria. However, they do exist and they are quite ill. The suicide rate is quite high. This is especially true if they have a previous psychiatric family history, which includes bipolar disorder. Similarly if there is a family history of panic disorder, I am very careful with these patients....

*Continued on Page 9*



## Complex Combination Treatment of PTSD

*Continued from Page 8*

Another problem that is specific to the military is that soldiers sometimes do not come forward with their symptoms because they are worried about their career. They think that once they are diagnosed with PTSD, they have no future in the military.

"In my experience, I always fight against this stigma. They may not be able to go back into combat, but they are still very effective soldiers in different roles. We also sometimes change their careers so that they can continue in the military....I usually see these patients every week at the beginning, then I space out the visits. However, in tandem with the medical officers, these patients are seen medically twice a week at the beginning and then spaced out.

"As far as I'm concerned, this is an understudied group of patients, who deserve much more from the people they serve. They have put their life on the line for us."

As noted above, if patients remain symptomatic with depression, anger, irritability, or flashbacks, Bakish recommends adding lamotrigine (Lamictal). Lamotrigine has anti-glutamatergic effects, decreasing release of glutamate, the major excitatory neurotransmitter in the brain. Thus, while levetiracetam enhances the actions of the inhibitory neurotransmitter GABA, lamotrigine decreases glutamatergic over-excitation; thus providing a dual mechanism for decreasing neuronal hyperexcitability and reactivity that can occur with PTSD.

If mood remains dysregulated and/or there is a positive family of bipolar disorder, Bakish sometimes augments the above regimen with **lithium carbonate**.

*Editor's Note: Bakish's treatment regimen is meant to target multiple neurotransmitter systems with moderate to high doses of a range of drugs that are not conventionally used or recommended in*

*treatment guidelines for the treatment of PTSD, which is sometimes compounded by traumatic brain injury. We highlight this treatment strategy he has used to treat many patients because too often patients with serious disability from PTSD are under-treated, and many elements of their symptomatology go unaddressed.*

*Bakish indicated that his treatment plan often takes several months to show notable clinical effects, but he reports that he often sees dramatic clinical improvement in symptoms of both PTSD and traumatic brain injury. In his experience, the longer they stay on their medication, the better they get.*

*In addition to Bakish's carefully sequenced protocol, there are still other potentially useful treatments for PTSD. The positive effects of **prazosin**, a norenergic alpha-1 receptor antagonist, are well-documented in three placebo-controlled trials by Murray Raskind et al. Prazosin is able to selectively inhibit nightmares associated with PTSD while leaving normal dreaming uninterrupted.*

***N-acetylcysteine** (NAC) is also worthy of consideration in the treatment of PTSD, as it has shown efficacy in both unipolar and bipolar depression, anxiety disorders, and addictions, including cocaine, heroin, marijuana, alcohol, and gambling, all of which are common in PTSD. There is also an early report of its positive acute effects in TBI by Michael E. Hoffer et al. in the journal PLOS ONE in 2013.*

*Another theoretical treatment that deserves further study would be augmentation of lamotrigine with **memantine** (Namenda). In a 2012 article, Anand et al. reported that memantine increased the antidepressant effects of lamotrigine in the initial weeks of treatment. Memantine also improved mood stability in patients with treatment-resistant bipolar disorder in a study by Koukopoulos et al. in 2012. In addition, as an FDA-approved treatment for memory loss in Alzheimer's disease, memantine holds the (as yet unstudied) possibility of helping treat the memory loss that often accompanies both PTSD and*

## Blood Pressure Drug Prazosin Effective for Nightmares and Other PTSD Symptoms

Researcher Murray Raskind has conducted a series of controlled studies, all with the same conclusion—the alpha-1 antagonist prazosin, used to treat high blood pressure, works for post-traumatic stress disorder (PTSD), especially in preventing nightmares. In his latest study, 67 soldiers were randomly assigned to either prazosin or placebo for 15 weeks. Doses were slowly titrated (to avoid low blood pressure and dizziness) to a possible maximum dose of 5mg at midmorning and 20mg at bedtime for men and 2mg at midmorning and 10mg at bedtime for women over a period of 6 weeks, based on whether the patients continued to experience nightmares.

Raskind found that prazosin was effective for trauma nightmares, sleep quality, global functioning, total score on a scale of PTSD symptoms, and hyperarousal. Side effects were minimal. Raskin concluded that prazosin "is effective for combat-related PTSD with trauma nightmares in active-duty soldiers, and benefits are clinically meaningful."

