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Bipolar Network News

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IV Ketamine 2 or 3 Times Per Week Improves Depression

We have written many times before about intravenous ketamine as a fast-acting antidepressant treatment that can produce results within hours. Unfortunately, these quick results tend to fade within a few days. Current research is focused on possible ways of extending ketamine's antidepressant effects.

A 2016 article by Jaskaran B. Singh and colleagues in the *American Journal of Psychiatry* reported that **giving depressed patients infusions of ketamine (0.5mg/kg of body weight) twice or three times per week improved their depression compared to placebo over a period of up to 2 weeks.**

Side effects included headache, anxiety, dissociation, nausea, and dizziness. The dissociation was temporary and improved with repeated dosing.

Mouse Study Shows That Ketamine Metabolite May Treat Depression with Fewer Side Effects

The drug ketamine has been used intravenously for years to rapidly treat depression, taking effect within hours. Unfortunately, its antidepressant effects fade in 3–5 days, and it has some unpleasant side effects. In larger doses ketamine is used as an anesthetic and sometimes as a club drug, for its ability to induce hallucinations and dissociation. It can be addictive as well.

A 2016 animal study by Todd Gould and colleagues published in the journal *Nature* identified a byproduct of ketamine that may be able to provide the drug's benefits without its side effects.

When the body breaks down ketamine, it produces several chemicals that are known as ketamine metabolites. The researchers found that one of these, called **hydroxynorketamine, reversed a depression-like state in mice, without producing the side effects that would be expected of ketamine.**

Gould and colleagues also determined that blocking the transformation of ketamine into hydroxynorketamine prevented ketamine's antidepressant effects.

Ketamine's unpleasant anesthetic and dissociative effects result from the blockade of a particular receptor for the neurotransmitter glutamate (the NMDA glutamate receptor). Researchers originally thought that the NMDA blockade was linked to ketamine's antidepressant effects, but this appears not to be the case. Instead, hydroxynorketamine seems to activate a different type of glutamate receptor, the AMPA receptor.

Gould and colleagues plan to test hydroxynorketamine in humans soon. Because it has already been present in the human body following ketamine administration, they expect it to be safe.

Oral Ketamine Relieves Depression in Patients with Chronic Pain

Ketamine, which is used as an anesthetic at higher doses, can also relieve depression within hours when delivered intravenously. A 2016 study by Morteza Jafarinia and colleagues in the *Journal of Affective Disorders* suggests that **oral ketamine may be helpful in the treatment of mild to moderate depression in people with chronic pain.**

The study compared 150mg daily doses of oral ketamine to 150mg daily doses of the anti-inflammatory pain reliever diclofenac over 6 weeks. When interviewed at week 3 and week 6, the ketamine group reported significantly fewer symptoms of depression than the diclofenac group.

In This Issue:

Antidepressant Brintellix Renamed Trintellix

You may notice the label on your prescription bottle changing. As of June, the antidepressant vortioxetine (formerly Brintellix) is now called Trintellix. The US Food and Drug Administration approved the change to reduce any possible confusion of the antidepressant with a blood-thinning medication called Brilinta.

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Weight Gain is a Common Issue with Antidepressants, But Buproprion is an Exception

A 2016 study by researcher David Arterburn and colleagues in the *Journal of Clinical Medicine* suggests that taking an antidepressant for two years is associated with an increase in body weight. Luckily, bupropion (trade name Wellbutrin) is an exception that may be a good choice for obese or overweight patients.

The researchers analyzed links between which antidepressants patients in a large health system in Washington State were prescribed and their body weight two years later.

The researchers used fluoxetine (Prozac) as a reference. Most antidepressants did not differ significantly from fluoxetine in terms of the weight gain experienced by people taking the drug.

There were a few exceptions. **Compared to non-smoking fluoxetine users, who gained an average of 4.6 pounds in two years, non-smoking bupropion users lost an average of 2.4 pounds.** (Smokers taking bupropion gained an average of 6.9 pounds.)

Sertraline was another exception. Sertraline users gained more than users of other antidepressants—an average of 10.5 pounds over two years.

SNRI Viloxazine May Be Reintroduced as ADHD Treatment

The pharmaceutical company Supernus identifies older drugs that may be repurposed to treat other disorders. The company believes it may have found a new use for the discontinued antidepressant viloxazine, as a treatment for attention deficit hyperactivity disorder (ADHD).

Viloxazine is a selective norepinephrine reuptake inhibitor, or NRI, that was approved in Europe but not in the US and was eventually removed from the market due to competition from other drugs. Its structure and mechanism of action resemble those of the ADHD treatment atomoxetine, so Supernus has begun trials of viloxazine for ADHD in adults.

At the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, the researchers reported that compared to placebo, viloxazine was about twice as likely to reduce ADHD symptoms. Side effects included nausea, decreased appetite, headache, and insomnia. Supernus hopes to create an extended release form of the drug for both adults and children.

