

Bipolar Network News

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Inflammation and Anti-Inflammatories in Depression

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Depression is often associated with increases in markers of inflammation in blood, which include IL-1, IL-6, TNF-alpha, and CRP. Risk factors for increased inflammation include stress, obesity, a diet high in omega-6 fatty acids, sedentary lifestyle, social isolation, low socio-economic status, smoking, and being female. Treatments such as lithium, other mood stabilizers, and antidepressants can all have anti-inflammatory effects.

At the International Congress of Neuropsychopharmacology in 2012, researcher Michael Berk reviewed data on inflammation in depression. Berk shared prospective data that in the general population, people whose levels of CRP fall within the highest third have the highest risk for a new onset of depression over the next 9 years, while those with CRP values in the lowest third (indicating low inflammation) had the least likelihood of becoming depressed.

Drugs with more direct anti-inflammatory properties are beginning to be studied in unipolar depression with some success. In a trial by Abbasi et al. published in the *Journal of Affective Disorders* in 2012, the anti-inflammatory COX-2 inhibitor celecoxib (Celebrex) when added to the selective serotonin reuptake inhibitor (SSRI) sertraline (Zoloft) had better antidepressant effects than the addition of placebo.

Sepaunjia et al. reported in *Neuropsychopharmacology* in 2012 that an anti-diabetes drug that also has anti-inflammatory properties, pioglitazone (Actos), also beat placebo in depression.

Laan et al. reported in the *Journal of Clinical Psychiatry* that the same was true of acetylsalicylic acid (ASA or aspirin).

Finally, Berk summarized data that the class of cholesterol-lowering drugs called statins are also able to decrease CRP and improve or prevent depression. Epidemiological data by Pasco et al. published in *Psychotherapy and Psychosomatics* showed that subjects without depression were less likely to develop a new onset of depression if they were treated with statins compared to those who were not. Stafford et al. reported in the *Journal of Clinical Psychiatry* in 2010 that patients taking statins had a 79% decreased likelihood of depression at 9 months of follow-up. A third study in Sweden showed that simvastatin, a lipophilic (fat-soluble) drug that can readily enter the brain, decreases the incidence of depression more than some of the non-lipophilic statins.

Moreover, a meta-analysis by O'Neil et al. reported that overall, statins had positive effects on mood.

Editor's Note: All these data come from studies of unipolar depression. They may be pertinent to bipolar depression, since elevated inflammatory markers have consistently been reported in bipolar depression. However, this cannot be assumed until appropriate studies are performed. (As usual, research in bipolar depression lags behind research in unipolar depression.)

Preliminary uncontrolled retrospective data from one study did suggest that those treated with lithium plus aspirin did better than those on lithium and no anti-inflammatory.

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Thus it may make sense for unipolar and bipolar depressed patients with risk factors for heart disease, such as a positive family history of heart disease and elevated cholesterol and triglycerides, to discuss with their doctors the possibility of starting statin treatment earlier rather than later. This is because depression itself is a major risk factor for heart disease, so statins might lower risk both by their approved indication of lowering cholesterol and by their apparent ability to help fend off new episodes of depression.

A more complicated issue would be the question of when, if at all, to use primary anti-inflammatory drugs in the adjunctive treatment of unipolar or bipolar depression. If nothing else works, they might be worth a try as an add-on. They might be used earlier in those with higher levels of inflammation, especially if there were more data indicating that those with inflammatory markers responded preferentially to primary anti-inflammatory drugs.

In the study by Abbasi et al., patients with elevated IL-6 had improvement in their depression after taking celecoxib,

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Treating Depression When No Measure of Inflammation is Available

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while in the study of a TNF-alpha inhibitor there was no overall positive effect in unipolar depression, but those who had the highest levels of CRP at baseline did show the most significant improvement and a significant drug-placebo difference. Anti-inflammatory agents might be considered in those with elevated inflammatory markers if their depressions did not respond adequately to first, second, or third attempts with more conventional options.

What about treating depression in the absence of available tests for inflammation?

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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Based on the findings to date, using anti-inflammatory treatments would possibly be worthy of consideration in those with treatment resistant illness, since in most of the positive studies, depressed patients were not specifically screened for inflammatory markers.

However, *this section must close with a reminder that patients and physicians should carefully discuss the risks and benefits of any treatment before it is begun.* While we attempt to discuss both positive effects and side effects in BNN, the preliminary data we report cannot be considered comprehensive, current, or even precisely accurate. We summarize data that has not been formally accepted in peer-reviewed literature, with the idea that patients, family members, and clinicians may find interesting information that prompts discussions between patient and doctor. Readers must consult primary sources for a more complete view of any topic discussed in BNN.

These cautions are especially important here because anti-inflammatory drugs have a range of potentially dangerous or even lethal side effects. Even aspirin carries a substantial risk of gastrointestinal bleeding

(perhaps in about 1 in 500 users), and patients die each year from this presumably safe over-the-counter medication. Cardiac risks are also being revealed for some non-steroidal anti-inflammatory drugs (NSAIDs). Given these potential side effects, discussions between patient and physician must take place before anti-inflammatory treatment is begun.

Since safety is an issue, it might make sense to use the safest agents first. The drugs with the best utility for treating inflammation may turn out to be the primary psychiatric drugs themselves, like antidepressants and lithium.

Other relatively safe anti-inflammatory drugs might include N-acetylcysteine (NAC), co-enzyme Q10, curcumin (a plant extract related to turmeric), and possibly statins and minocycline. The next group, with more potential side effects, might include NSAIDs such as the COX-2 inhibitor celecoxib and aspirin. The next group, which gets more exotic, expensive, and data-poor, might include erythropoietin (often used to treat anemia) and the TNF-alpha inhibitors used to treat rheumatoid arthritis.

Immune Mechanisms Are Important to the Emergence of Defeat Stress-Induced Depressive Behaviors in Mice

At a recent scientific meeting, researcher Georgia E. Hodes presented evidence that **in mice, the immune system may play a role in behaviors that resemble human depression.** Repeated social defeat stress (when an intruder mouse is threatened by a larger mouse defending its territory) is often used as a model to study human depression. Animals repeatedly exposed to social defeat stress start to exhibit social avoidance and lose interest in sucrose. Hodes et al. determined that interleukin 6 (IL-6), an inflammatory cytokine, or signaling molecule, secreted into the

blood was crucial to these behaviors. **When the researchers injected mice with antibodies that block the effects of IL-6, or when they irradiated the mice's peripheral immune system to prevent the formation of IL-6, the depressive behaviors did not emerge following defeat stress.**

Editor's Note: There are increasing data that immunological and inflammatory mechanisms play a role in human affective disorders, and these preliminary data raise the possibility that blocking some immune mechanisms more directly in humans could be a novel therapeutic approach to explore in the future.

Inflammatory Markers May Predict Response to Antidepressants

There appears to be a link between inflammation and depression. In the journal *Neuropsychopharmacology*, Cattanes et al. reported in 2013 that compared to controls, **depressed patients had significantly higher baseline levels of inflammatory cytokines, less glucocorticoid receptor function, less neuroplasticity, and fewer neuroprotective factors**. Certain variables predicted response to treatment, while others were seen only in responders, and still others changed in everyone who received antidepressant treatment regardless of how well they responded.