*traumatic brain injury. Memantine is a weak blocker of the glutamate NMDA receptor, while the rapid-acting intravenous antidepressant drug ketamine is a potent blocker of this receptor. There was a positive report of ketamine's effectiveness in treatment-resistant PTSD by Adriana Feder et al. in the journal JAMA Psychiatry in 2014.*

*We are indebted to David Bakish, MD for sharing his wide experience in treating patients with severe PTSD with the readers of the BNN. We again apologize for the mix-up in attribution of his unique approach.*

## A Re-Kindling Process Produces Late-Onset PTSD

Not everyone who experiences trauma develops post-traumatic stress disorder (PTSD) immediately. Researchers are discovering that some people go on to develop symptoms like flashbacks or intrusive thoughts, anxiety, and withdrawal, sometimes after long periods of being asymptomatic. Two studies provide hints about the mechanism of this late-onset (or delayed-type) PTSD.

In an article by Danny Horesh et al. published in the journal *Psychiatry Research* in 2013, a reported 16.5% of 675 Israeli veterans of the 1982 conflict with Lebanon developed late-onset PTSD after a completely non-symptomatic period. **The number of deployments soldiers were sent on and the number of terror incidents they experienced within Israel after the war were correlates of the late-onset PTSD, while continuous post-war employment was a protective factor reducing late-onset PTSD.**

In a study of 260 older adults (above age 60) who survived the destruction around Galveston Bay, Texas by Hurricane Ike in 2008, Robert H. Pietrzak et al. reported in the *Journal of Psychiatry Research* in 2013 that 5.3% developed late-onset PTSD. In this case as well, a greater number of subsequent traumatic and stressful life events (and in particular financial difficulties) was associated with late onset of PTSD. The majority of participants in Pietrzak's study (78.7 %) had no to few PTSD symptoms, while 16.0% had chronic PTSD symptoms from the outset persisting through assessments at three months and 15 months.

*Editor's Note: These two studies reveal that upon prospective follow-up, a small but substantial group of patients (5–16%) develop a late-onset type of PTSD. Acute*

*onset PTSD has been closely linked to new trauma in adulthood, especially following the occurrence of previous (childhood) traumas. The late-occurring variety of PTSD seems to appear after an incubation period, and appears to be closely associated with the occurrence of new traumatic events during the well interval. These new events may result in a kindling-like effect, where repetition of subthreshold stimuli come to evoke a full-blown episode. PTSD appearing after repeated traumatic experiences may operate in a similar fashion to seizures that gradually emerge following repeated electrical stimulation of the amygdala (i.e. amygdala kindling).*

*In the fifth issue of the BNN from 2012, we wrote about a process by which traumatic memories go through an initial period of consolidation and then are later re-consolidated. During this reconsolidation process, a window opens five minutes to one hour after active recall of the memory, during which old memories are subject to long-term revision. This extinction of traumatic memories is being used in the treatment of acute PTSD, and therapy involving eye movement desensitization and reprocessing (EMDR) also makes use of these principles through active recall and subsequent reworking of the traumatic memory within the reconsolidation window.*

*Since the experience of new traumas following an initial severe trauma appears to be related to the development of late-onset PTSD, it may be possible to desensitize the old and new traumatic memories by reworking them in the reconsolidation window after active recall, and thus potentially prevent the development of the late-onset type of PTSD.*

## Ketamine for Chronic PTSD

We reported in BNN Volume 17, Issue 6 in 2013 on researchers' efforts to treat symptoms of post-traumatic stress disorder using the drug ketamine. This research by Adriana Feder et al. has now been published in the journal *JAMA Psychiatry*.

In the study of 41 patients with post-traumatic stress disorder, **patients showed a greater reduction in symptoms 24 hours after receiving intravenous (IV) ketamine than after taking IV midazolam**, a benzodiazepine used as an active placebo control because it produces anti-anxiety and sedating effects similar to ketamine's. The patients ranged in age from 18 to 55 years of age and were free of other medication for two weeks before the study. Ketamine was also associated with reduction in depressive symptoms and with general clinical improvement, and side effects were minimal.

## Acute Steroid Injection May Ward Off PTSD

Low cortisol after a trauma is a risk factor for developing chronic post-traumatic stress disorder (PTSD). Researcher Joseph Zohar studied has been researching the effects of steroids on the development of PTSD and presented some findings at the 2014 meeting of the International College of Neuropsychopharmacology (CINP).