Schizophrenia Drug May Treat ADHD with Impulsive Aggression

The atypical antipsychotic drug molindone was used to treat schizophrenia for decades before it was pulled from the market in 2010 for business reasons. Now Supernus Pharmaceuticals is studying whether a reformulation of the drug may be used to treat attention deficit hyperactivity disorder (ADHD) that is accompanied by impulsive aggression.

Supernus tested an extended-release form of molindone in 118 children aged 6–12 with ADHD and impulsive aggression. They received either placebo or between 12mg and 54mg per day of molindone for 39 days. **Those children who received between 12mg and 36mg per day of molindone showed fewer symptoms of impulsive aggression that those who received placebo.** Side effects included headache, sedation, and increased appetite. Supernus says that clinical trials of molindone will continue.

Editor's Note: molindone has relatively little effect on body weight.

Depression Elevates Stroke Risk

Depression has been linked to increases in medical problems such as cardiovascular disease. A new study shows that depression is linked to increased risk of stroke, even when symptoms of depression are in remission.

The 2015 study, by Paola Gilsanz and colleagues in the *Journal of the American Heart Association*, focused on health and retirement. It included over 16,000 adults aged 50 and up who were interviewed every two years about their health history.

Previous studies have shown a link between depression and stroke risk. Like those studies, the study by Gilsanz and colleagues found that **people who were depressed during two consecutive interviews were more than twice as likely to have a stroke in the subsequent two-year period than those who reported few depressive symptoms in the first two visits.**

What is new is that in this study, people who were depressed in the first interview but not in the second interview were still at 66% greater risk for a stroke than those with no depression. Those who were depressed only during the second interview not at greater risk for a stroke, implying that depression takes more than two years to affect stroke risk.

Gilsanz and colleagues suggest that they don't know how depression, remission, and stroke risk interact over the longer term. It is possible that stroke risk diminishes the longer a patient's depression stays in remission.

It is not clear why depression increases strokes, though some have speculated that depression causes irregular heartbeats. There is not as yet any support for that theory, but high blood pressure, rigid veins, or sticky platelets may be other explanations.

Inflammation Linked to Post-Stroke Depression

A 2016 study in the journal *Psychoneuroendocrinology* confirms that high levels of inflammatory cytokines in the blood are linked to higher risk of depression following a stroke.

The study, by Hee-Ju Kang and colleagues, followed 222 stroke sufferers for one year. Two weeks following the stroke, their levels of inflammatory cytokines IL-6 and IL-18 were measured. They were also assessed for depression both at the two-week point and one year later. The researchers also observed whether or not the participants were treated with statins, which are often prescribed to lower stroke risk and also have anti-inflammatory effects.

Those participants who had depression following their strokes (either at two weeks or at one year) tended to be older, to have a history of depression or stroke, to have a more severe stroke, and to have a stroke location toward the front of the brain.

Having any depression following the stroke was associated with higher levels of IL-6 and IL-18. This was particularly true of those participants who were not taking a statin. Among those taking statins, the statins may have interfered with the link between inflammatory cytokines and post-stroke depression. In the statin group, the only significant finding was a link between levels of IL-6 and depression at the two-week mark.

Statins Can Help Treat Depression

Depression and poor cardiovascular health often go hand in hand. Now it seems a treatment for high cholesterol may also help treat depression. A 2016 study by E. Salagre and colleagues in the *Journal of Affective Disorders* analyzed evidence from 3 earlier studies of drugs called statins, which inhibit an enzyme needed for the production of cholesterol, for people with depression.

The three studies included a total of 165 participants taking an antidepressant (citalopram or fluoxetine) for moderate or severe depression. Of these participants, 82 were prescribed a statin (lovastatin, atorvastatin, or simvastatin) in addition to the antidepressant, while the remaining were given a placebo in addition to the antidepressant. **After 6 to 12 weeks, those who had received a statin reported greater improvement in their depression than those who had received a placebo.** No serious side effects were reported.

These data are also consistent with other studies showing that women on statins had fewer depressions over subsequent years than those not taking statins.

SSRIs and Statins Better than SSRIs Alone

A large study in Denmark suggests that taking selective serotonin reuptake inhibitor (SSRI) antidepressants alongside cholesterol-lowering statin drugs improved depression more than SSRIs alone. The findings, by Ole Köhler and colleagues were reported in the *American Journal of Psychiatry* in 2016.

The study included 872,216 people in Denmark's national health care database who took SSRIs between 1997 and 2012. The most common SSRIs were citalopram, sertraline, and escitalopram. Of these people taking SSRIs, 13.0% also took a statin drug, typically simvastatin. **Those patients who were taking both an SSRI and a statin were less likely than those taking an SSRI alone to be hospitalized for any psychiatric problem, or for depression specifically.**

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Mindfulness-Based Cognitive Therapy May Improve Depression More Than Fitness Intervention

In a study by researcher Stuart Eisendrath and colleagues, people with treatment-resistant unipolar depression responded better to an intervention that combined mindfulness training with cognitive therapy than to one that included exercise, nutrition counseling, and music therapy.

