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The New News About Lithium

Robert M. Post, Editor-in-Chief of the *BNN*, recently published an open access article in the journal *Neuropsychopharmacology*, "The New News About Lithium: An Underutilized Treatment in the United States." Here we summarize the main points of the publication, including: the multiple benefits of lithium, its relative safety, predictors of lithium responsiveness, and principles for treatment.

Benefits of lithium

Lithium prevents both depressions and manias in bipolar disorder, and also prevents depressions in unipolar disorder and can augment antidepressant effects acutely. In addition to these mood benefits, lithium has antisuicide effects. Lithium also enhances the efficacy of atypical antipsychotics and other mood stabilizers when used in combination with them.

Lithium is good for the brain. It has been shown to reduce the incidence of dementia. Lithium increases the volume of the hippocampus and cortex, and can increase the production of new neurons and glia. It also protects neurons. In animals, lithium has been shown to reduce lesion size in neurological syndromes that are models for human disorders such as AIDS-related neurotoxicity, ischemic/hemorrhagic stroke, traumatic brain/spinal cord injury, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), fragile X syndrome, Parkinson's disease, retinal degeneration, multiple sclerosis, alcohol-induced degeneration, Down's syndrome, spinocerebellar ataxia-1, and irradiation.

Lithium's benefits include more general ones as well. It can increase the length of telomeres, bits of DNA on the ends of chromosomes that protect them during replication. Short telomeres have been linked to various illnesses and the aging process. Lithium also decreases the incidence of several medical illnesses and enhances survival.

Side Effects Are Often Benign, Treatable

Lithium side effects are more benign than many people think. Even low levels of lithium may be therapeutically sufficient.

About fifteen percent of people taking lithium develop a thyroid deficiency, which can readily be corrected with thyroid hormone replacement. Diabetes insipidus, a hormone disorder characterized by thirst and heavy urination, can be minimized with amiloride.

Creatinine increases may occur with long-term lithium use. These usually start after 30 years of taking the drug and tend not to progress to end-stage renal disease in people taking lithium, as they do in people taking anticonvulsants.

Hyperparathyroidism (high levels of calcium) is rare and can be treated with surgery. Tremor can be treated with propranolol. Weight gain on lithium is usually minimal.

Predicting a Good Response to Lithium

Research has found that some people are more likely to have a good response to lithium treatment than others. A family history of mood disorders, especially bipolar disorder, is one of the number one predictors. Lack of anxiety and substance abuse comorbidity also predict a better response to lithium.

People who have euphoric manias respond better to lithium than the two-thirds of women and 40% of men who have dysphoric (anxious, irritable) manias. Those who have discrete mood episodes separated by well intervals in between are also more likely to respond well to lithium.

The pattern of a person's manias and depressions may also affect whether they respond well to lithium. Mania followed by depression and then a well interval (a pattern known as M-D-I) is associated with a better lithium response than depression followed by mania and then a well interval (D-M-I).

Starting ongoing preventative treatment with lithium after fewer mood episodes predicts a better response than beginning later in the course of illness, after many episodes.

It is notable that perhaps the majority of people with bipolar illness in the US do not fit this profile. For these patients, lithium would need to be augmented with an anticon-

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vulsant drug, a mood stabilizer (lamotrigine, valproate, or carbamazepine), or an atypical antipsychotic.

New Principles of Treatment

A 2013 article by Lars V. Kessing and colleagues in the *British Journal of Psychiatry* showed that after a first episode of mania, patients randomized to receive two years of comprehensive treatment involving medications, psychotherapy, psycho-education, and illness monitoring had fewer relapses over a period of six years than patients who received treatment as usual. That is, early excellent treatment can improve the long-term course of illness.

At the 2016 meeting of the International Society of Bipolar Disorders, researcher Lakshmi Yatham emphasized the importance of starting ongoing preventative treatment after a first mania. Yatham and colleagues found that cognitive deficits associated with a first mania recover over the course of the next year, but only if the patient experiences no further episodes during this period.

A 2017 study by Michael Berk and colleagues in the *British Journal of Psychiatry* found that when patients were randomized to one year of lithium or quetiapine following a first mania, both groups improved considerably, but had some residual symptoms.

However, after the first six months, lithium brought about more improvement than quetiapine on all measures, including mania, depression, functioning, cognition, and brain imaging. Thus, **preventive treatment should begin after a first manic episode, and use of lithium should definitely be considered.**

The recurrence of stressors, mood episodes, and bouts of substance use can snowball, making episodes, stressors, and substance use more likely to occur and to become more severe in the future. This process is called sensitization, and it drives illness progression.

Unfortunately, sensitization is based on memory-like epigenetic changes to the shape of DNA that can have a lasting effect on gene transcription and vulnerability to illness, even for a patient's offspring. This means limiting stress and substance abuse and using preventive medication to avoid episodes is not only important to recovery, but can also reduce the accumulation of adverse epigenetic marks on DNA.

If substance abuse cannot be prevented, it should be treated using off label treatments if necessary, since there are no US Food and Drug Administration-approved treatments for the combination of substance abuse and bipolar disorder.

Illness education should be paired with treatment at all stages of bipolar disorder (early, mid, and late). It can help patients better understand and monitor their illness and adhere to ongoing preventive treatment.

Psychotherapy can also help prevent episodes, modulate stressors, and reduce the risk of suicide.