Higher baseline levels of inflammatory markers interleukin 1B, macrophage inhibitory factor (MIF), and tumor necrosis factor TNF-alpha were each associated with nonresponse to antidepressant treatment, and the three combined accounted for 50% of the variance in response—that is, they were the major predictor of whether a patient responded to treatment.

Levels of other factors changed in only those patients who responded well to antidepressants. The biggest changes were the normalization in levels of the neurotrophic factors BDNF and VEGF.

Several other markers normalized with antidepressant treatment regardless of whether the patients responded to treatment, and these included decreases in cytokines interleukin-1B and MIF and improved glucocorticoid receptor function.

The three different kinds of findings about these biomarkers were observed regardless of what type of antidepressant was used—SSRI versus tricyclic nortriptyline (which blocks norepinephrine reuptake).

Editor's Note: This study replicates other studies in depression where signs of inflammation have been observed, including increases in inflammatory cytokines, decreases in glucocorticoid receptor function (needed to suppress high levels of

the stress hormone cortisol) and lower levels of neuroplasticity and neuroprotection markers. This, however, is one of the first studies to show that levels of these markers at baseline may predict response to antidepressant treatment.

Also novel are the findings that while some high interleukin levels at baseline predicted antidepressant non-response, other ones normalized only in responders, and still others changed with treatment independent of whether the patients' depression improved. These exciting findings require replication, but suggest the future possibility of personalized medicine, that is, choosing medications based on an individual biochemical marker profile. Eventually direct use of anti-inflammatory agents may be necessary in those with the highest levels of cytokines (predicting non-response to conventional antidepressant treatment). The same types of studies are needed in bipolar depression to determine the relationship between these inflammatory markers and treatment response.

CRP in Blood Predicts Onset of New Episode in Childhood Mood Disorders

At the 2013 meeting of the International Society for Bipolar Disorders, researcher Barbara Gracious presented evidence that **increased levels of high sensitivity c-reactive protein (hsCRP), a marker of inflammation, were associated with an increased risk for developing a full-blown mood episode in 71 youth** (average age 13.8) participating in a study called Longitudinal Assessment of Manic Symptoms (LAMS-2). The children were selected for the study because they had manic symptoms that were not severe enough to meet criteria for a diagnosis of bipolar I or II disorder. This research has not yet been published in a peer-reviewed journal, but the

abstract can be found in first 2013 supplement of the journal *Bipolar Disorders* (page 67).

CRP levels are also known to predict cardiovascular disease and Type II diabetes. Levels of 25-OH vitamin D, TNF-alpha, and IL-6 did not predict a later mood disorder.

Editor's Note: These data suggest the importance of assessing CRP and other markers in youth who are either prodromal (having early symptoms of a mood disorder) or at high risk because of a family history of a mood disorder.

The next step for clinical research would be to determine what treatment might decrease CRP and whether it would also prevent the development of mood episodes.

Immune Therapy Studied in Alzheimer's Disease Fails

Following some research that inflammatory changes occur in patients with Alzheimer's disease, **immunotherapy with intravenous immunoglobulin (IVIG), a treatment typically used to treat autoimmune diseases and neurological problems, was investigated in Alzheimer's**. The treatment consists of a mix of antibodies derived from the blood plasma of thousands of young, healthy blood donors, which are then delivered in a slow intravenous infusion. IVIG not only includes antibodies to particular proteins implicated in Alzheimer's disease, but it also has general anti-inflammatory effects.

A particular dosage of IVIG (0.4g/kg every two weeks) seemed to completely stop progression of Alzheimer's in the four patients who received it consistently for three years as part of a small open study. (Twenty other patients received other doses of IVIG or received placebo for part of the time, and the cognitive functioning of these patients deteriorated.) However, a large, double-blind, randomized study of IVIG did not show that the treatment had greater efficacy than placebo.

Lithium Reverses Effects of Oxidative Stress on Mitochondrial Function

Oxidative stress has been implicated in a wide range of illnesses, but what is it exactly? Our bodies use the oxygen we breathe to burn the fuel we get from food, and while this is a natural process, it produces byproducts known as free radicals, which are unstable molecules that can strip electrons from other molecules in a process called oxidation. Antioxidants (such as vitamin C) act as a source of electrons, helping keep other cells stable and healthy. **Oxidative stress refers to the stress on our bodies from the normal effects of free radicals combined with environmental stressors like tobacco smoke or radiation.**

In work presented at the 2013 meeting of the Society of Biological Psychiatry, Anna Andreason showed that **over-activity of neurons increases oxidative stress through the production of reactive oxygen species (ROS).** These are a type of free radicals that can damage cells in two ways: nitrosylation of proteins (adding nitric oxide to a thiol molecule), and oxidation, which results in more lasting effects on synaptic structures. The chemical compound rotenone damages mitochondria by

producing ROS, and Andreason found that **lithium was able to reverse this production and reverse the adverse effects of oxidative stress.**

Lithium Has an Array of Positive Effects

Editor's Note: The ability of lithium to protect mitochondria (the energy storehouse of a cell) adds to an increasingly long list of lithium's neurotropic and neuroprotective benefits. Lithium increases cell survival factors BDNF and Bcl-2, increases markers of neuronal integrity such as n-acetylaspartic acid (NAA), increases the volume of the hippocampus and cortex, and now helps protect mitochondria from oxidative stress.

Lithium also increases the length of telomeres, which cap the ends of chromosome and protect them from damage during the DNA replication that occurs each time a cell divides. Short telomeres are associated with many kinds of medical and psychiatric diseases, as well as shorter life spans. No wonder that in addition to preventing mania and depression it has other clinical benefits, such as preventing memory deterioration, medical mortality, and suicide.

Anti-Inflammatory Celecoxib Improved Depression When Added to Escitalopram

Research has previously shown a link between stress, inflammation, and mood disorders. Anti-inflammatory treatments are now being explored for depression.

In an abstract presented at the 2013 meeting of the Society of Biological Psychiatry, Nadia Alvi et al. reported that **the commonly used anti-inflammatory COX-2 inhibitor celecoxib (Celebrex) showed better antidepressant effects than placebo when added to the selective serotonin reuptake inhibitor (SSRI) antidepressant escitalopram (Lexapro) in an 8-week study.**

While this research has not yet been peer-reviewed, it can be found in the 2013

convention supplement (9S) to the journal *Biological Psychiatry* as abstract #661.

Editor's Note: These data replicate a previous study and are consistent with an emerging literature that shows there are increases in signs of inflammation in both unipolar and bipolar depression. It remains to be determined whether those patients whose blood shows markers of inflammation (such as increases in C-reactive protein (CRP), interleukins 1 and 6, and TNF-alpha) are more likely to respond to anti-inflammatory treatment than patients who do not show these signs of inflammation.

Salt Implicated in Autoimmune Diseases

Autoimmune diseases, in which the body's immune system begins to attack healthy tissue, have become much more common in recent decades. Some autoimmune problems are related to overproduction of TH17 cells, immune cells that produce a particular inflammatory protein (interleukin-17), but it is not clear why some people's bodies start producing too many TH17 cells. **Three studies published in the journal Nature in 2013 suggest that salt may play a role.** They were recently summarized in *Scientific American*.