The 173 participants had failed to respond to at least two different antidepressant medications. During the study period, all participants were taking an antidepressant, but none were receiving other types of therapy.

After eight weeks, the mindfulness-based cognitive therapy (MBCT) group showed greater improvement in their depression symptoms than the exercise and nutrition group. Of the MBCT group, 29.58% had a large reduction in symptoms, while 17.19% of the comparison group showed a similarly large reduction in symptoms.

A subgroup of the participants also received functional magnetic resonance imaging (fMRI) as part of the study. While completing a task related to emotional working memory, the MBCT group showed enhanced activation of the dorsal lateral prefrontal cortex (to levels seen in non-depressed people). This area is related to executive control of depression and memory functions. The MBCT group also showed reduced activation of the ventral lateral prefrontal cortex compared to the comparison group. Members of the MBCT whose depression symptoms had improved also showed better regulation of the amygdala during the task compared to the exercise and nutrition group.

The research was presented at the 2016 meeting of the American Psychiatric Association.

Psilocybin May Improve Treatment-Resistant Depression

A small, uncontrolled study in the journal *Lancet Psychiatry* suggests that **psilocybin, an ingredient in hallucinogenic mushrooms, relieved depression symptoms for up to three months in seven of 12 participants with unipolar depression that had not responded to at least two antidepressant medications.**

Psilocybin has a different mechanism of action than typical treatments for depression. It activates 5HT2A serotonin receptors.

The participants, who had moderate to severe depression, were given two oral doses of psilocybin, a low dose (10mg) to establish the safety of the intervention, and a higher dose (25mg) seven days later. Psychedelic effects (anxiety, confusion, nausea, and headache) peaked within two to three hours and had dissipated by six hours after the intervention.

Depression began to improve within 24 hours after the 25mg dose. Depression symptoms were significantly improved by one week after the intervention. Eight of the 12 participants had a complete remission of their depression after one week, and this lasted the full three months in five participants. By the end of the three months, a total of seven of the 12 participants met the criteria for response to psilocybin.

The study's authors, led by Robin L. Carhart-Harris, suggest that **their preliminary results warrant more systematic investigation of psilocybin, but because there was no comparison group in this study, a large placebo effect cannot be ruled out.**

Methylene Blue May Help Bipolar Depression

We have previously reported on the research by Martin Alda and colleagues that **the chemical compound methylene blue had positive effects in patients with bipolar depression.** The research was published in the *British Journal of Psychiatry* in 2016.

Now a new article by Ashley M. Feen and colleagues in the *Journal of Neurotrauma* reports that **methylene blue has an antidepressant-like effect in mice with traumatic brain injury (TBI).** Methylene blue reduced inflammation and microglia activation in the animals. Methylene blue reduced levels of the pro-inflammatory cytokine Il-1b and increased levels of the anti-inflammatory cytokine Il-10.

These findings are of particular interest as many patients with classical depression (and no brain injury) have abnormal levels of these inflammatory markers. It remains to be seen whether methylene blue is more helpful in those patients with elevated inflammatory markers and if levels of the markers can predict treatment response or not.

Methylene blue causes urine to turn blue, so low doses of the compound are used as a placebo. Alda and colleagues reported that the active dose 195mg reduced depression and anxiety significantly more than the placebo dose (15mg) in a 13-week crossover study. In that study, methylene blue was added to lamotrigine which had not had a complete enough effect.

In a 1986 study by G.J. Naylor and colleagues in the journal *Biological Psychiatry*, patients were treated with either 15mg/day or 300mg/day of methylene blue for one year and crossed over to the other dose in the second year. Participants

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Study Shows FDA Drug Safety Warning on Citalopram Backfired

In August 2011, the US Food and Drug Administration issued a warning that doses of the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram (Celexa) that exceeded 40mg/day could prolong the QT interval, a measure of heart rate used to diagnose abnormal heart rhythms. A study of records from the Veterans Health Administration showed that **35,848 veterans whose dose of citalopram was reduced from an average of 64mg/day to under 40mg/day faced increased deaths, hospitalizations for any cause, and hospitalizations for depression specifically after the reductions.**

The FDA warning meant to prevent heart problems had the unintended consequence of increasing hospitalizations and deaths among the veterans affected. These findings by Thomas S. Rector and colleagues were published in the *American Journal of Psychiatry* in 2016.

Editor's Note: There are some similarities between this case and findings by researchers Andrew Nierenberg and Andrew Stoll, who noticed that patients taking 40mg/day of fluoxetine (Prozac) had better long-term outcomes than those taking 20mg/day, even though those taking 40mg were more ill and more likely to relapse at the start of the study.

Researchers Ellen Frank and David Kupfer found that 90% of unipolar depressed patients relapsed when their antidepressant doses were halved, even though they had been stable for 5 years before the change.

These and the findings from Rector and colleagues lead this editor to believe that reducing the dosage of effective treatments should not be done without reason – that is, in the absence of side effects, or simply to achieve the minimal effective dose. Dose reductions without cause not only may increase the risk of relapse, but may also put the patient at increased risk of developing tolerance to the medication, for example hastening the onset of 'Prozac poop-out.'

