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Bipolar Network News

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Lithium Responders and Non-Responders Have Different Neuron Characteristics

A 2017 study in the journal *Molecular Psychiatry* suggests that **by observing the neurons of a person with bipolar disorder, you can predict whether they will respond to lithium treatment.** The drug is effective in approximately 30% of those to whom it is prescribed.

Researchers led by Shani Stern and Renata Santos used stem cell research to analyze neurons from people with bipolar disorder and healthy controls.

People with bipolar disorder shared some neuron features, namely a large, fast after-hyperpolarization (a phase in which the cell's membrane changes), which is followed by a resting period before the neuron can fire again. The large, fast hyperpolarization in people with bipolar disorder speeds up this cycle, leading to fast and sustained neuron firing.

This study replicated previous findings by the same researchers, that people with bipolar disorder are more sensitive to stimuli. In people with bipolar disorder, the threshold for a neuron to fire drops with each subsequent after-hyperpolarization.

Chronic lithium treatment reduced this hyperexcitability in some patients—and these were the patients who had a good response to lithium treatment.

Stern and colleagues programmed a computer to recognize the electrophysiological features of the neurons from lithium responders and non-responders.

The computer could then analyze the neurons of a patient whose response to lithium was unknown and predict with a greater than 92% success rate whether that patient had responded well to lithium treatment.

In This Issue:

Anticonvulsant Topiramate Plus Antipsychotic Medication Works Better for Schizophrenia Spectrum Disorders Than Antipsychotics Alone

A 2016 meta-analysis has shown that the combination of the anticonvulsant topiramate and antipsychotic medication reduces symptoms of schizophrenia spectrum disorders more than antipsychotic medication alone. Researchers led by Christoph U. Correll analyzed the results of eight studies in which the topiramate-antipsychotic combination was compared to antipsychotics alone or with placebo.

The combination of topiramate and antipsychotic medication was superior at reducing general psychopathology, including both negative and positive symptoms of schizophrenia. The combination was also associated with lower body weight and body mass index (BMI) compared to antipsychotics alone.

The studies included in the meta-analysis used a variety of antipsychotic medications. When these were compared, the combination of topiramate and clozapine was more effective than other combinations at reducing psychopathology. However, the combination of topiramate and clozapine was also associated with less weight loss than combinations using other antipsychotics.

In terms of side effects, topiramate was associated with more paresthesia (a burning or prickling sensation, often in the hands or feet) than placebo.

The study was published in the *Journal of Clinical Psychiatry*.

FDA Approves Valbenazine as Treatment for Tardive Dyskinesia

A new drug valbenazine (trade name Ingrezza) has been approved by the US Food and Drug Administration for the treatment of tardive dyskinesia. Tardive dyskinesia, a side effect of long-term use of antipsychotic medication, consists of involuntary movements of the tongue, face, torso, arms, and legs. It can interfere with walking, talking, and breathing.

The approval followed 20 clinical trials of valbenazine that included a total of more than 1000 participants who had symptoms of tardive dyskinesia in addition to schizophrenia, schizoaffective disorder, or bipolar disorder.

In a 2017 article in the *American Journal of Psychiatry*, researcher Robert A. Hauser and colleagues reported that **patients who received 80 mg/day of valbenazine had a significant reduction in tardive dyskinesia symptoms after six weeks compared to those who received placebo.** Participants who received 40 mg/day of valbenazine also had reductions in symptoms, although not as dramatic as with the higher dose.

Serious side effects of valbenazine include sleepiness and lengthening of the QT interval, which can increase heart arrhythmias. The FDA notes that people who already have abnormal heartbeats due to a long QT interval should not take valbenazine. In addition, people taking the drug should avoid driving or operating heavy machinery until they know how valbenazine affects them.

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The *BNN* is published 4–6 times a year by investigators working with patients with bipolar disorder to better understand the long-term course of illness. The newsletter is available free of charge to all who request it.

Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in abstract or pre-publication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact or omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the *BNN*.

Dr. Post has consulted on behalf of drug companies including Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

The opinions expressed in the BNN are solely those of Dr. Post, and do not represent the views of any scientific entity or foundation.