In the first study, researchers developed a model of how TH17 cells are controlled. In the second, they observed how immune cells are produced over a period of several days. The researchers noticed that a protein called serum glucocorticoid kinase 1 (SGK1), which is known to regulate salt in cells, seemed to act as a signal for TH17 production. Mouse cells in high-salt environments had more SGK1 and produced more TH17. The third study confirmed the connection with salt using both mouse cells and human cells.

While mice with multiple sclerosis (an autoimmune disease) worsen on a high-salt diet, it is not clear that salt in the diet is related to TH17 production. It is also not clear that slowing TH17 production is the answer to autoimmune diseases since autoimmunity differs across patients and disorders. However, in any event, low-salt diets are recommended for general health concerns, such as blood pressure.

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Telomere Length Important for Physical and Mental Health

Elizabeth Blackburn (who won the Nobel Prize for medicine in 2009) gave a spectacular plenary lecture at the 2013 meeting of the American Psychiatric Association, in which she described the role of telomeres in psychiatric and other medical disorders. **Telomeres are the strands of DNA at the end of each chromosome that protect the integrity of the DNA each time the cell replicates.** The end is capped to prevent damage, degeneration, and genetic instability. A minimum length must be maintained for the protection of the cells.

Telomeres shorten with aging and with each cell replication. They also shorten as a function of childhood adversity, stressors in adulthood, and number of episodes of depression. When a cell's telomeres get too short, the cell enters a period of senescence, meaning it no longer replicates. Senescence is associated with a variety of adverse events, including the possibility of apoptosis (cell death), pro-inflammatory effects,

and pro-tumor effects. The cell can begin to resemble a rotten apple that spreads its ill effects to others nearby. These effects can predispose a person to diseases such as diabetes, depression, attention deficit hyperactivity disorder (ADHD), anxiety disorders, pulmonary fibrosis, aplastic anemia, cardiovascular disorders (stroke and heart attack), osteoarthritis, immune abnormalities, dementia (in women), and premature aging.

Certain lifestyle alterations can increase telomere length, such as mindfulness/yoga training, exercise, sleep, omega-3 fatty acids, and having a positive purpose or meaning in life. Telomeres can also be lengthened by a synthetic enzyme called telomerase.

Other lifestyle factors can shorten telomeres or make telomerase less effective. Chronic stress can decrease the activity of telomerase by 50%. For people serving as the caregiver of a loved one, the longer the duration of this stress, the shorter the length of telomeres. High levels of

what Blackburn described as cynical hostility also decrease telomere length.

*Editor's Note: Here we have more evidence that stress can affect our genes. We have written before about epigenetics, the study of the process by which environmental events such as stress can leave behind methyl and acetyl groups on DNA and histones that affect how easily DNA is turned on or off. Now it seems that stress can also have profound effects on the telomeres that cap each strand of DNA and keep it stable. An overly high proportion of short chromosomes is associated with a range of psychiatric and medical illnesses. This type of non-hereditary influence on genes could mediate some of the long-term effects of the environment on health. The good news for patients with bipolar disorder is that M. Schalling et al. found that **treatment with lithium lengthened telomeres**. Perhaps the bottom line of this whole collection of fascinating data is: Take good care of your telomeres, and they will take care of you.*

Antibiotic Minocycline Could Improve Bipolar Depression

In an abstract presented at the 2013 meeting of the Society of Biological Psychiatry, Iosifescu et al. reported that **the antibiotic minocycline, which has showed anti-inflammatory, neuroprotective, and mitochondrial-sparing effects in animal models, brought about improvement in patients with bipolar depression.** Doses of 100mg to 300mg per day were successful in this small open study.

There are some positive placebo-controlled data in patients with schizophrenia who were prescribed this antibiotic. However, until now it had not been studied in bipolar disorder. The preliminary data reported here suggest that controlled double-blind studies of this agent are needed in bipolar depression.

The abstract (#497) can be found in the 2013 convention supplement (9S) to the journal *Biological Psychiatry*.

Short Telomeres, More Depressions, and Risk of the Common Cold

Too many depressions in unipolar and bipolar disorder are associated with multiple risks. These include social and employment losses, dysfunction and disability, cognitive dysfunction, reduction in hippocampal volume (in unipolar depression), increases in medical comorbidity, increased risk of cardiovascular disease, and endocrine abnormalities (see the 2012 article by this author Post et al. in the *Journal of Psychiatric Research*).

To this list we can now add short telomeres. Telomeres sit at the end of DNA strands and shorten with each cell replication. A person's percentage of short telomeres increases with aging. **The number of depressions a patient with bipolar II disorder has had is also associated with a higher percentage of short telomeres.** The magnitude of the difference in telomeres is equivalent to 10 years of aging.

An article by Cohen et al. published by the *Journal of the American Medical Association (JAMA)* in 2013 suggests that **short telomeres can even be linked to increased vulnerability to viral infections causing the common cold.** Depression has also been linked to various immune deficiencies. Whether direct alteration in immune function is responsible or whether this is mediated via telomere length remains to be determined.

Editor's Note: The moral of this story is that patients should stay on effective treatment long-term to prevent depressions in the recurrent affective disorders. This means antidepressants for unipolar depression, and mood stabilizers and atypical antipsychotics for bipolar depression. Prevent depressions and protect your brain and your telomeres (and as a bonus, you may not get so many colds).

One Doctor's Protocol for the Treatment of Severe PTSD

Note: The following article discusses "off-label" treatments for the treatment of PTSD or traumatic brain injury, i.e. those which are not approved by the Federal Drug Administration (FDA) for these purposes. In some instances, there is no controlled research to support the use of these drugs in patients with PTSD. Thus the ideas noted here cannot be taken as anything more than anecdotal information from personal experience. Patients and physicians must make their own decisions about any of the strategies reported in this or other issues of BNN.

At a recent scientific conference, Vaishali P. Bakshi, a renowned Canadian psychopharmacologist, shared a novel treatment strategy he has developed for patients with exceptionally profound degrees of post-traumatic stress disorder (PTSD), which, particularly among military veterans, can be compounded by traumatic brain injury.

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 therapies (in which the patient is gradually exposed to more of the stimuli that triggered symptoms) are the recommended psychotherapy, but despite these methods some patients remain highly disabled.

Bakshi's typical treatment algorithm goes well beyond these treatment guidelines to find solutions for hard-to-treat patients. He first addresses sleep disturbance, which often occurs in PTSD. He suggests the anticonvulsant **levetiracetam (Keppra)**, starting at doses of 150mg per night and increasing to 500-1000mg as tolerated. 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. In order to further enhance sleep effects, Bakshi adds **trazodone** at 50-150mg per night as needed.

Instead of selective serotonin reuptake inhibitors (SSRIs), Bakshi 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. Theoretically, **duloxetine (Cymbalta)** is another SNRI that could be used.

Another component of Bakshi's treatment plan is **topiramate (Topamax)**, which can target many comorbidities of PTSD, including alcohol and substance abuse, particularly stimulant abuse. In addition, topiramate has efficacy in anger attacks, which often accompany PTSD.

In patients with ongoing problems with depression and/or cognition, Bakshi adds **bupropion (Wellbutrin)**. Bupropion enhances dopamine levels in the nucleus accumbens, thus adding dopamine effects to the serotonin and noradrenergic effects of the SNRIs.

If patients remain symptomatic with depression, anger, irritability, or flashbacks, Bakshi then 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 the neuronal hyperexcitability and reactivity that can occur with PTSD.