It is also important to be alert to emerging symptoms in children at high risk for bipolar disorder due to their family history. Interventions involving lifestyle improvements (such as nutritious diet, regular exercise, and good sleep habits), psychosocial therapy, or medication may be needed. Early, effective treatment may prevent the onset of full-blown illness or lessen its severity.

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Study Suggests Magnesium Could Improve Mild to Moderate Depression as Much as SSRIs

Researcher Emily Tarleton and colleagues report in a 2017 article in the journal *PLoS One* that over-the-counter magnesium may improve mild to moderate unipolar depression with efficacy similar to that of selective serotonin reuptake inhibitor (SSRI) antidepressants.

Magnesium is a mineral that can fight inflammation.

The 126 participants in the open study had an average age of 52. Compared to not taking magnesium, **taking 248 mg/day of magnesium produced statistically significant improvement in depression and anxiety symptoms after only two weeks.**

The magnesium was well-tolerated by participants. Tarleton and colleagues hope to replicate their findings with a larger and more diverse population.

Making Lithium Treatment More Tolerable For Patients

In an article in *Psychiatric Times*, Chris Aiken describes seven ways to improve lithium's tolerability. Since many researchers, including *BNN* Editor-in-Chief Robert M. Post, have suggested that lithium should be used more often as a treatment for bipolar disorder, ways of making its side effects more manageable are of great interest. Here we summarize Dr. Aiken's seven points and add a few perspectives of our own.

Aiken writes that "when it comes to the side effects that matter most to patients—sedation, weight gain, and cognition—lithium's tolerability ranks right behind lamotrigine." In fact, lithium plus lamotrigine is an excellent combination, as lithium excels at preventing manias while lamotrigine excels at depression prevention.

Post's philosophy is that **many of lithium's side effects can be avoided in the first place through judicious dose titration.** He suggests gradually increasing dosage, and stopping before side effects become difficult, or reducing a dosage that has already become a problem. The idea is to avoid lithium side effects even if blood levels of lithium remain below clinically therapeutic levels. Post suggests using lithium at whatever dose is not associated with side effects.

Many of lithium's positive therapeutic effects emerge at low doses, and if this improvement is insufficient, the rest of the needed efficacy can be achieved by adding other medications. As noted above, lamotrigine is a good option for break-through depression, as is lurasidone. For breakthrough mania, the mood stabilizers valproate and carbamazepine or an atypical antipsychotic can be added to lithium.

A little-appreciated option for enhancing lithium's mood stabilizing effects is nimodipine, a dihydropyridine calcium blocker. It has both antimanic and antidepressant efficacy without lithium's side effects. Research showed that a year on the combination of lithium and nimodipine was more effective than a year of either drug alone.

If a patient taking lithium experiences a tremor at a dose that is not fully effective, nimodipine can be added in order to lower the lithium dose enough to eliminate the tremor.

Nimodipine specifically blocks the calcium influx gene CACNA1C that has been repeatedly been associated with the vulnerability to bipolar disorder and depression.

If side effects do occur on lithium, they can often be managed. The following suggestions are adapted from Aiken's article with input from Post.

Tremor responds to beta blockers and high dose vitamin B6 (900-1200mg/day), which may also improve restless legs resulting from atypical antipsychotics.

Gastrointestinal side effects of lithium can also be treated. Taking lithium with food or using extended-release preparations can improve nausea. Immediate release preparations are better for diarrhea. Lopiramide (Imodium), milk of magnesia, or nimodipine (which tends to be constipating) may also improve diarrhea.

While **weight gain** on lithium is usually minimal (a few pounds in the first year), problems with overweight can be treated with topiramate, zonisamide, or the combination of bupropion and naltrexone.

Erectile dysfunction is occasionally attributed to lithium, and a controlled trial suggested that aspirin can help. As in other cases of erectile dysfunction, sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) can also be used.

Decreased renal function can be lessened with use of lower doses and once daily (nighttime) dosing. Amiloride can decrease the increased urine volume that comes with lithium-induced diabetes insipidus (based on lithium's blockade of the actions of vasopressin or antidiuretic hormone.) Amiloride may also decrease fibrotic changes in the kidney. For patients who respond well to lithium but eventually must discontinue its use due to renal side effects, substituting nimodipine is likely to be an effective alternative. Researcher Steven L. Dubovsky has reported that lithium responsiveness is a predictor of response to calcium channel blockers.

Thyroid disorders are a typical side effect of lithium. Out-right hypothyroidism can be treated with thyroid hormone replacement consisting of either T4 (Synthroid) or T3 (Cytomel). Thyroid stimulating hormone (TSH) from the pituitary tends to increase on lithium, as if it were trying harder to keep the thyroid secreting enough thyroid hormone. Even in the absence of low hormone levels, high levels of TSH should be treated with T4 (Synthroid), and keeping TSH levels below 2.4 may prevent relapse into a depression. Lithium does not induce anti-thyroid antibodies (as in Hashimoto's disease), but may exacerbate thyroid abnormalities in those who already have them.

Some **dermatological symptoms** can occur on lithium. One is acne, which can be treated with minocycline (100mg/twice per day). Another is psoriasis, which is sometimes considered a contraindication for using lithium, but can be treated with omega-3-fatty acids (4–6 gm/day). At least one study found that psoriasis in people taking lithium improved when the patients took the nutritional supplement inositol (6 gm/day).