When long-term maintenance drug therapy is going well, it may be best to be conservative and stay the course. Conversely, in the absence of a good long-term response, be as active and creative as possible to achieve mood stabilization.

Creatine Supplements May Speed Up Response to Escitalopram, Improve Brain Connectivity

Antidepressants can take weeks to begin working, and researchers have been investigating ways to speed up this process. A 2012 study by In Kyoon Lyoo and colleagues in the *American Journal of Psychiatry* found that among 52 women taking the selective serotonin reuptake inhibitor (SSRI) antidepressant escitalopram (Lexapro) for unipolar depression, **those who were prescribed an additional creatine supplement had earlier and greater decreases in depression symptoms than those who received a placebo in addition to the escitalopram.**

The difference between the two groups was evident by the second week of treatment. At the end of the 8-week study, 52% of those who received creatine had achieved remission, compared to 26% of those in the placebo group.

Creatine, a supplement sometimes used by weightlifters, increases cellular energy. The women received 3g/day of creatine for the first week of the study, and 5g/day thereafter.

The same research group recently published more data from their creatine study. The new article by Sujung Yoon and colleagues in the journal *Biological Psychiatry* shows that following the creatine supplementation, the women in the creatine group had greater levels of N-acetylaspartate (a sign of healthy neurons) in their prefrontal cortex and also had greater levels of brain connectivity than women in the placebo group.

Statins (continued)

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Depression is known to be correlated with inflammation throughout the body. Statins reduce this inflammation as well as lowering cholesterol. A 2013 study by Ahmad Ghanizadeh and Arvin Hedayati in the journal *Depression and Anxiety* showed that the SSRI fluoxetine and the statin lovastatin reduced depression severity compared to fluoxetine alone.

The combination of SSRIs and statins did not seem to reduce deaths or suicidal behavior compared to SSRIs alone. Statins have some side effects, but combining them with antidepressants did not increase the risks associated with their use.

Methylene Blue (continued)

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had significantly less depression during the year of taking the active 300mg/day dose.

The FDA has issued a warning about the danger of a serotonin syndrome if methylene blue is combined with serotonin active agents (presumably because it inhibits MAO-A). Symptoms of the serotonin syndrome can include lethargy, confusion, delirium, agitation, aggression, decreased alertness, and coma. Neurological symptoms, such as jerky muscle contractions, loss of speech, muscle tension, and seizures; or autonomic symptoms, such as fever and elevated blood pressure, are also common. Patients should call their doctor if they are taking a serotonergic psychiatric medication and develop any of the above symptoms.

Certain 'Nutraceuticals' Aid Depression

A systematic review of research on the value of pharmaceutical-grade nutritional supplements, or 'nutraceuticals,' in depression treatment has found that several do indeed improve depression symptoms.

The 2016 review by Jerome Sarris and colleagues in the *American Journal of Psychiatry* found that **the following nutraceuticals primarily produced positive results compared to placebo: omega-3 fatty acids (primarily EPA or ethyl-EPA); vitamin D; l-methylfolate (a more potent form of folic acid); and S-adenosyl methionine or SAMe, a beneficial amino acid derived from the toxin homocysteine with the help of folate.**

Editor's Note: Most but not all of these compounds can also be useful in bipolar depression. Omega-3 fatty acids and vitamin D are helpful to many patients. L-methylfolate is particularly helpful to the 30% of the population with a MTHFR deficiency that interferes with the ability of folate to break down homocysteine. SAMe is an exception – while it is effective in unipolar depression, it may cause switching into mania in patients with bipolar disorder.

The researchers identified a few additional nutraceuticals that each had one study supporting their use—creatine, sometimes used by weightlifters to provide extra energy to muscles; folinic acid, which can protect bone marrow and other cells during chemotherapy; and a combination of amino acids.

Results from studies that compared other compounds to placebo were mixed. Those included studies of zinc, folic acid, vitamin C, and the amino acid tryptophan. A study of inositol, a compound found in plants that is not normally digestible, had nonsignificant results.

No serious side effects were observed in any of the studies of nutraceuticals, though some caused minor digestive disturbances.

Editor's Note: Another beneficial nutraceutical that did not appear in the review article is N-acetylcysteine. After six to eight weeks, NAC can improve bipolar depression and anxiety compared to placebo. It can also reduced habits and addictive behaviors in non-bipolar patients. These include cocaine and gambling addition, alcohol and nicotine use, trichotillomania (compulsive hair-pulling), obsessive compulsive disorder (OCD), and irritability in autism.

Carnitine Reduced Body Weight and Insulin Resistance in Women with PCOS

Carnitine is an amino acid derivative sometimes used as a nutritional supplement. A 2016 study by Mansooreh Samimi and colleagues published in the journal *Clinical Endocrinology* found that carnitine supplementation reduced weight and insulin resistance in women with polycystic ovary syndrome (PCOS).