If mood remains dysregulated, Bakshi sometimes augments the above regimen with **lithium carbonate**.

Editor's Note: Bakshi's treatment regimen is meant to target multiple neurotransmitter systems with moderate doses of a range of drugs that are not conventionally used or recommended in treatment guidelines for the treatment of PTSD. 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. Bakshi 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 addition to Bakshi's suggested treatment regimen, there are other potentially useful treatments for PTSD. The positive effects of **prazosin**, a noradrenergic alpha-1 receptor antagonist, are well documented in 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 and gambling, all of which are common in PTSD.

Another theoretical treatment that deserves study would be augmentation of lamotrigine with **memantine (Namenda)**, as in 2012 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 traumatic brain injury.

In Veterans, Post-Traumatic Stress Disorder Is Associated With Autoimmune Illnesses

At a recent scientific meeting, Thomas Neylan and colleagues reported that post-traumatic stress disorder (PTSD) may be connected to autoimmune illnesses. In their study, **673,277 veterans of the US military who had served in Iraq and Afghanistan were screened for the development of PTSD. The illness was diagnosed in 31% of the veterans, and those individuals had a higher incidence of autoimmune-related disorders including thyroiditis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and systemic lupus erythematosus.**

Neylan's research group specifically examined those whose disorders developed after the onset of the PTSD, and found that the statistical relationship between their illnesses and PTSD was strong. However, the researchers also found that there was evidence of a similarly strong relationship in the other direction: veterans who were first diagnosed with some of these same autoimmune difficulties also went on to develop PTSD.

Many previous clinical and pre-clinical studies have linked altered immune and autoimmune mechanisms to severe stressors such as those that are involved in PTSD. This is the first study to unequivocally demonstrate the relationship in an extraordinarily large number of patients.

Editor's Note: These findings resemble those that suggest that among the general population, childhood adversity is associated with an increased incidence of a variety of medical disorders in adulthood. Similarly, in the Bipolar Collaborative Network in which this editor (Post) is an investigator, we found that a history of childhood adversity in patients with bipolar disorder was associated with an increased incidence of a variety of medical illnesses in adulthood, including some related to immune and autoimmune function.

More research that would measure inflammatory markers in PTSD and mood disorders is needed. It would also be important to ascertain whether treatment of mood disorders and PTSD reduces the risk of autoimmune disorders.

Prazosin Treats PTSD Nightmares

Patients with PTSD often struggle with nightmares, but a treatment normally used for high blood pressure may also be able to prevent these sometimes horrific dreams. In a study that marks the third replication of this finding, Murray Raskind, a researcher from the University of Seattle, reported that **prazosin was significantly better than placebo at selectively blocking nightmares in 77 Iraq war veterans with PTSD in a 15-week trial.** (Interestingly, normal dreaming was uninterrupted.)

Editor's Note: Prazosin is a noradrenergic alpha-1 receptor antagonist. Doses of this drug must be titrated upward slowly over a period of 6 weeks to avoid orthostatic hypotension (a sudden fall in blood pressure that occurs when a person stands up). Maximum doses achieved in this study were 5mg mid-morning and 20mg at night (although 10mg at night is often effective). This treatment, although not FDA-approved, is increasingly being used in veteran populations and other patients with PTSD.

N-acetylcysteine Improves Blast-Induced Mild Traumatic Brain Injury

Michael E. Hoffer et al. reported in the journal *PLoSOne* in 2013 that **veterans with blast-induced mild traumatic brain injury had a better acute outcome when they were given the antioxidant N-acetylcysteine (NAC) within the first 24 hours after the trauma** versus when they were given placebo during the same period. Forty-two percent of those receiving placebo had a good acute outcome, while 86% of those receiving N-acetylcysteine had a good acute outcome. Memory loss, sleep disturbance, dizziness, and headaches all improved more in the N-acetylcysteine group. NAC's benefits diminished when it was given 3 or 7 days after the trauma.

Editor's Note: These data add to the growing list of neuropsychiatric

syndromes in which NAC has shown efficacy. These include schizophrenia, bipolar depression, unipolar depression, cocaine and heroin addiction, gambling addiction, trichotillomania (compulsive hair-pulling), obsessive-compulsive disorder (as an adjunctive treatment to SSRIs), and improvement in irritability and stereotypy (repetitive behaviors) in children with autism.

Given what appears so far to be a relatively benign side effects profile for NAC, and the potential for severe consequences from traumatic brain injury (TBI), a case for wider use of NAC (for example in emergency rooms) might be made.

The mechanisms of action of NAC in different syndromes remains to be clarified. Researcher Michael Berk used NAC in schizophrenia and bipolar disorder and

more recently in unipolar depression because it has antioxidant properties. Peter Kalivas found that NAC can normalize glutamate in the reward area of the brain through actions on the cystine-glutamate exchanger, and it also increases clearance of glutamate by increasing the glutamate transporter in glial cells. NAC decreases the amount of cued glutamate release in a part of the brain called the nucleus accumbens, which may be helpful in recovery from pathological habits. NAC also has anti-inflammatory and perhaps neuroprotective effects, and it increases brain-derived neurotrophic factor (BDNF), which protects neurons and is important for long-term learning and memory. Which of these many actions might be important in the treatment of PTSD is not yet known.

Proven Treatments for Fibromyalgia and Chronic Fatigue Syndrome

At the 2012 meeting of the Collegium Internationale Neuro-Psychopharmacologicum (CINP), a symposium was held to discuss fibromyalgia and chronic fatigue syndrome, two illnesses that remain mysterious.

Fibromyalgia

Fibromyalgia is more common in women than in men and is characterized by aching all over, decreased sleep, stiffness upon waking, and most prominently, being tired all day, as well as a host of other symptoms including headache, dizziness, and gastrointestinal upset. Researcher Siegfried Kasper suggested that treating fibromyalgia requires more than just medication. His approach is known as **MESS, which stands for medication, exercise, sleep management, and stress management.**

Medications to treat the illness include the serotonin-norepinephrine reuptake inhibitors (SNRIs) milnacipran (Savella) and duloxetine (Cymbalta), the GABA-active drug pregabalin (Lyrica), and if tolerated, low doses of the tricyclic amitriptyline (Elavil).

According to Kasper, SSRIs and anti-inflammatory drugs don't

work, and benzodiazepines decrease the deepest phase of sleep (stage 4) and can exacerbate the syndrome.

Recommended exercise is moderate, graded (to a pulse of about 120, or at a level where the patient can still talk, but can't sing), and should be done in the early morning rather than the late afternoon where it might interfere with sleep.

Good sleep hygiene is recommended, such as keeping the same sleep schedule every day and abstaining from caffeine (even in the morning).

Working on developing active coping strategies for stressors that are likely to occur is a good idea. Mindfulness and other meditative techniques may also be helpful. Joining a support group (that encourages exercise rather than discouraging it) was also recommended.

Chronic Fatigue Syndrome

At the CINP meeting researcher Simon Wessely discussed chronic fatigue syndrome (CFS), which has many overlaps with fibromyalgia. He reported that careful controlled study of more than 15,000 individuals has indicated that the illness is

not associated with a viral infection. Just as many people with and without chronic fatigue syndrome were found to be infected with a virus.