Aiken concludes his article by saying, **"Lithium is among the top-ranked, but least utilized, therapies for bipolar disorder, treatment-resistant depression, and suicidality. Patients with those problems deserve a trial of it, and it's our job to make those trials as tolerable as possible."**

Midday Bright Light Therapy Improved Bipolar Depression

A study by Dorothy S. Kit and colleagues published in the *American Journal of Psychiatry* in 2017 found that delivering bright white light therapy to patients with bipolar depression between the hours of noon and 2:30pm improved their depression compared to delivering inactive dim light, and did not cause mood switches into mania. The study included 46 patients with moderate bipolar depression, no hypomania and no psychosis.

The active therapy group was exposed to broad-spectrum bright white fluorescent light at 7,000 Lux while the inactive group received dim red light at 50 Lux. Both groups were instructed to sit 12 inches from the light and face it without looking directly at it. The therapy began with 15-minute afternoon sessions and increased to 60 minutes per day by 4 weeks. Participants were assessed weekly. Remission rates increased dramatically in the active group beginning in the fourth week. **At weeks 4 through 6, the remission rate for those in the active bright light group was 68.2% compared to only 22.2% in the dim light group.**

Mean depression scores were better in the treated group, as were global functioning and response rates.

Some participants were taking antidepressants concurrently, and these participants were evenly distributed across the two study groups.

An earlier pilot study by the same researchers had found that bright light therapy delivered in the morning was followed by some hypomanic reactions or bipolar cycling. The midday sessions did not cause any mood switching.

Bright light therapy is often used to treat seasonal affective disorder (SAD) using a 10,000 Lux light box. This study took place mostly during the fall and winter months.

Editor's Note: Bright light therapy is generally safe and boasts a high remission rate. Light boxes can be acquired without a prescription and are portable and easy to use. Midday light may have the best results and the least risk of provoking a mood switch into mania.

FDA Approves Extended-Release Aripiprazole Injected Monthly to Prevent Manic and Mixed Episodes in Bipolar I

In 2017 the US Food and Drug Administration approved a monthly injectable form of the atypical antipsychotic drug aripiprazole, Abilify Maintena, for the prevention of manic and mixed episodes in bipolar I disorder. The intramuscular injections are available for monotherapy in preparations of 300 mg or 400 mg. Maintena did not prevent depressive episodes.

Maintena is already FDA-approved for the treatment of schizophrenia and Tourette's syndrome in adults.

The approval for bipolar I disorder follows a 52-week phase 3, double-blind, placebo-controlled randomized trial. Participants were experiencing a manic episode during screening for the study, met the criteria for bipolar I disorder, and had had at least one prior manic or mixed episode severe enough to require treatment.

Compared to placebo, Maintena in once-a-month injections delayed the recurrence of any mood episode following the initial manic episode at screening. When the researchers separated their analysis based on type of episode, **Maintena reduced manic and mixed episodes compared to placebo, but did not do a better job than placebo at preventing depressive episodes.**

An oral antipsychotic must be administered for 14 days following the first injection of Maintena. The extended-release injection is available as 300 mg– or 400 mg–strength powder that may be reconstituted, or as prefilled syringes.

Editor's Note: Because Maintena is delivered as a once-a-month injection, it may be helpful for patients who struggle to take daily oral medications.

Inflammation Predicts Poor Response to Sleep Deprivation with Light Therapy

A 2017 article by Francesco Benedetti and colleagues in the *Journal of Clinical Psychiatry* reports that people with bipolar depression who have higher levels of certain inflammatory markers may have a poor antidepressant response to the combination of sleep deprivation and light therapy, compared to those with lower levels of inflammation.

The study included 37 participants with bipolar disorder who were in the midst of a major depressive episode. Of those, 31 participants (84%) had a history of poor response to antidepressant medication. The patients were treated with three cycles of total sleep deprivation and light therapy within one week, a combination that can often bring about a rapid improvement in depression.

Depression improved in a total of 23 patients (62%) following the therapy. **Blood analysis showed that compared to those who had a good response, the non-responders had higher levels of five intercorrelated inflammatory markers: IL-8, MCP-1, IFN-gamma, IL-6, and TNF-alpha.** Those with higher body mass index had more inflammation, indirectly decreasing response to the therapy.

One Night of Sleep Deprivation Can Rapidly Improve Depression

One night of sleep deprivation can bring about rapid improvement in depression symptoms the following day. A 2017 meta-analysis by Elaine M. Boland and colleagues in the *Journal of Clinical Psychiatry* summarizes the findings from 66 studies of sleep deprivation for unipolar and bipolar depression and finds that **the technique produced a response rate of 45% in randomized controlled studies.**

It did not seem to matter whether patients experienced full or partial sleep deprivation, whether they had unipolar or bipolar depression, or whether or not they were taking medication at the time. Age and gender also did not affect the results of the sleep deprivation.

Extending the Effects

While sleep deprivation can rapidly improve depression, the patient often relapses after the next full night of sleep. There are a few things that can prevent relapse or extend the efficacy of the sleep deprivation. The first is lithium, which has extended the antidepressant effects of sleep deprivation in people with bipolar disorder.