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Levels of Amino Acid Proline Interact with COMT Genotype to Affect Negative Symptoms

In a 2016 article, researcher Catherine L. Clelland and colleagues reported that a patient's levels of the amino acid proline interact with their genetic profile to influence the seriousness of their negative symptoms. Negative symptoms of schizophrenia and bipolar disorder include flat affect and lack of volition and can be some of the hardest symptoms to treat.

High levels of proline in the central nervous system have been linked to schizophrenia. Proline is a precursor to the neurotransmitter glutamate, and high proline levels have been found to alter glutamate and dopamine signaling in mice. This is one of the factors affecting negative symptoms.

The other factor affecting negative symptoms is the COMT gene. The enzyme catechol-o-methlyl transferase (COMT) metabolizes dopamine in the prefrontal cortex. There are several common versions of the gene for COMT. The most efficient is known as val-158-val, identifying that the gene has two valine amino acids at position 158. People with high proline levels and the val-158-val version of the COMT gene had fewer negative symptoms than people with high proline levels and another version of the gene, val-158-met (indicating one valine and one methionine amino acid at position 158).

Clelland and colleagues hypothesized that **high proline levels may actually counteract the dopamine shortages common in the prefrontal cortex in people with the val-158-val genotype of COMT, which is more efficient at breaking down dopamine in this region.**

The mood stabilizer valproate increases proline levels. In the study, which was published in *Translational Psychiatry*, people with schizophrenia and the val-val genotype had fewer negative symptoms when treated with valproate than those with the val-met genotype who received the same treatment.

BNN Editor Robert M. Post Wins Mogens Schou Award for Research from the International Society for Bipolar Disorder

On May 4, 2017, at the annual conference of the International Society for Bipolar Disorders (ISBD) in Arlington, Virginia, Dr. Robert M. Post, Editor-in-Chief of *Bipolar Network News*, was presented the Mogens Schou Award for Research. It is one of the most prestigious honors in the field of research on bipolar disorder.

Mogens Schou was a Danish psychiatrist and researcher whose research in the 1950s led to lithium's use in the treatment of bipolar disorder.

Upon the announcement of the award by Dr. Marion Leboyer, who received the Schou research award in 2011, Dr. Post received a standing ovation. The following comments are adapted from Dr. Post's acceptance speech.

"It is the highest honor I could imagine to receive an award from the ISBD in the name of Mogens Schou. Not only did Schou pioneer the development of lithium for the recurrent mood disorders, but he beat back the British naysayers and critics (Michael Shepherd and Harry Blackwood) by conducting the definitive long-term controlled studies of lithium, and then continued to promote its benefits.

In Schou's obituary, fellow researcher Dr. Paul Grof wrote,"What was most striking and profound about him was his love and compassion for people." Schou himself said upon receiving an award, "For me every single patient whose life was changed radically by lithium outweighs honors and awards."

Thus, it is only appropriate that I relay some of the new data on the broad clinical effects of lithium, especially since lithium today is used way too infrequently, particularly in the United States. This list is a bit too condensed, but **LITHIUM: increases neuroprotective factors and neurogenesis** (adults like me in the room are happy to know that we are still making new neurons). **Lithium increases the volume of the hippocampus and cortex, and blocks cell death.**

Lithium prevents mania, depression, and even recurrent unipolar depression, and reduces suicides 10-fold.

Lithium lengthens telomeres [bits on the ends of DNA that protect it during cell replication] back to normal, enhances health and longevity, **decreases the incidence of some neurological diseases (including dementia), and half a pill a day for one year prevents the progression of mild cognitive impairment.**

Remarkably, higher trace amounts of lithium in drinking water prevent suicide in the general population. This has now been shown in more than a half dozen studies that compare naturally occurring levels of lithium in the water in different geographic areas.

No other drug comes close to having this range of benefits. So I can only reiterate a message Schou was determined to spread in his final years: "We need to use lithium more often."

If Schou had seen the excess of childhood-onset bipolar disorder in the United States, he would surely have lobbied for better treatment of these young people and more treatment research.

I thank the ISBD for this great honor and the opportunity to try to foster Schou's ideals."

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.