However, like the myth that vaccines cause autism, the myth that chronic fatigue is associated with a virus remains popular despite the lack of evidence. A large randomized study validated Wessely's treatment techniques, but he has continued to be vilified for the position that the illness is not virally based. The study showed that **patients who participated in cognitive behavior therapy and graded exercise improved more than those who received conventional medical management.**

Wessely thought the most important cognitive change to make was accepting that exercise is not harmful for patients with chronic fatigue syndrome, and is in fact helpful and therapeutic. Many older treatment approaches had advocated rest, rest, and more rest, or even "intensive rest." However, Wessely indicated that this would be counterproductive, as the patient would lose muscle mass and cardiovascular conditioning, and would become even more tired and chronically fatigued.

Nerve Stimulation Device May Reduce Migraines

Migraine headaches are a neurological condition in which throbbing headaches (usually on one side of the head) are accompanied by other symptoms such as nausea and sensitivity to light or sound. A recent study suggests that a device worn as a headband that can stimulate the trigeminal nerve through the skin can reduce incidence of migraines. The device, called Cefaly, is produced by Belgian company STX-Med.

In the randomized controlled study by Schoenen et al. published in *Neurology* this year, using the device for 20 minutes a day for 3 months reduced migraine days by 25% and reduced migraine attacks by 19%.

Sixty-seven patients who had at least 2 migraines per month were randomized to receive either treatment with the Cefaly device or a sham stimulation that caused a tingling sensation without stimulating the trigeminal nerve.

Schoenen told *Medscape Medical News* that the device may be a useful addition to current treatments, and has the benefit of not producing side effects.

The device is already available in Europe, Canada, and several South American and Middle Eastern countries. It is currently awaiting approval in the US. In those countries where it is approved, it does not require a prescription and can be bought directly by a patient at a cost of €295 or \$299 (CAD).

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The Myth of Neurogenesis in Adult Primates

In a plenary lecture at the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in Istanbul in 2012, Pasco Rakic, professor of neuroanatomy at Yale University, may have debunked a myth of modern medicine, one that we have cited in many previous BNNs. Despite what has been written by famous neuroscientists and published in the most prestigious journals, including *Science*, *Cell*, and *PNAS*, based on data in rodents, Rakic presented evidence that neurogenesis does not occur to any substantial extent in adult primates.

Two decades ago, data in rodents and other species clearly indicated that neurogenesis, the creation of new neurons, occurred in adult animals, especially in the dentate gyrus of the hippocampus. Thousands of papers were written on the subject, and neurogenesis was understood to be possible in adult humans as well. It was even suggested based on data in rodents that the mechanism of action of antidepressants was dependent on neurogenesis. However, Rakic argues that most of the research on neurogenesis was based on faulty data.

Rakic found that while rats do have neurogenesis into adolescence, it diminishes greatly in older adult animals. In primates, neurogenesis in the cortex ends before birth. In the primate dentate gyrus of the hippocampus, there is some postnatal neurogenesis, but it rapidly drops toward zero in the first months of life. Rakic concludes: "We are as old as our neurons...or slightly younger."

Why should primates have permanent stores of neurons when rodents and other lower animal species get new

ones further into their lifespan? Rakic postulates that for primates, neurons must hold experience-dependent memories necessary for the survival of the species, and turning them over would endanger the permanence of this memory. Whatever the reason, it is disappointing to find out that the revolutionary discovery of adult neurogenesis in rodents so widely presumed to also occur in adult primates and humans may not be correct.

This has clinical implications. If we don't get replacement hippocampal neurons like rats do, it is even more important to protect

the billions of neurons that we do have. **There are many things that endanger neurons, including inflammation, oxidative stress, high cortisol, poor diet, psychosocial adversity, and episodes of depression and mania.** Greater numbers of mood episodes are associated with increasing degrees of cognitive dysfunction because of these many factors. A startling statistic from Denmark by Lars Kessing is that having four or more hospitalizations for depression (either unipolar or bipolar) doubles the risk for a diagnosis of dementia in late life. Thus, it looks like too many episodes hurt the brain.

However, on the positive side, the mood stabilizers (lithium, lamotrigine, valproate, and carbamazepine) and some atypical antipsychotics prevent episodes and increase brain-derived neurotrophic factor (BDNF). The evidence is best for lithium having neuroprotective effects that can be directly observed in humans. BDNF facilitates the creation of new synapses and helps protect neurons, and is produced in selected neurons in the

Lithium Increases Hippocampal Volume

There is some evidence that lithium can affect brain structure, particularly the size of various parts of the brain. A study by Hajek et al. presented at the 2013 meeting of the International Society of Bipolar Disorders examined patients with bipolar disorder who had either received lithium for at least two years (37 patients) or had received under three months of treatment with lithium (19 patients), and compared the size of the hippocampus in these two groups and one control group (50 people). The patients with bipolar disorder all had the disorder for at least 10 years (25 years on average) and had had a minimum of five episodes.

Those treated with lithium long-term had greater hippocampal volume than the non-lithium patients (despite having spent more time in episodes of illness), and equal volume to healthy controls. Measurements were collected via magnetic resonance imaging (MRI), and analyses were done two different ways to avoid being confounded by the changes lithium may have on water balance in the brain, a phenomenon that was recently found to affect MRI images.

Editor's Note: These data add to the large number of studies in animals and humans indicating that lithium, in addition to preventing episodes and suicides, may have neurotrophic and neuroprotective effects.

brain and decreases with stress and affective episodes, further endangering neurons. Since many effective treatments prevent both episodes and their associated decreases in BDNF in addition to directly increasing BDNF, they may have a dual positive benefit. Thus a not unreasonable mantra for patients with recurrent mood disorders is: "Prevent Episodes, Protect the Brain."

"We are as old as our neurons...or slightly younger."

Childhood Adversity and Epigenetic Pockmarks

Maltreatment in childhood may have a lasting impact on health through epigenetics. Epigenetics refers to the idea that events and substances in the environment can affect the structure of DNA by adding chemicals (often methyl or acetyl groups) onto DNA and histones (structures around which DNA is wound) in such a way that the DNA is more or less likely to be transcribed and activated to produce new proteins. Thus our DNA is shaped not only by the genetic inheritance we receive from our parents, but also by events in the environment (which do not alter the sequence of DNA but can influence how easily the DNA gets turned on to produce proteins in our bodies.)

A 2013 study by Divya Mehta et al. in the *Proceedings of the National Academy of Sciences* analyzed the childhoods of adult patients with PTSD and found that patients' profiles of disease-related gene expression and DNA methylation in blood differed greatly depending on whether or not they had experienced abuse in childhood. **Adults who had been abused as children were about twice as likely to show patterns of DNA methylation accompanying their PTSD-related changes in gene expression.**

The implication of this research is that childhood trauma can leave a series of epigenetic pockmarks on a person's DNA, affecting the way the DNA produces proteins, potentially for the rest of that person's life.