The second strategy to prevent relapse is a phase change. This means going to sleep early in the evening the day after sleep deprivation and gradually shifting the sleep schedule back to normal. For example, after an effective night of sleep deprivation, one might go to sleep at 6pm and set their alarm for 2am. Then the next night, they would aim to sleep from 7pm to 3am, the following night 8pm to 4am, etc. until the sleep wake cycle returns to a normal schedule.

A 2002 article by P. Eichhammer and colleagues in the journal *Life Sciences* suggested that repetitive transcranial magnetic stimulation (rTMS), electromagnetic stimulation of the scalp over the prefrontal cortex, could help maintain improvement in depression following a night of partial sleep deprivation for up to four days.

Bright light therapy may also help. Researcher A. Neumeister and colleagues reported in the journal *Biological Psychiatry* in 1996 that 3,000 Lux light could stabilize the antidepressant effects of partial sleep deprivation for up to seven days.

In a 2000 article in the journal *Psychiatry Research*, C. Colombo and colleagues reported that morning light therapy improved the antidepressant effectiveness of three cycles of total sleep deprivation in people with bipolar disorder. The light, delivered at 150 Lux and 2,500 Lux, reduced sleepiness in the sleep-deprived subjects, and this reduced sleepiness was associated with a better response. Lithium also improved the effectiveness of sleep deprivation in the same bipolar population, but combining both lithium and light therapy with sleep deprivation did not produce a cumulative effect.

In a table in a 2003 article in the journal *Dialogues in Clinical Neuroscience*, Ulrich Voderholzer lists predictors of an antidepressant response to sleep deprivation in depressed patients, including: arousal, variability of mood swings, daily or day-to-day mood variations, melancholic depression, depression prompted by internal factors, and the bipolar subtype. Age, sex, severity or duration of depression, duration of illness, earlier treatments, and patients' expectations did not predict response.

Studies by *BNN* editor Robert M. Post found that timing sleep deprivation as a patient approached recovery from a depression often triggered the patient out of the depressive episode completely.

Vagus Nerve Stimulation Improves Depression When Other Treatments Fail

Vagus nerve stimulation (VNS) has been approved by the US Food and Drug Administration as an adjunctive therapy for treatment-resistant unipolar and bipolar depression since 2005. The treatment consists of a pacemaker-like device implanted under the skin in the chest that delivers regular, mild electrical pulses to the brain via the left vagus nerve.

A 2017 study by Scott T. Aaronson and colleagues in the *American Journal of Psychiatry* reports that over a 5-year period, people with treatment-resistant depression who received VNS did better than those who received treatment as usual. The 795 participants at 61 US sites had either a depressive episode that had lasted for at least two years or had had three or more depressive episodes and had failed to respond to at least four treatments, including electroconvulsive therapy (ECT). **Over five years, those who received VNS had higher response rates (67.6% versus 40.9%) and higher remission rates (43.3% versus 25.7%) compared to those who received treatment as usual.**

While the study by Aaronson and colleagues was non-blind and non-randomized, it suggests that VNS could be helpful in the long-term management of treatment-resistant unipolar and bipolar depression.

Editor's Note: VNS was FDA-approved for treatment-resistant seizures in patients aged 12 and older in 1997 and for children 4 years and older in 2017. It was also approved for cluster headaches in 2017. Insurance coverage and reimbursement for VNS is typically available for these neurological conditions, but not for the treatment of depression. This is an unfortunate example of the stigmatization of psychiatric illness – when an FDA-approved device can be kept from people in need of treatment.

An Overview of Ketamine for Treatment-Resistant Depression

A 2017 series of articles by researcher Chittaranjan Andrade in the *Journal of Clinical Psychiatry* reviews the last 10 years of research on ketamine, the anesthetic drug that in smaller doses (0.5 mg/kg of body weight) can bring about rapid antidepressant effects. Ketamine is typically delivered intravenously (though it can also be delivered via inhaler, injected under the skin or into muscles, and least effectively by mouth). **Ketamine can improve depression in less than an hour, but its effects usually fade within 3 to 5 days. Repeating infusions every few days can extend ketamine's efficacy for weeks or months.**

Andrade cited a 2016 meta-analysis of nine ketamine studies by T. Kishimoto and colleagues in the journal *Psychological Research*. The meta-analysis found that compared to placebo, ketamine improved depression beginning 40 minutes after IV administration. Its effects peaked at day 1 and were gone 10–12 days later. Remission rates were better than placebo starting after 80 minutes and lasting 3–5 days.

Several studies have found that ketamine also reduces suicidality.

Andrade reported that both effectiveness and side effects seem to be dose-dependent within a range from 0.1 mg/kg to 0.75 mg/kg.

Side effects of ketamine are typically mild and transient. A 2015 study by Le-Ben Wan and colleagues (also in the *Journal of Clinical Psychiatry*) that Andrade cited reported that in 205 sessions of ketamine administration, the most common side effects were drowsiness, dizziness, poor coordination, blurred vision, and feelings of strangeness or unreality. The feelings of unreality (dissociative effects) diminish with repeated infusions. Heart and blood pressure may also temporarily increase as a result of ketamine administration.

One study found that ketamine could speed up and add to the effects of the selective serotonin reuptake inhibitor (SSRI) antidepressant escitalopram (Lexapro). A meta-analysis of 10 randomized controlled trials found that ketamine did not improve the effects of electroconvulsive therapy.

Ketamine has some history as a recreational club drug (sometimes known as 'K' or 'special K'), and can be misused or abused.