Twenty-five patients who experienced a traumatic event and showed acute stress symptoms were given either a single high-dose injection of hydrocortisone (100–140 mg) or a placebo within six hours of the trauma. Follow-up evaluation took place after two weeks, one month, and three months. **Those who received this single high dose of hydrocortisone had lowered stress symptoms and less subsequent PTSD compared to those who received placebo.**



## Agomelatine in an Animal Model of Post-Traumatic Stress Disorder

At the 2014 meeting of the International College of Neuropsychopharmacology (CINP), researcher Joseph Zohar presented a poster on the effects of early post-stressor intervention with the drug agomelatine in animals who showed behavioral and molecular responses to stress that served as a model of post-traumatic stress disorder (PTSD).

Agomelatine is available clinically as an antidepressant in Canada and Europe (but not in the US), and can also reduce anxiety and re-synchronize circadian rhythms. Agomelatine is a melatonin (MT1/MT2) receptor agonist and a serotonin 5HT<sub>2C</sub> antagonist (increasing dopamine and norepinephrine in the frontal cortex).

Long-term behavioral, molecular and structural effects of the drug were assessed in animals. Adult male Sprague-Dawley rats were exposed to the scent of a predator for 10 minutes,

and one hour later they were treated acutely for this stress with agomelatine (50mg/kg i.p.) or placebo.

Agomelatine decreased the prevalence of extreme, PTSD-like behavioral and biochemical responses to the stressor, such as freezing in place and increased corticosterone. Agomelatine also normalized decreases in brain-derived neurotrophic factor (BDNF) observed in the dentate gyrus of the hippocampus, the cortex (layer III), and the basolateral amygdala. In line with this, agomelatine-treated stressed animals displayed significantly increased number and length of dendrites at glutamate synapses in several locations in the hippocampus (including the dentate gyrus and CA1) and reversed the hippocampal neuronal retraction observed in the rats who were given the placebo.

Agomelatine also affected the expression of clock genes in the rats,

which regulate biorhythms. These genes lead to the production of the major clock gene proteins Per1 and Per2. Agomelatine normalized Per1 increases in three parts of the brain: the CA3, another location of glutamate neurons near the dentate gyrus; the suprachiasmatic nucleus over the optic chiasm, important for circadian rhythms; and the basolateral amygdala. Per2, a protein that also drives circadian rhythms, increased in the CA1 synapse of the hippocampus, the suprachiasmatic nucleus and the basolateral amygdala of the stressed rats.

**The researchers concluded that the data provide “initial evidence that a single dose of agomelatine administered in the acute aftermath of stress promotes recovery while promoting enhanced neuronal and synaptic plasticity and connectivity in the secondary prevention of PTSD in this model.”**

## Clarifying the Role of Melatonin Receptors in Sleep Through Genetically Modified Mice

The antidepressant agomelatine (which is available in many countries, but not the US) and the anti-insomnia drug ramelteon (Rozerem) both act as agonists at melatonin M1 and M2 receptors. New research by Stefano Comai et al. is clarifying the role of these receptors in sleep.

In the study, mice who were genetically altered to have no M1 receptor (MT1KO knockout mice) showed a decrease in rapid eye movement (REM) sleep, which is linked to dreaming, and an increase in slow wave sleep. Mice who were genetically modified to knock out a different receptor, M2, (MT2KO knockout mice) showed a decrease in slow wave sleep. The effects of knocking out a particular gene like M1 or M2

end up being opposite to the effect of stimulating the corresponding receptor.

**The researchers concluded that MT1 receptors are responsible for REM sleep (increasing it while decreasing slow wave sleep), and MT2 receptors are responsible for slow wave non-REM sleep.**

The new information about these melatonin receptors may explain why oral melatonin supplements can make a patient fall asleep faster, but do not affect the duration of non-REM sleep. The authors suggest that targeting MT2 receptors could lead to longer sleep by increasing slow wave sleep, potentially helping patients with insomnia.

## Antidepressant Use Dropping in Bipolar Disorder in Spain

In the clinic of researcher Eduard Vieta in Barcelona, a study was recently completed showing that antidepressant use in patients with bipolar disorder (where antidepressants are not effective) had dropped from around 50-60% in 2007 (in Baldessarini's study) to about 30% in 2013 and 2014, and conversely lithium, anticonvulsants, and atypical antipsychotics, which have much more evidence of efficacy, were all used much more often, or about 60% of the time.

*Editor's Note: Hopefully these data from Spain will soon be matched by similar data in the US showing that evidenced-based treatments for bipolar depression are in fact being used instead of antidepressants, which can have adverse effects, such as switching into mania or cycle acceleration.*

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