In the study, 60 overweight women with PCOS were randomized to receive either 250mg/day carnitine supplements or placebo. **After 12 weeks, the carnitine group had lost an average of about 3 kg compared to the placebo group, and centimeters off their waist and hip measurements. Carnitine supplementation also lowered fasting blood glucose, insulin levels in blood, and insulin resistance compared to placebo.**

Metabolized B Vitamins Improve Depression in People with MTHFR Deficiency

MTHFR is an enzyme needed for the body to metabolize vitamin B9, also known as folate or folic acid. It also helps convert the toxic amino acid homocysteine into the antidepressant amino acid S-adenosyl-methionine (SAMe). However, a significant segment of the population (some estimate 40%) have a genetic mutation in the MTHFR gene that interferes with the body's ability to break down B vitamins and is linked to higher levels of homocysteine. MTHFR mutations are also linked to depression.

A 2016 study by Arnold W. Mech and Andrew Farah in the *Journal of Clinical Psychiatry* found that **treating people with major depression and a MTHFR deficiency using a combination of micronutrients and already metabolized B vitamins improved their depression and reduced their homocysteine levels compared to placebo.**

The study included 330 adult patients with major depression and one of two genetic variants in the MTHFR gene—C677T or A1298C. Of those who received the metabolized vitamins, 82.4% showed reduced homocysteine levels. Those who received placebo showed a small average increase in homocysteine. The vitamin group also saw a large drop in depression symptoms on average after 8 weeks, with 42% achieving full remission. There were no side effects.

These findings suggest that homocysteine levels play a role in depression and that metabolized B vitamins can be an effective treatment for depression, particularly in those with a MTHFR deficiency. A metabolized B vitamin that is commercially available is L-methylfolate. It is estimated to be four times more potent than folate itself.

The More Plant Protein Eaten, The Better for Longevity

A long-term study of 130,000 nurses and other health professionals found that eating more plants lowered risk of death over several decades. A 3% increase in calories from plant protein was associated with a 10% lower risk of death during the study period.

The research, by Mingyang Song and colleagues in the journal *JAMA Internal Medicine*, found that the more animal protein consumed, the higher the risk of death from cardiovascular disease during the study. **A 10% increase in the proportion of calories from animal protein was associated with a 2% increase in deaths.** This association was worse for people who were obese or heavy drinkers.

Song and colleagues suggest that plants are a better source of calories than are animal products, and that fish or chicken are better choices than processed red meat.

Researcher Dariush Mozaffarian recommends eating plant-based foods like fruits, nuts, seeds, beans, and non-starchy vegetables, but avoiding those like French fries or white bread that have little nutritional value.

Vegan Diet Can Lead to Vitamin B12 Deficiency

Vitamin B12 deficiency is a risk associated with a vegan diet. B12 deficiency can lead to depression, anemia, and even irreversible neuron damage, according to researcher Drew Ramsey, who spoke on the topic at the 2016 meeting of the American Psychiatric Association.

A study of vegans showed that 52% were deficient in vitamin B12, while another 23% had insufficient levels of the vitamin. B12 is found in the highest concentrations in certain seafoods and liver. It is also found in dairy products, eggs, fortified breakfast cereals, and is available in supplement form.

Women who eat a vegan diet while pregnant may not be providing their offspring with enough nutrients, according to researcher Emily Deans, who also spoke at the meeting. **A case series on 30 vegan mothers found that 60% of their offspring had developmental delays and 37% showed cerebral atrophy.**

Deans said that eating no meat is associated with higher rates of depression, anxiety, and worse quality of life.

Ramsey believes that while the North American diet is probably weighted too heavily toward animal products, seafood remains an important source of B12.

Tart Cherry Juice Improved Recovery from Exercise in Soccer Players

A recent study by Glyn Howatson and colleagues in the journal *Nutrients* found that tart cherry juice helped soccer players recover after muscle-damaging exercise better than a placebo.

The 16 athletes in the study were randomly assigned to receive either a Montmorency tart cherry concentrate mixed with water twice a day for four days prior to and three days following exercise, or a drink with the same number of calories but less than 5% fruit content on the same schedule.

The semiprofessional male soccer players (aged 21 to 29) showed better performance on sprints, jumps, and agility tests; less inflammation; and less muscle soreness when taking tart cherry juice compared to the placebo drink.

Editor's Note: Tart cherry juice is rich in polyphenols, chemicals found in plants with anti-oxidant effects. The juice also has melatonin-like effects, improving sleep in people with insomnia.

Cinnamon Improves Memory in Mice

A recent study found that mice that ate more cinnamon got better and faster at learning. In the 2016 study by Kalapada Pahan and colleagues in the *Journal of Neuroimmune Pharmacology*, mice were separated into good learners and poor learners based on how easily they navigated a maze to find food. **After the poor learners were fed cinnamon for a month, they could find the food more than twice as quickly as before.**

The benefits of cinnamon come from sodium benzoate, a chemical produced as the body breaks down the cinnamon. Sodium benzoate enters the brain and allows the hippocampus to create new neurons.