While there have been many studies of ketamine's antidepressant effects, Andrade concludes that none is of a standard to justify US Food and Drug Administration approval for the drug. It is hoped that larger, more rigorous trials will be completed in the next few years. However, ketamine is already being used widely to treat treatment-resistant unipolar and bipolar depression.

TDCS Better Than Placebo But Not as Good as Escitalopram at Improving Unipolar Depression

An article by André R. Brunoni and colleagues in the *New England Journal of Medicine* reports that transcranial direct current stimulation (tDCS) can treat unipolar depression more effectively than placebo, but not quite as effectively as the selective serotonin reuptake inhibitor (SSRI) antidepressant escitalopram. TDCS consists of a constant, low direct current applied to the scalp via electrodes.

The study included 245 patients with moderate to severe depressive symptoms, many of whom also had anxiety disorders. To minimize the placebo effect, patients all participated in sessions wearing tDCS gear and received a daily pill. However, one group received real tDCS treatment but placebo pills, a second group received sham tDCS but real escitalopram pills, and the third group received both sham tDCS and placebo pills.

The real tDCS treatment consisted of 30-minute sessions of tDCS every day for 15 consecutive weekdays, then seven once-a-week treatments. The escitalopram dosage was 10 mg/day for three weeks, then 20 mg daily.

Ten weeks into treatment, **those who received escitalopram showed the greatest improvement in depression. Those who received tDCS showed slightly less improvement, but still significantly more than those who received neither treatment.** Cognitive performance either improved or stayed the same in all the groups.

In terms of side effects, those who received escitalopram were more likely to report sleepiness or severe constipation. Those who received tDCS reported more skin redness/tingling, itching, tinnitus, and nervousness. Two patients in the tDCS group had new-onset mania during treatment. There were no suicides, hospitalizations, or other serious side effects.

Botox for Depression

Several recent clinical trials have suggested that Botox injections between the eyebrows may improve depression. The theory is that decreasing muscle tension could reduce feelings of depression, instead of depression causing muscle tension. In a phase 2 double blind multicenter trial of 258 women with depression, participants were randomized to receive 30 units of Botox, 50 units of Botox, or placebo. **Those who received the 30-unit injections showed significantly greater improvement in depression at three weeks and nine weeks compared to those who received placebo.** However, it was not superior to placebo at the primary endpoint of the study, six weeks, and the 50-unit dosage was not superior to placebo. Both doses were well tolerated.

Botox is derived from botulinum toxin, which can relax tense muscles. It is also being explored as a treatment for migraine headaches. The manufacturer, Allergan, expects to move forward with phase 3 trials of Botox for depression.

Best Antidepressants for Post-Stroke Depression

A recent meta-analysis in the journal *BMJ Open* analyzes the efficacy and tolerability of 10 different antidepressants given to treat depression following a stroke. The meta-analysis incorporated data from 12 trials and a total of 707 participants. **Reboxetine was the most effective antidepressant, followed by paroxetine, doxepin, and duloxetine.** Sertraline, fluoxetine, and nefiracetam failed to outperform placebo in the treatment of post-stroke depression.

In terms of tolerability, paroxetine had the least side effects and led to significantly fewer discontinuations than doxepin, citalopram, and fluoxetine. After paroxetine, the most tolerable drugs were sertraline and nortriptyline. The least tolerable drug was citalopram.

Researchers led by Yefei Sun suggested that paroxetine might be the best antidepressant to prescribe after a stroke due to its efficacy and good tolerability. Fluoxetine might be the worst due to its poor efficacy and poor side effects profile.

Editor's Note: Multiple randomized controlled trials suggest that antidepressants can be helpful for anyone who has a stroke, both to decrease depression and to improve neurological and functional outcomes.

Intranasal Ketamine for Bipolar Disorder

An in-press article due out in January 2018 by Demitri F. Papolos and colleagues in the *Journal of Affective Disorders* reports that **intranasal ketamine delivered every three to four days reduced symptoms of bipolar disorder in 45 teens** (aged 16 years on average). The teens treated in one private practice had the 'fear-of-harm' subtype, which in addition to bipolar symptoms is characterized by treatment resistance, separation anxiety, aggressive obsessions, disordered sleep, and poor temperature regulation.

The repeated administration of ketamine produced long-lasting positive results, improving bipolar symptoms as well as social function and academic performance. Many participants reported via survey that they were much or very much improved after being treated for durations ranging from 3 months to 6.5 years. Side effects were minimal and included sensory problems, urination problems, torso acne, dizziness, and wobbly gait.

The ketamine was delivered to alternating nostrils via 0.1 ml sprays that included 50–200 mg/ml of ketamine in 0.01% benzalkonium chloride. Patients were instructed to increase the dosage just up until it became intolerable and then repeat the last tolerable dose every three to four days. Final doses ranged from 20–360 mg. The mean dose was 165 mg (plus or minus 75 mg) delivered every 3 days.

Papolos and colleagues called for placebo-controlled clinical trials based on the positive results from this open study.