Ambien Linked to Emergency Room Visits, Other Risks

Zolpidem, better known by one of its trade names, Ambien, is widely prescribed for the short-term treatment of insomnia. It can sometimes cause adverse reactions, particularly among women and the elderly. The Substance Abuse and Mental Health Services Administration (SAMHSA) has reported that **over a recent 5-year period, emergency department visits for adverse reactions to zolpidem increased by almost 220%.**

Peter Delaney, Director of SAMSHA's Center for Behavioral Health Statistics and Quality, suggested that doctors should consider alternative strategies for treating insomnia, including improving sleep hygiene by avoiding caffeine, exercising regularly, and sleeping in a quiet, dark room. He also suggested that doctors should be aware of what other medications a patient is taking, and ideally all of a patient's prescriptions should be collected from the same pharmacy, so the pharmacist can act as a second pair of eyes identifying possible drug interactions.

Women and men metabolize zolpidem differently, and according to Sam Fleishman of the American Academy of Sleep Medicine, many women can still be impaired by the drug 8 hours after taking it. In 2013, after reports of adverse reactions to zolpidem increased, the Federal Drug Administration (FDA) required manufacturers of drugs containing zolpidem to reduce the recommended dose for women by half, from 10 mg to 5 mg, or 12.5 mg to 6.25 mg for the extended-release version. The FDA also suggested halving the dosage prescribed to the elderly, and reducing the recommended dose for men.

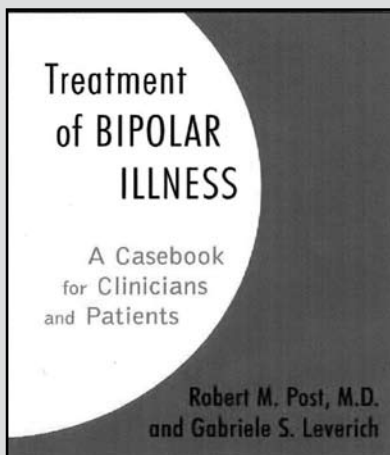
Some of the adverse reactions to drugs containing zolpidem include daytime drowsiness, dizziness, hallucinations, sleepwalking, and even "sleep driving." When combined with antianxiety medications, narcotic pain relievers, or alcohol, zolpidem's sedative effects can be enhanced to dangerous levels.

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From W.W. Norton & Company:

Treatment of Bipolar Illness: A Casebook for Clinicians and Patients

ROBERT M. POST, MD
and
GABRIELE S. LEVERICH, LCSW, BCD



BNN editors have written a book to provide physicians, patients and family members with the latest information about the illness and its treatments.

In a review in the *Journal of Psychiatric Practice*, Mark Frye of the Mayo Clinic gave the book 5 stars and wrote:

"This textbook by Post and Leverich is the most up-to-date, comprehensive visual teaching guide on the phenomenology, longitudinal course, and treatment of bipolar disorder currently available."

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BDNF Is Decreased in Depression and Mania

Brain-derived neurotrophic factor (BDNF), which protects neurons and is necessary for long-term memory, can be measured in blood. In a symposium on bipolar disorder at the 2012 meeting of the Society of Biological Psychiatry, researcher Flavio Kapschinski reviewed evidence from several meta-analyses showing that **low levels of BDNF in the blood correlate with severity of an episode of depression or mania**. In addition to the findings that BDNF levels are low during a mood episode, there are other reliable biomarkers of illness, including increases in intracellular calcium, increases in cortisol and failure to suppress cortisol by dexamethasone, and a variety of indices of inflammation and oxidative stress.

There are several common variants of the gene responsible for the production of BDNF, depending on which types of amino acids appear in its coding—valine or methionine. The Val66Val allele of proBDNF is the most frequently occurring in the population, and is the best-functioning variant. Those with a methionine substitution (Val66Met or Met66Met) have less efficient forms of BDNF. Researcher Jair Soares reported that **the Met allele was associated with deficits in declarative memory in patients with bipolar disorder, and was also associated with smaller volume of the anterior cingulate gyrus**.

Researcher Ghanshyam N. Pandey reported that **patients with pediatric or adult bipolar disorder had decreased BDNF protein and mRNA levels in platelets and lymphocytes compared to controls**. Treatment significantly increased these BDNF levels in the pediatric, but not in the adult bipolar subjects. These measurements in blood are consistent with findings that there are decreases in BDNF in the hippocampus and prefrontal cortex of patients who died while depressed or who committed suicide compared to controls.

Gap in Life Expectancy Between Psychiatric Patients and the General Population Grows

A study published by Lawrence et al. in the journal *BMJ* in 2013 suggests that the gap in life expectancy between psychiatric patients and the general population is widening. This was due more to poor physical health than to suicide.

Investigators at the University of Western Australia in Perth found that within that geographic region, the gap in life expectancy for males with all mental disorders combined compared to males in the general population increased from 13.5 years in 1985 to 15.9 years in 2005. For females, the gap increased from 10.4 years in 1985 to 12.0 years in 2005.

Editor's Note: Data from the US suggest even greater loss of years of life expectancy

in those with serious mental illnesses. In the best case, patients in Virginia lost an average of 13 years of life expectancy compared to the general population, while in some western states up to 28 years of life expectancy were lost by the average patient.

Cardiovascular disease is one of the biggest contributors to these almost unbelievable statistics. It is possible that short telomeres resulting from stressors, episodes of depression, abused substances, and a variety of poor life-style factors such as smoking and lack of exercise also contribute to this huge deficit in longevity. Other factors that can co-occur with bipolar illness, such as inflammation, high cortisol, and oxidative stress, are likely problematic as well.

U.S. Patients with Bipolar Disorder Have More Stressors in Childhood and Prior to Illness Onset

In research published since 2008, our Editor-in-Chief Robert M. Post and colleagues in the Bipolar Collaborative Network have compared patients with bipolar disorder in the United States to those in Germany and the Netherlands. **Compared to the European sample, patients in the US have more genetic vulnerability to bipolar disorder (by having a parent with bipolar disorder), earlier onsets of their illness, more complicated courses of illness, greater treatment resistance, and more medical comorbidities**. Patients in the US also have more psychosocial stress.

The researchers are now turning their attention to these psychosocial vulnerabilities, and in a new paper that will be published in *Psychiatry Research* (late in 2013 or early in 2014), the authors show that patients in the US had more stressors both in childhood and just prior to the onset of their illness. **Childhood stressors analyzed in the study were verbal abuse, physical abuse, and**

sexual abuse. Stressors in adulthood included indicators of a lack of social support, troubles with finances or employment, lack of access to health care, and medical comorbidities.

The stressors patients experienced just prior to their most recent episode of bipolar illness were related to: stressors in childhood, an earlier age of illness onset, anxiety and substance abuse comorbidity, lower income, both parents having an affective illness such as depression, and feeling more stigma.

The new research suggests that for patients with bipolar disorder in the US, adverse life events in childhood and later in life are more prevalent than they are for patients in the Netherlands or Germany. Earlier and more effective approaches to these stressors, such as the Family-Focused Therapy developed by David Miklowitz and Kiki Chang, could potentially slow the onset or progression of bipolar illness in this country.

High Level of Calcium Intake and Supplements May Be Harmful

In a study of over 60,000 women, Swedish researcher Karl Michaëlsson et al. found that those **women with the highest intakes of calcium (>1400mg/day) were at higher risk of mortality, particularly from cardiovascular causes such as cardiovascular disease and heart disease** (but not stroke), than women with calcium intakes of between 600 and 1000mg/day. The research was published in the journal *BMJ* in 2013.

While calcium dietary supplements were not associated with elevated risk per se, those women with the highest calcium intake levels who also took

supplements had a risk of mortality from all causes that was more than 2.5 times that of women with similar total calcium intake who did not take supplements.