Feeding cinnamon to the poor learning mice normalized their levels of receptors for the neurotransmitter GABA, closing the gap with good learners. Sodium benzoate also improved the structural integrity of some brain cells. Cinnamon also can help sensitize insulin receptors.

Doctors hope these findings may eventually contribute to treatment research on Alzheimer's and Parkinson's diseases.

Cinnamon should be consumed in moderate quantities because the Chinese variety most commonly found in North American supermarkets has high levels of coumarin, a compound that can be toxic to the liver when consumed in large quantities. Ceylon (Sri Lankan) cinnamon has lower levels of coumarin.

Antipsychotic Use During Pregnancy Most Likely Safe

A new study suggests that women can continue using antipsychotic medications during the first trimester of pregnancy without meaningfully increasing the risk of birth defects in their offspring.

The study, by Krista F. Huybrechts and colleagues in the journal *JAMA Psychiatry*, looked at Medicaid users who filled at least one prescription for an antipsychotic medication during their first trimester of pregnancy, when an embryo's vital organs are formed, and went on to have a live birth. Birth defects, including cardiac malformations, in these children were identified in the first 90 days after delivery and compared to the number of such abnormalities in the children of women on Medicaid who did not receive a prescription for an antipsychotic drug during the first trimester of pregnancy. The number of abnormalities was slightly higher in the children of women who had received atypical antipsychotics than in those who had not, and slightly lower in the children of women who had received a typical antipsychotic than in those who had not.

Huybrechts and colleagues concluded that **taking an antipsychotic medication during the first trimester of pregnancy does not meaningfully increase the risk of birth defects in the offspring.**

However, **the children of women who took the antipsychotic risperidone did have a small increased risk of birth defects, including cardiac malformations.** The researchers called for additional study of risperidone use during pregnancy.

SSRI Use During Pregnancy Linked to Adolescent Depression in Offspring

A 2016 article by Heli Malm and colleagues in the *Journal of the American Academy of Child and Adolescent Psychiatry* suggests that **in utero exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants may increase the risk of depression in adolescence. However, the study included potentially confounding factors.** It is possible that women who took SSRIs during pregnancy had more severe depression than those who went unmedicated during pregnancy. The mothers in the study who took SSRIs also had more comorbid conditions such as substance abuse.

Editor's Note: Women should balance the risks and benefits of antidepressant use during pregnancy, since depression itself can have adverse effects on both mother and fetus. It has recently been established that SSRI use during pregnancy does not cause birth defects, so women with depression that has not responded to non-pharmaceutical interventions such as psychotherapy, omega-3 fatty acid supplementation, exercise, mindfulness, and repeated transcranial magnetic stimulation (rTMS) may still want to consider SSRIs.

A STUDY ASSESSING YOUR CHILD'S MOOD AND BEHAVIOR

Parents, if your child (aged 2 – 12) has mood or behavioral difficulties, we would like to enlist your participation in a study called the Child Network. Parents who enroll in the study will complete an online rating checklist of their children's symptoms once a week by a secure web-based system.

Parents can then print out a chart of these ratings that depicts their children's symptom course and response to treatment and bring it to the children's physician This should help facilitate early recognition and treatment of a range of common psychiatric disorders that begin in childhood.

If you are interested in participating in this study, go to http://bipolarnews.org and click on the tab for Child Network. For more information, see page 11 of this issue, call 301-530-8245, or email questions to childnetworkbnn@gmail.com.

Research Study
Principal Investigator: Robert L. Findling, MD, MBA
IRB Study #00026940

Father's Age, Behavior Linked to Birth Defects

For decades, researchers have known that a pregnant mother's diet, hormone levels, and psychological state can affect her offspring's development, altering organ structure, cellular response, and gene expression. It is now becoming clear that a father's age and lifestyle at the time of conception can also shape health outcomes for his offspring.

Older fathers have offspring with more psychiatric disorders, possibly because of increased incidence of mutations in sperm.

A 2016 article by Joanna Kitlinska and colleagues in the *American Journal of Stem Cells* reviewed findings from human and animal studies about the links between fathers' behaviors and their offspring's development.

Father's behavior can shape gene expression through a phenomenon described as epigenetics. Epigenetics refers to environmental influences on the way genes are transcribed. **While a father's behavior is not registered in his DNA sequences, it can influence the structure of his DNA or the way in which it is packaged.**

Kitlinska suggests that these types of findings should eventually be organized into recommendations for prospective parents. More research is also needed into how maternal and paternal influences interact with each other.

Fathers Important to Fetal Health, Too

Findings from the article by Kitlinska et al.:

- A newborn can have fetal alcohol spectrum disorder even if the mother doesn't drink. "Up to 75% of children with [the disorder] have biological fathers who are alcoholics," says Kitlinska.
- Father's alcohol use is linked to low birth weight, reduced brain size, and impaired cognition.
- Dad's obesity is linked to enlarged fat cells, diabetes, obesity, and brain cancer in offspring.
- A limited diet in a father's early life may reduce his children and grandchildren's risk of death from cardiovascular causes.
- Dad's advanced age is correlated with higher rates of schizophrenia, autism, and birth defects in his children.
- Psychosocial stress on dads can affect their children's behavioral traits.