Taking SSRI Antidepressants May Increase Stroke Risk

A Taiwanese study published in the *Journal of Clinical Psychiatry* in 2017 finds that taking selective serotonin reuptake inhibitor (SSRI) antidepressants can increase risk of stroke. The study by Chin-Hong Chan and colleagues analyzed eight years of data from Taiwan's National Health Insurance Research Database, comparing people who had taken SSRIs for at least two consecutive months to those who had not. **First onset strokes were more common among people who had taken SSRIs, and the higher stroke rates in this group persisted for three years after exposure.**

Ischemic strokes (which occur when a blood vessel carrying blood to the brain is obstructed) were more common than hemorrhagic strokes (which occur when a weak blood vessel ruptures). Younger adult participants exposed to SSRIs were more likely to have strokes, while people older than 65 saw only a slight increase in stroke risk from taking SSRIs. More strokes occurred during the first three years of SSRI treatment than later in treatment.

Chan and colleagues suggest that these strokes are caused by cerebral microbleeding or by overcorrection of hemostasis, the process by which the body slows or stops bleeding by constricting blood vessels and coagulating blood.

Probiotics May Improve Depression As Well As IBS

A pilot study of people with irritable bowel syndrome (IBS) suggests that taking a probiotic nutritional supplement can improve depression as well as gastrointestinal upset.

In the 2017 study published in the journal *Gastroenterology*, researcher Maria Pinto Sanchez and colleagues at the Farncombe Family Digestive Health Research Institute found that **when those with IBS took a probiotic, their co-occurring depression improved more than it did in people with IBS who took a placebo.**

Senior author Premysl Bercik suggested the study confirms that the microbiota environment in the gut affects what goes on in the brain, opening new avenues for the treatment of psychiatric diseases.

The study included 44 adults with IBS who also had mild to moderate anxiety and depression. For 10 weeks, half received a daily dose of the probiotic Bifidobacterium longum NCC3001, while the others received placebo.

After 6 weeks, 64% of the probiotic group saw improvement in their depression, compared to 32% of the placebo group. Functional magnetic resonance imaging (fMRI) showed brain changes associated with the improvement in mood.

The researchers are planning larger trials of probiotics.

Augmentation Strategies for Negative Symptoms of Schizophrenia

In a 2017 article in the journal *JAMA Psychiatry*, Christoph U. Correll and colleagues reviewed 42 secondary strategies to treat schizophrenia when the primary antipsychotic treatment has an incomplete effect. **Many people with schizophrenia show only a limited response to antipsychotic drugs, so additional treatments are often necessary,** but currently there are no US Food and Drug Administration guidelines for combination treatment.

Correll and colleagues compiled data from 29 meta-analyses covering 381 individual trials. They found that while the meta-analyses were well done, the quality of the data in the original studies was lacking.

Focusing on Negative Symptoms

However, since the negative symptoms of the illness such as apathy, withdrawal, and blunted emotional response are the hardest to treat, any amount of improvement in this area could be particularly helpful. Large to moderate effect sizes were reported for the effectiveness of the following medications in reducing negative symptoms (in decreasing order): serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants, serotonin type 3 receptor active drugs (such as ondansetron), lamotrigine, acetylcholine esterase inhibitors, testosterone, the antibiotic minocycline, the anticonvulsant topiramate, antipsychotics, estrogen active compounds, any antidepressant, and modafinil.

The review did not include the positive findings on the antioxidant n-acetylcysteine (NAC). Researcher Michael Berk and colleagues reported in the journal *Biological Psychiatry* in 2008 that patients who received NAC in addition to maintenance treatment for schizophrenia saw more improvement in 24 weeks than those who received a placebo in addition to their normal treatment.

Clozapine, the most effective antipsychotic drug for patients with treatment-resistant schizophrenia, was not successfully augmented by any of the strategies in this review article. However, a few studies have found that adding the antipsychotic aripiprazole to clozapine treatment helps improve symptoms of schizophrenia and allows for a reduction in clozapine dosage, which improves tolerability. Studies have also shown that electroconvulsive therapy (ECT) can augment clozapine in people with treatment-resistant schizophrenia.

Editor's Note: Given the serious impairment faced by people with schizophrenia, which is often driven by negative symptoms, some of these augmentation strategies deserve careful trials in individual patients. This is especially true of approaches that also work on positive symptoms (such as lamotrigine) or ones that pose little risk of side effects, such as NAC and minocycline.

FDA Approves New Higher Dose of Valbenazine for Tardive Dyskinesia

The US Food and Drug Administration has approved an 80 mg capsule dose of valbenazine (Ingrezza) for tardive dyskinesia (jerky, involuntary movements of the face, especially the mouth and tongue, fingers and body that can be a side effect of antipsychotic medication). Valbenazine, a selective vesicular monoamine transporter 2 inhibitor, was the first drug FDA-approved for tardive dyskinesia. **The FDA initially approved a dosage of 40 mg/day in April 2017. The 80 mg/day dose was approved in October 2017.**

The new approval was based on a 6-week clinical trial in which 80 mg of valbenazine improved tardive dyskinesia significantly compared to placebo. Improvement continued over 48 weeks of treatment.

Liraglutide Decreased Body Weight, Improved Glucose Tolerance and Cardio Health in Schizophrenia

A 2017 article by Julie R. Larsen and colleagues in the journal *Archives of General Psychiatry* reported that the drug **liraglutide, a treatment for type 2 diabetes, improved certain health measures in people with schizophrenia who were overweight and prediabetic and being treated with the atypical antipsychotics olanzepine or clozapine.**

In the 16-week trial, patients received a daily 2 mg injection of liraglutide under the skin or placebo. Liraglutide decreased body weight, improved glucose tolerance, and improved cardio-metabolic measures. Weight decreased by more than 10 pounds on average compared to placebo.