Calcium levels in blood are tightly controlled by the body, but very low or very high calcium intake levels can override this control, causing imbalances.

The efficacy of calcium supplements for conditions such as osteoporosis or chronic kidney disease has not been established, and a healthy balanced diet and avoidance of water filters that remove calcium from drinking water may be best.

Health Benefits from Chocolate

Very dark chocolate made mostly from cocoa beans may be good for you. Cocoa is high in flavanols, which belong to a class of antioxidants called flavonoids. **Dark chocolate has been associated with lowered risk of heart attack and stroke, improvements in cognition, lower body mass index (BMI, a weight to height ratio), dilation of blood vessels and lower blood pressure, and improved cholesterol profiles.** This is despite containing a lot of saturated fat. Among a study of 37,000 Swedish men, individuals who ate at least 1.8oz of dark chocolate a week had a 17% lower risk of stroke than those who ate less than 0.4oz a week.

Moderation is important. Two ounces of dark chocolate contain about 440 calories, so while a little may be good, a lot may not be so good. Watch out for milk chocolate and highly processed chocolates with great quantities of sugar added, they contain more calories and fewer health benefits.

A balanced diet and regular exercise are keys to good health, but don't feel too guilty if you top off a balanced meal with a piece of the dark stuff.

Cinnamon's Positive Effects in Type II Diabetes

Cinnamon has multiple positive effects that were affirmed in a meta-analysis by Robert W. Allen et al. in *Annals of Family Medicine* in 2013. **Cinnamon lowered blood sugar, insulin levels, triglycerides, and low-density lipoproteins ("bad" cholesterol) while increasing high-density lipoproteins ("good" cholesterol).** Cinnamon did not lower hemoglobin A1C, a global measure of glucose dysregulation, but that result could be explained by the short durations of some of the studies included in the meta-analysis.

Editor's Note: Cinnamon's role in the fight against type II diabetes remains to be determined, but a little bit may help those with diabetes or at risk for it. The researchers who produced the meta-analysis could not make a recommendation about how much cinnamon to add to one's diet because the studies included in the meta-analysis had explored a wide range of doses.

Safe Upper Limit of Vitamin D Identified

A recent study confirmed that low levels of vitamin D can increase risk of death and determined a safe upper limit for vitamin D levels. The research, published by Yosef Dror et al. in the *Journal of Clinical Endocrinology & Metabolism*, showed that safe blood levels of vitamin D are between 20 and 36ng/mL. People with levels above or below this range were at greater risk of mortality or acute coronary syndrome.

Dror suggests that supplement dosages should be specifically tailored to individuals based on levels in their blood.

The research comes from 54 months of data collection during which 422,822 members of Clalit Health Services, an Israeli health maintenance organization, were tested for vitamin D levels. Only 3% percent of this population were at risk because of high levels of the vitamin, while 62% were at risk due to low levels of vitamin D.

Editor's Note: Watch out for low vitamin D3. Even if a patient's levels of D3 are in the normal range, supplementation can help antidepressants work better. According to a study published by Khoraminy et al. in the Australian and New Zealand Journal of Psychiatry in 2013, adding 1500 IU of vitamin D3 to the treatment regimen of depressed patients taking fluoxetine (Prozac) improved their response significantly.

Iodine Deficiency in Pregnancy May Affect Fetus

A study published in the *Lancet* in 2013 reports that **even mild iodine deficiency during pregnancy can have adverse effects on IQ and cognitive development in the fetus.** This occurs because of the deficiency's effects on thyroid function.

Editor's Note: Eat fish, drink milk and take a vitamin supplement with 140 to 150mcg of iodine.

Bicycling Fast May Improve Parkinson's Symptoms

Bicycling at speeds of 77–80 rpm seems to benefit patients with Parkinson's disease. After neuroscientist Jay Alberts and one of his patients rode a tandem bicycle across Iowa to raise awareness of the illness, he noticed that her symptoms had improved. He had ridden in front, setting a pace that forced her to pedal faster. Their experience inspired the study, in which 26 patients with Parkinson's were assigned to either ride a stationary bike at their own pace, or ride at a forced rate, where a trainer in the front seat of a tandem bicycle controlled the pedaling rate, which was at least 30% faster than the voluntary rates. After 8 weeks of thrice weekly pedaling, the forced-rate group saw a 35% improvement in symptoms, compared to no improvement in the voluntary-rate group.

Study authors used functional connectivity magnetic resonance imaging (fcMRI) to measure levels of blood oxygen in the brain before, immediately after, and 4 weeks after the 8 weeks of exercise therapy. In the fast pedaling group, task-related connectivity between the primary motor cortex and the posterior part of the thalamus improved. Some cortical regions in the brain showed less activity, suggesting that Parkinson's patients who usually must use these areas to compensate for their motor deficits required less of this alternative brain activity after the exercise therapy. The research was presented at the Radiological Society of America's annual meeting in 2012.

Obesity and Bipolar Disorder Risks

David Bond presented research at the 2013 meeting of the International Society of Bipolar Disorder about the connections between obesity and the course of bipolar disorder. Bipolar disorder has some of the highest rates of obesity among all psychiatric illnesses. **Obese patients with bipolar disorder have more episodes of depression, more suicide attempts, worse response to psychiatric medications, and more cognitive impairment between episodes of illness.**

Bond also found that higher body mass index (BMI) was associated with reduced white and gray matter volume in the brain, greater cognitive impairment, increased risk of Alzheimer's

disease, and increased glutamate concentration in the hippocampus (which is potentially neurotoxic) and decreased NAA (a marker of neuronal integrity). Those with 7% weight gain or higher in the first year of treatment show a greater loss of volume in the frontal and temporal lobes.

Editor's Note: These data again speak to the importance of maintaining good lifestyle habits such as proper diet and exercise to attempt to slow or prevent the development of obesity. Also avoiding medications for bipolar disorder with the greatest liability for weight gain and using some that can help with weight loss would be good topics for discussion with a treating physician.

Most Online Pharmacies Fake, Says FDA

In late 2012, the Federal Drug Administration announced that **97% of online pharmacies violated state or federal laws and/or safety and practice standards** set by the National Association of Boards of Pharmacy. Medications sold by fake pharmacies may be fake, expired, contaminated, not approved by the FDA, or unsafe.

Here are some warning signs that may mean an online pharmacy is fake:

- Allows you to buy medications without a prescription.
- Offers prices that are too good to be true.
- Sends spam emails offering discount prices.
- Is located outside the US.
- Is not licensed in the US.

Real pharmacies are licensed by the state where they are located. They should provide a physical address and phone number, where you can reach a pharmacist who can answer your questions.

Statin Benefits for Mood, Brain, and Heart Seem to Outweigh Diabetes Risk

Statins are a class of drugs that are the most commonly prescribed treatment for high cholesterol. They can reduce risk of heart attack and stroke in people with a history of cardiovascular disease. **New research is beginning to clarify statins' other effects, which on the negative side can include increased risk of diabetes and liver and muscle inflammation, and on the positive side can include reduced risk of cataracts and prevention of depression and dementia.**

In late 2012, the American Heart Association Scientific Sessions included a discussion of five new studies suggesting that the cardiovascular benefit of taking statins is worth the slightly increased risk of diabetes. Researchers at the conference explained that **cardiovascular events are much more serious than the small increase in risk of diabetes.** While all five studies showed an increase in diabetes risk,

the absolute increase was low and depended on the patients' level of risk prior to treatment and how high their doses of statins were. There are strategies that can reduce diabetes risk in statins users, including using bile-acid sequestrants, reducing niacin, and monitoring glucose. Consensus at the conference was that statins' cardiovascular benefits are so important that the drugs shouldn't be avoided because of concerns about diabetes.