In Rats, Mother's Exercise Habits Affect Those of Offspring

A recent study suggests that when a mother rat exercises during pregnancy, her offspring will exercise more too.

In the study, published by Jesse D. Eclarinel and colleagues in *The FASEB Journal*, pregnant mother rats were placed in cages that each contained an exercise wheel. One group had access to a working wheel on which they could run. The other group had the same wheel, but it was locked so that they couldn't use it for running. **Daughters of the rats who ran during pregnancy ran more in adulthood** (both at 60 days and 300 days after birth) than daughters of the rats who couldn't run during pregnancy.

While it is a mystery why this occurs, it is consistent with other data about the ways that a parent's experiences can influence the next generation, even when the offspring don't grow up with the parents.

For example, father rats conditioned to associate a specific smell with fear of an electric shock have offspring that also fear that smell (but not other smells).

Drug use is another example. Father rats given access to cocaine have offspring that are less interested in cocaine. Interestingly, father rats exposed to marijuana have offspring that are more interested in opiates.

Experiences with drugs or stress are thought to affect the next generation via 'epigenetic' marks on ova or sperm. These marks change the way DNA is packaged, with long-lasting effects on behavior and chemistry. Most marks from a mother's or father's experiences are erased at the time of conception, but some persist and affect the next generation.

The nature versus nurture debate is getting more and more complicated. Parents can influence offspring in a number of ways: 1) genetics; 2) epigenetics in the absence of contact between parent and offspring after birth; 3) epigenetic effects of behavioral contact—that is, parents' caring and warmth versus abuse and neglect can affect offspring's DNA expression too. All these are in addition to any purely behavioral influence a parent may have on their offspring via discipline, teaching, being a role model, etc.

Editor's Note: The moral of the story is, choose your parents wisely, or behave wisely if you yourself become a parent.

In Small Study, High Intensity Light Therapy Boosts Libido in Men

The same type of high-intensity light therapy used to treat seasonal affective disorder (SAD) and as an adjunctive treatment for non-seasonal depression has been found to boost testosterone and improve sexual satisfaction in men with low libido.

In a study by Andrea Fagiolini and colleagues, **men with low sexual desire or trouble getting aroused were exposed to the high intensity light (10,000 Lux) for a half hour upon waking. Compared to men who used a lightbox that filtered the light to only 100 Lux, men exposed to the high-intensity light for two weeks showed increased testosterone in the blood and reported greater sexual satisfaction.** Testosterone levels increased from around 2.1 ng/ml to 3.6 ng/ml in the high-intensity light group. (There were no significant changes in the comparison group.) Light therapy is quite safe for people without eye problems.

Fagiolini explained that in the Northern hemisphere, testosterone production declines from November to April and then rises again through the spring and summer, peaking in October. He suggests that the light therapy mimics the effect of summer light on the body, perhaps by inhibiting the pineal gland, which secretes hormones.

Fagiolini and colleagues hope to replicate the study with a greater number of participants and to determine how long the results may last.The study of 38 participants was presented at the 29th Congress of the European College of Neuropsychopharmacology in 2016.

Cool Head May Help Insomnia

The US Food and Drug Administration recently approved a device that improves sleep by cooling the forehead. People with insomnia often have an active frontal cortex that keeps their thoughts racing as they try to fall asleep, preventing deeper, more restorative sleep. Through conducting functional brain imaging studies, researcher Eric Nofzinger found that cooling participants' foreheads to a precise level during the night improved the quality of their sleep.

The sleep studies included more than 230 patients observed over 3800 research nights. One such study found that participants reached stage 1 and stage 2 sleep faster when they used the device.

Nofzinger founded the company Cerêve to produce the new bedside device, which pumps cooled fluid to a pad worn on the forehead. The company expects to release the device in 2017.

Insomnia may affect as many as 55 million Americans, frustrating them at night and leading to decreased alertness the following day. Sleeping pills are the most common treatment, but they can also cause impairment the following day.

Smoking Ban in New Jersey Jails Drastically Reduced Deaths of Inmates with Mental Illness

Policy changes by the New Jersey Department of Corrections drastically reduced the availability of tobacco products in New Jersey jails between 2005 and 2014. Prison commissaries reduced their stock of tobacco, prices increased, sales to minors were banned, and facilities were designated tobacco-free (including for staff and visitors).

Along with this reduction in the availability of tobacco products, the Department of Corrections also introduced smoking cessation programs, began offering nicotine replacement lozenges in commissaries, and increased treatment for tobacco use.

A surprise consequence of the decision to go tobacco-free was a drastic reduction of deaths among prison inmates with mental illness. The mortality rate for these inmates dropped by 48%. In contrast, the mortality rate for inmates without mental illness remained flat before and after the tobacco ban.

People with mental illness are at increased risk of mortality, particularly from cardiovascular illnesses. Now it seems that eliminating tobacco use can go a long way toward improving health and reducing mortality for these people.