Liraglutide is derived from a human metabolic hormone. It binds to the same receptors as does the metabolic hormone GLP-1, which stimulates insulin secretion.

See page 11 for information about a study of children at risk for bipolar disorder.

Simvastatin Looks Promising in Treatment of Negative Symptoms of Schizophrenia

The statin drug simvastatin (Zocor) enhances the effects of risperidone on negative symptoms of schizophrenia, according to a 2017 article by Soode Tajik-Esmaeeli and colleagues in the journal *International Clinical Psychopharmacology*.

In the 8-week study, **40 mg/day of simvastatin enhanced the effects of 4–6 mg/day of the antipsychotic risperidone on negative symptoms of schizophrenia, such as apathy and withdrawal, but not positive symptoms such as hallucinations or delusions.**

Other statins, lovastatin and pravastatin, have not had a similar effect, possibly because they do not cross the blood-brain barrier as easily as simvastatin does.

Simvastatin has other benefits as well. Like all statins it decreases lipid levels, reducing cardiovascular disease. People with schizophrenia and bipolar disorder are at especially high risk for cardiovascular disease.

Simvastatin also decreases inflammation (lowering IL-1 alpha and TNF-beta levels) and may be neuroprotective, as it increases brain-derived neurotrophic factor (BDNF), a protein that protects neurons and is important for learning and memory. Inflammation is increasingly implicated in schizophrenia and bipolar disorder.

There is also some evidence that statins can prevent depressions over long-term follow-up. Studies in women without depression and men who had recently had heart attacks both showed that those taking statins had a lower rate of future depression than those not taking statins.

Editor's Note: These findings suggest a potential 5-fold benefit to simvastatin: 1) It reduces negative symptoms in schizophrenia. 2) It reduces inflammation. 3) It increases BDNF. 4) It decreases cardiovascular disease risk by lowering lipid levels. 5) It may prevent future depressions.

See page left for other approaches to augmenting schizophrenia treatment. *In addition, nutritional supplements vitamin D3 and folate. Patients with psychosis often have vitamin D deficits. Folate supplements can reduce homocysteine, which has been linked to cognitive deficits in schizophrenia.*

Even Light Exercise Prevents Future Depressions

A 2017 article in *The American Journal of Psychiatry* suggests that regular leisure-time exercise of any intensity can protect against future depressions.

The study by Samuel B. Harvey and colleagues followed a group of 33,908 healthy adults for 11 years. The researchers found a link between regular leisure-time exercise and reduced incidence of future depression (but not anxiety). This link occurred regardless of the intensity of the exercise, and most of the effect occurred at low levels of exercise. **Analysis suggested that 12% of future cases of depression could be prevented if all participants fit one hour of physical activity into their week.**

A small part of the benefit came from the social and physical health benefits of exercise.

Harvey and colleagues suggested that from a public health perspective, increasing population levels of exercise modestly could lead to a substantial decrease in depressions.

Editor's Note: Alongside maintenance treatment, in the form of antidepressants for unipolar depression or mood stabilizers and atypical antipsychotics for bipolar disorder, exercise could provide some benefits in preventing future depressions.

A New Treatment for Disruptive Mood Dysregulation

The 2013 update to the *Diagnostic and Statistical Manual of Mental Disorders*, or the *DSM-5*, included a new diagnosis of disruptive mood dysregulation disorder. Children with persistent, severe temper outbursts and irritable or angry moods that are out of proportion to circumstances may be diagnosed with the disorder. However, there is not much specificity to the diagnosis and few treatment studies have been done to help clinicians and parents determine how to manage symptoms of the disorder.

A poster presented at the 2017 Psych Congress reported that **a medication protocol consisting of an anticonvulsant drug to stabilize moods and temper outbursts and a dopamine agonist to reduce irritability, impulsivity, and concentration problems reduced rates of re-hospitalization.** The retrospective study by researchers D. Matthews and G. Matthews included 91 children and adolescents who were prescribed the anticonvulsant oxcarbazepine and the dopamine agonist amantadine following hospitalization for severe aggression, mood instability, and impulsivity. Those who stuck to the regimen with minimal changes for one year had an 8% re-hospitalization rate compared to a 26% re-hospitalization rate among those who discontinued the regimen or substituted other drugs.

Editor's Note: Oxcarbazepine has a long-acting preparation, Oxtellar, that can be given all at night.

Amantadine (Symmetrel) not only is a dopamine agonist used for Parkinson's disease, but is also an antiviral and a blocker of glutamate NMDA channels. It stabilizes the closed state of the NMDA channel.

Expectations Can Affect Treatment Efficacy

A 2017 article by Vanda Faria and colleagues in the journal *EBioMedicine* reports that **when patients with social anxiety disorder were told they were being treated with an active drug, they had a response rate three times higher than patients who were given the same drug but told it was an inactive placebo. The researchers suggest that the way treatments are presented to patients affects whether they work.**

In the study by Faria and colleagues, patients with social anxiety were given the selective serotonin reuptake inhibitor (SSRI) antidepressant escitalopram for nine weeks. Some were told they had received escitalopram, while some were told they had received a placebo. Not only did those who were told they were taking escitalopram see greater reductions in their anxiety, they also showed more connectivity between the posterior cingulate and the amygdala, a region that is crucial to mediating anxiety.