In addition, statins' beneficial effects on mood have been reported for several years. In 2010, an epidemiological study by Pasco et al. in *Psychotherapy and Psychosomatics* showed that **subjects without depression were less likely to develop a new onset of depression if they were treated with statins compared to those who were not.** Stafford et al. reported in the *Journal of Clinical Psychiatry* in 2010 that patients taking statins had a 79%

decreased likelihood of depression at 9 months of follow-up. Moreover, a 2012 meta-analysis by O'Neil et al. in *BMC Medicine* reported that overall, statins had positive effects on mood.

A recent huge Taiwanese study of statins suggests that the drugs can also prevent dementia. At the European Society of Cardiology congress in 2013, Tin-Tse Lin reported that among 58,000 people studied, **those taking the highest dosage of statins had a threefold decrease in risk of developing pre-senile and senile dementia.** He explained that it was the potency of statins such as atorvastatin and rosuvastatin that provided the cognitive benefit. However it is high doses that lead to less benign side effects such as liver and muscle inflammation.

A separate US study presented at the congress showed that **statin use also lowered risk of developing cataracts by 19%.**

Citicoline Might Improve Memory

We've written before that the dietary supplement citicoline improved depression in both unipolar and bipolar patients with methamphetamine dependence, reduced cocaine use in bipolar depressed patients with cocaine dependence, and improved cognition in healthy middle-aged women. Findings from a 2013 Italian study by Gareri et al. published in *Clinical Interventions in Aging* suggests that **citicoline improves vascular-based mild cognitive impairment in older adults**, though the study was not randomized, so its results may not be reliable. Citicoline is a natural substance found in the brain and the liver that can also be taken as a nutritional supplement.

The study examined 349 patients over age 64 (mean age 79.9) who had memory impairment

and evidence of vascular lesions in the brain (but not Alzheimer's disease). Participants who received citicoline (500mg twice daily for 9 months) scored better on a memory examination at 3 months and at the completion of the study, while participants who did not receive citicoline performed worse on the exam. Those who received citicoline also saw some statistically non-significant improvement in mood.

The researchers believe that citicoline's effects may also extend to Alzheimer's dementia because citicoline contributes to the synthesis of acetylcholine. (Most Alzheimer's drugs inhibit the breakdown of acetylcholine).

Side effects were minimal, and included occasional excitability or restlessness, digestive intolerance, and headaches.

Mindfulness Training Improves Depression and Stress in Adolescents

A recent study in the UK compared students whose schools instituted the 9-week international Mindfulness in Schools Program (MiSP) curriculum to those who were taught a standard curriculum. Students at schools with MiSP were taught techniques for sustaining attention aimed at changing their thoughts, actions, and feelings.

Students who participated in MiSP training had fewer depressive symptoms immediately after the training and three months later. They also reported lower stress and greater well-being at follow-up. Those students using the techniques they learned in the program more consistently had

Continued on Page 15

Higher Levels of Caffeine in Blood May Be Associated With Less Dementia

Alzheimer's disease and other kinds of dementia can be devastating. Researchers are looking for treatments and lifestyle choices that may prevent, slow, or lessen the likelihood of serious dementia. Some epidemiological research in humans and other studies of animals has suggested that consumption of coffee or caffeine may help protect against the development of Alzheimer's disease. A 2012 study by Arendash et al. published in the *Journal of Alzheimer's Disease* sought to clarify the connection between coffee and cognitive status. The researchers also collected data on biomarkers in blood.

In patients with mild cognitive impairment, those patients whose blood levels of caffeine were 1200 ng/mL or higher (an amount that would result from drinking 3–5 cups of coffee daily) did not develop dementia during the following two to four years, while half of those whose blood levels of caffeine were below this threshold did. Moreover, those patients who had

mild cognitive impairment at the beginning of the study had lower levels of caffeine than those who had normal cognitive functioning at that time.

Patients with mild cognitive impairment who later developed dementia had low levels of three biomarkers in their blood – the neurotrophic factor granulocyte colony-stimulating factor (G-CSF), the anti-inflammatory cytokine IL-10, and the pro-inflammatory cytokine IL-6. This suggests that low levels of these biomarkers may be a predictor of impending Alzheimer's disease. G-CSF, in particular, has shown beneficial effects on cognition in mice.

Since half of patients with lower levels of caffeine did not develop dementia, it is clear that caffeine is far from being the only factor that could affect cognitive functioning. Arendash suggested that other factors may include levels of cognitive and physical activity, hypertension (high blood pressure), and antioxidant intake, especially from fruits and vegetables.

Editor's Note: This study of caffeine was not randomized and is subject to other interpretations. For example, people who drink less coffee may have more hypertension, which is associated with dementia risk. However, the study does raise the possibility that caffeine could have positive effects on the brain (especially if it does not make a patient anxious or insomniac).

The caffeine findings are also supported by studies of dementia in mice. Long-term administration of caffeine to these animals resulted in a similar biomarker profile and prevented cognitive impairment.

Other treatments may also be useful in preventing cognitive decline. In BNN Volume 16, Issue 5 from 2012, we wrote about a one-year prospective study published by Forlenza et al. in the British Journal of Psychiatry in 2011 that showed that lithium at the small dose of 150mg per day reduced the rate of cognitive decline in those with mild cognitive impairment compared to placebo.

Mindfulness Training

Continued from Page 14

better scores for depression, stress, and well-being than their peers who used the techniques less often. The study by Kuyken et al., which was published in the *British Journal of Psychiatry* in 2013, included 522 students between the ages of 12 and 16.

Psychological well-being has been linked to better learning and performance in school, in addition to better social relationships. Researchers suggested that because this kind of mindfulness training is designed to help students deal with everyday stressors and experiences, it has benefits for all students, regardless of their level of well-being.

Preventing Cognitive Decline in Bipolar Disorder

Here are some suggestions from BNN Editor-in-Chief Robert M. Post, MD for preventing or treating cognitive decline in patients with bipolar disorder.

1. Prevent Episodes with Long-term Prophylaxis
2. Decrease Sedating or Impairing Drugs
3. Add Folate to Decrease Homocysteine
4. Treat Depression to Full Remission
5. Consider Adding:
 - a. Bupropion (Wellbutrin) for Mood and ADHD
 - b. Modafinil (Provigil) or Armodafinil (Nuvigil) for Attention, ADHD, and Mood
 - c. A Stimulant for ADHD
6. Add Lithium at 150mg/day for Neuroprotection in Mild Cognitive Impairment
7. Add Levitracetam at 125mg/day to Decrease Hippocampal Hyperactivity
8. Treat Dementia Symptoms Early with:
 - a. Memantine (Namenda) AND/OR
 - b. Acetylcholine Esterase Inhibitors Such As Donepezil (Aricept)
9. Consider Adding an Anti-inflammatory Agent

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