National Academy of Sciences, Engineering and Medicine Issues Report on the Health Effects of Cannabis

In early 2017, the National Academy of Sciences, Engineering, and Medicine issued its first comprehensive report on cannabis since 1999. Shifting public opinion over the past few decades has led to 28 states and the District of Columbia legalizing medical uses of marijuana, and eight states and DC legalizing recreational marijuana use. *The Health Effects of Cannabis and Cannabinoids: Current State of Evidence and Recommendations for Research* is intended to address the lack of accepted standards to guide individuals in deciding whether and how to use cannabis safely. In addition to summarizing recent health-related findings on cannabis, the report also offers recommendations to guide future research.

The report shares findings about possible therapeutic benefits to cannabis use as well as health impacts relating to areas such as cancer, respiratory disease, immunity, pre- and post-natal health.

There were several notable findings with regard to mental health. The committee that issued the report found substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.

The committee also found moderate evidence of a link between cannabis use and increased symptoms of mania and hypomania in people with bipolar disorder who use cannabis regularly. The report also describes moderate evidence of an association between heavy cannabis use and increased suicidal ideation and suicide attempts.

There was also moderate evidence that regular cannabis use is linked to social anxiety disorder.

The report described factors that may lead to problem cannabis use. The committee found substantial evidence that being male, smoking cigarettes, and beginning cannabis use at an earlier age are risk factors for developing problem cannabis use.

There was moderate evidence of a link between cannabis use and the development of a substance dependence or substance abuse disorder for substances including alcohol, tobacco, and other illicit drugs.

In the realm of psychosocial functioning, the committee found moderate evidence that acute cannabis use is associated with impairment in the cognitive domains of learning, memory, and attention.

The strongest findings with regard to beneficial effects of marijuana were that **cannabis can treat chronic pain in adults, and that oral cannabinoids can reduce chemotherapy-induced nausea and vomiting and improve multiple sclerosis spasticity symptoms.** There was also moderate evidence that cannabinoids (particularly an extract called nabiximols) can improve short-term sleep outcomes in people with a variety of ailments. Some of the beneficial effects of marijuana have been linked to the cannabidiol compound, as opposed to the THC in marijuana, which causes the psychoactive effects of the drug.

Editor's Note: The link between cannabis use and psychosis risk is strong, and reason enough to avoid marijuana use. See page right to learn more about how a common variant of the COMT gene that influences dopamine metabolism increases this risk in young users. The more efficient val-val allele of COMT increases risk of psychosis by depleting dopamine in the prefrontal cortex.

Continuing Marijuana After First Psychosis Increases Risk of Relapse

A 2016 article in the journal *JAMA Psychiatry* reports that continuing to use cannabis after a first episode of psychosis increases risk of relapse. The study by Sagnik Bhattacharyya and colleagues employed longitudinal modeling to determine the role of cannabis use in psychotic relapse. The researchers followed 90 women and 130 men for two years after a first episode of psychosis, and found that **the more marijuana they used, the more likely they were to have a relapse of psychosis.**

Relapse rates were highest (59.1%) for participants who used pot continuously following their first episode of psychosis. Relapse rates were lower (36.0%) for those who used cannabis intermittently thereafter, and lowest (28.5%) among those who discontinued cannabis use after their first episode of psychosis.

A statistical test known as a cross-lagged analysis was used to establish that cannabis use affected later relapse, rather than relapse of psychosis leading to further cannabis use.

Another statistical strategy using fixed-effect models revealed that risk of psychotic relapse was 13% higher during times of cannabis use than during periods of no cannabis use.

These findings offer some hope that the likelihood of psychosis relapse can be reduced, since ongoing cannabis use is a risk factor that can be modified, unlike family history or genetics. Bhattacharyya and colleagues called for research into interventions that can help discourage cannabis use in people who have had a first episode of psychosis.

Editor's Note: N-acetylcysteine, a nutritional supplement sold in health food stores, can reduce cannabis use compared to placebo in teen users.

Early Cannabis Use and BDNF Gene Variant Increase Psychosis Risk

Normal variations in genes can affect risk of mental illness. One gene that has been implicated in psychosis risk is known as BDNF. It controls production of brain-derived neurotrophic factor, a protein that protects neurons and is important for learning and memory. Another important gene is COMT, which controls production of the enzyme catechol-O-methyltransferase, which breaks down neurotransmitters such as dopamine in the brain.