This finding is in line with other research that has found that patients' thoughts and expectations during treatment can affect the efficacy of that treatment.

Researcher Isaac Marks found that patients with obsessive compulsive disorder (OCD) with fear of contamination who were told to avoid things they feared, such as touching a toilet seat, did not fare any better than those taking placebo pills. However, those taking SSRIs who tried new behaviors like touching a toilet seat learned that they could do so without a major fear response, and their phobias improved.

Several studies have shown that expectations of antidepressant efficacy have a big effect on whether patients with unipolar depression improve after beginning treatment with SSRIs. Bret R. Rutherford and colleagues reviewed findings on expectancy in major depressive disorder in a 2010 article in the journal *Current Psychiatry Review*.

When patients are presented with a drug and encouraged to believe it will work, they may gain the confidence to try out new behaviors or ways of looking at things, whether that means exploring new social situations for someone with social anxiety, or feeling hopeful and breaking the habit of negative rumination for someone with depression. As the study by Faria and colleagues shows, expectations can even change patterns of brain connectivity.

Studies of repetitive transcranial magnetic stimulation (rTMS), in which electromagnets placed near the scalp stimulate electrical impulses in the brain, have shown that patients with depression who engage in positive thoughts and conversations with their rTMS provider during the stimulation improve more than those who sit passively. If a patient engages in their habitual negative ruminations during rTMS, these might even be cemented by the rTMS-induced release of glutamate and brain-derived neurotrophic factor (BDNF), which are both involved in learning and memory processes and what has been called experience-dependent neuroplasticity.

Thus, a patient's thoughts and outlook during treatment may be important to the therapeutic outcomes achieved. While expectations may not be sufficient to produce an effect on their own, it does seem that thoughts and behaviors can improve a treatment's efficacy.

It's now faster and easier to join the Child Network!

The consent form for the Child Network has been simplified. If you previously tried to sign up and gave up in frustration, please try again. The new consent form is much easier to complete.

The Child Network is a study designed to evaluate how children with mood disorders are being treated for their illness. Parents who enroll in the study complete an online checklist of their child's symptoms once a week using a secure web-based system. Parents of children aged 2–12 who have mood or behavioral problems should consider joining. See page 11 for more information.

As a benefit, parents can print out a chart of their child's symptoms and responses to treatment to show the children's physician. This should facilitate early recognition and treatment of a range of common psychiatric disorders that begin in childhood.

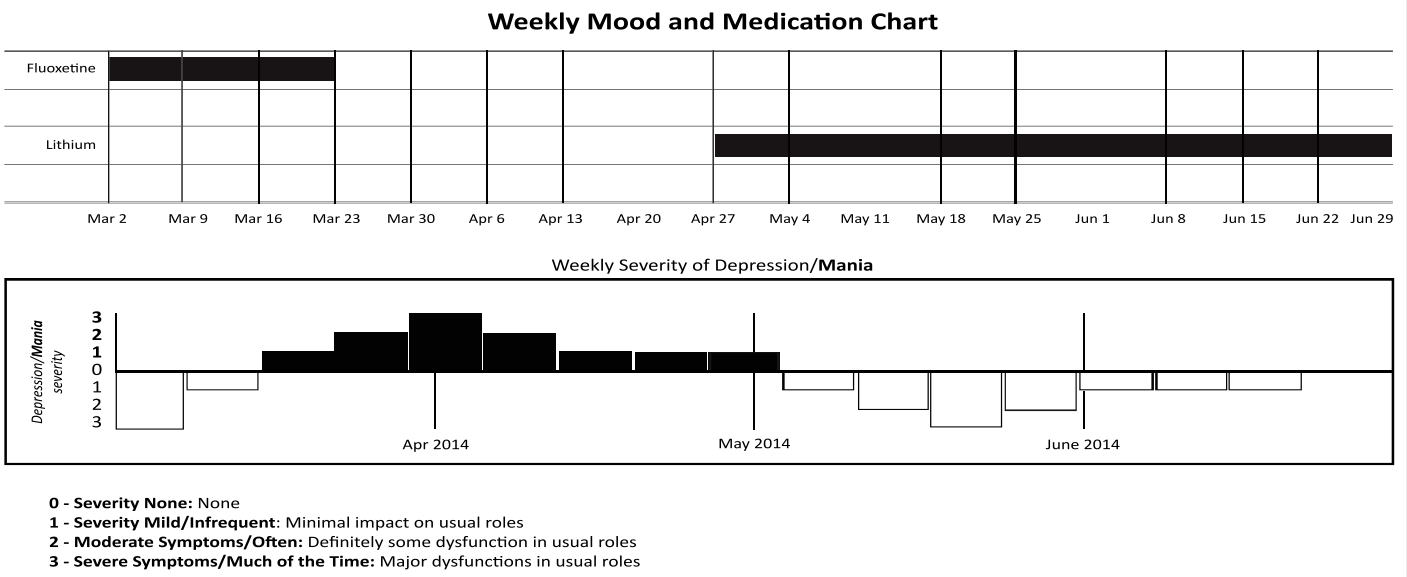
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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 **bipolarnews.org** and click on the tab for the Child Network or go directly to 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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