TDCS Can Change Sleep Duration

A German study published in 2016 suggests that transcranial direct current stimulation (tDCS) can affect the duration of a person's nightly sleep. Lukas Frase and colleagues compared the effects of two different tDCS parameters and a sham stimulation on the sleep patterns of 19 healthy volunteers. The research was published in the journal *Neuropsychopharmacology* in 2016.

TDCS is a treatment in which an anode and a cathode electrode placed on the skull are used to apply a steady, low-level current of electricity to the brain.

Bi-frontal anodal stimulation, intended to increase arousal, significantly decreased total sleep time compared to the other two interventions.

Bi-frontal cathodal stimulation, intended to decrease arousal, did not increase total sleep time, possibly because there is a 'ceiling' beyond which good sleepers do not sleep longer.

EEG analysis showed that the anodal stimulation did increase arousal, while cathodal stimulation decreased it.

The research increases what is currently known about sleep-wake regulation by showing that total sleep time can be decreased using anodal tDCS. The researchers hope this knowledge can contribute to future treatments for disturbed arousal and sleep.

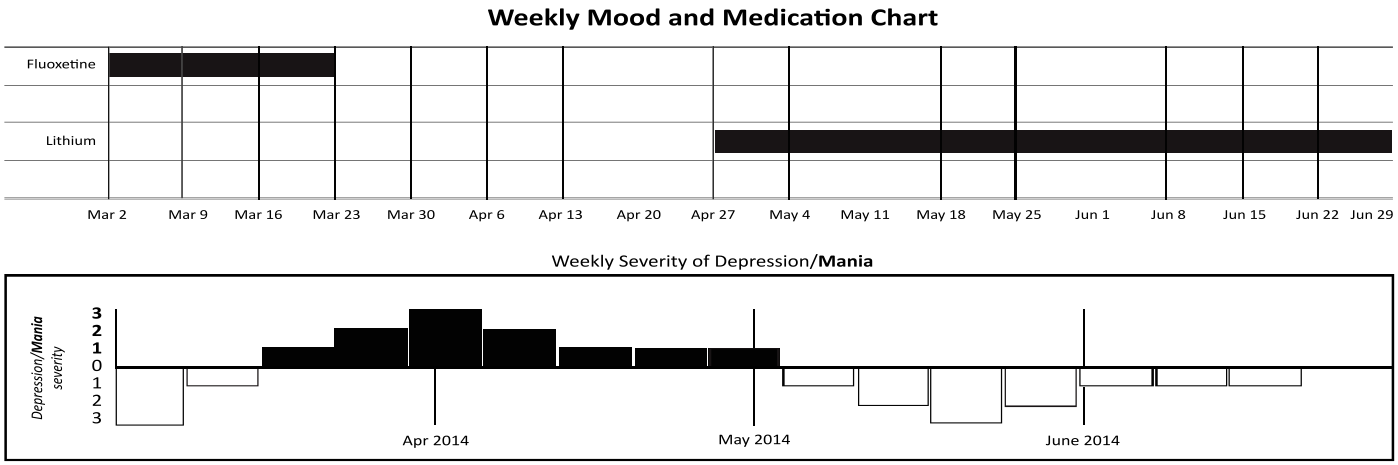
Is Your Child at Risk for a Mood Disorder? Join the Child Network

74% of children who have a parent with bipolar disorder (Axelson et al. 2015) and 80% of those who have a parent with unipolar depression (Weissman et al. 2006) will develop a major psychiatric illness upon long-term follow up. These illnesses, including depression, anxiety, oppositional behavior, substance abuse, often go unrecognized for long periods of time.

Joining the Child Network could help families and doctors identify these illnesses earlier.

The Child Network is specifically for parents of children ages 2 to 12 who are at high risk for a mood disorder or have symptoms of a mood disorder. Parents assess their child weekly using a secure website. There is also a short demographic questionnaire and a more detailed symptom checklist to be filled out once a year. The network will collect information about which treatments children are already taking, how effective they are, and for which children.

We believe that this network will be helpful to its participants. Parents will be able to print out the ongoing weekly ratings in a graphic form so that the child's symptoms and responses to any treatments they receive over time can easily be visualized (as illustrated below).



0 - Severity None: None
1 - Severity Mild/Infrequent: Minimal impact on usual roles
2 - Moderate Symptoms/Often: Definitely some dysfunction in usual roles
3 - Severe Symptoms/Much of the Time: Major dysfunctions in usual roles

We hope that this brief description of the Child Network study helps to orient you to its purpose. Please urge parents to use this new tool. Visit http://bipolarnews.org and click on the tab for the Child Network or http://bipolarnews.org/?page_id=2630 to learn more about the Child Network and to access the informed consent documents.

Thank you for your time and interest in the Child Network.

Robert M. Post, MD and Michael Rowe, PhD
Bipolar Collaborative Network, and
Robert L. Findling, MD, MBA, Principal Investigator
This research study is IRB approved by the Johns Hopkins University School of Medicine
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