Several forms of these genes appear in the population. These normal variations in genes are known as polymorphisms. Certain polymorphisms have been linked to disease risk. A study by Anna Mané and colleagues published in the *Journal of Psychiatric Research* in 2017 explored links between COMT and BDNF polymorphisms, cannabis use, and age at first episode of psychosis.

Mané and colleagues found that among 260 Caucasians being treated for a first episode of psychosis, **the presence of a BDNF polymorphism known as val-66-met and a history of early cannabis use were associated with younger age at psychosis onset.**

The val-66-met version of BDNF occurs in 25-35% of the population. It functions less efficiently than a version called val-66-val.

The researchers also found that males were more likely to have used cannabis at a young age.

Editor's Note: In the general population, marijuana use doubles the risk of developing psychosis. Previous data had indicated that the risk was higher for those with a COMT polymorphism known as val-158-val that leads to more efficient metabolism of dopamine in the prefrontal cortex. The resulting deficits in dopamine increase vulnerability to psychosis compared to people with the val-158-met version of the COMT gene.

The new study by Mané and colleagues suggests that a common form of BDNF may be associated with an earlier onset of psychosis. Bottom line: Pot is dangerous for young users and can induce psychosis, particularly in people at genetic risk. Pot may be legal in many places, but heavy use in young people remains risky for mental health and cognitive functioning.

The company Genomind offers genetic testing for BDNF and COMT variants as part of a routine panel.

Cannabis Use May Cause Schizophrenia

Cannabis use has been linked to schizophrenia risk, and new genetic research suggests a causal relationship between the two. In a 2017 article in the journal *Molecular Psychiatry*, researcher Julian Vaucher and colleagues reported that **lifetime cannabis use was linked to schizophrenia even when the researchers controlled for 10 genotypes weakly associated with lifetime cannabis use.** This makes it unlikely that the schizophrenia caused the cannabis use, suggesting instead that it is the cannabis use that leads to a schizophrenia diagnosis.

Vaucher and colleagues also controlled for genetic associations between cigarette smoking and cannabis use to eliminate cigarette use as a third variable causing the association between cannabis and schizophrenia.

The study by Vaucher and colleagues included 34,241 people with schizophrenia and 45,604 healthy controls.

Early Marijuana Use Linked To Abnormal Brain Function, Low IQ

A study of depression and marijuana use found that using marijuana before the age of 17 was linked to abnormal brain function and lower IQ. In a 2016 article in the journal *Acta Psychiatrica Scandinavica*, researcher Elizabeth Osuch and colleagues described a study that compared four categories of youth: frequent pot users with depression, frequent pot users without depression, those with depression who did not use pot, and healthy individuals who did not use pot. The researchers also compared those who began using pot after the age of 17 to those who began earlier.

The main findings were that brain function in the areas of reward processing and motor control differed across the four groups. Depression was linked to deficits in brain function. Marijuana use did not correct these deficits, and in some parts of the brain, worsened them.

Those who had used marijuana before the age of 17 had abnormalities in memory, visuo-spatial processing, self-referential activity, and reward processing. Those who had started using marijuana at younger ages also had lower IQ scores.

It's now faster and easier to join the Child Network! See page 11.

Decriminalization of Marijuana Linked to Lower Educational Attainment

As more states pass laws allowing the use of medical marijuana, and some are decriminalizing recreational marijuana use, researchers are examining possible negative consequences of loosening these drug policies. Researcher Andrew Plunk and colleagues reported in a 2016 issue of the journal *Drug and Alcohol Dependence* that states where medical marijuana has been legalized have seen dropout rates increase among high school seniors. Educational attainment after high school has decreased as well.

Plunk stressed that while policies that allow medical marijuana and decriminalize recreational marijuana use may have benefits, it is also important to study any possible negative consequences of these policies. He compared marijuana to alcohol and cigarettes, substances that are legal for adults to use but also negatively impact users' health. Plunk told Medscape Medical News that as marijuana gets approved for medical uses, kids may begin to see the drug as less risky.

Plunk and colleagues used datasets from the US Census and the American Community Survey from 1990 to 2012, which included a total of 5,483,715 people of high school age. Compared to young people in states with no legalized marijuana policies, those in states with medical marijuana had a 0.40 percentage point increase in the probability they would not receive a high school diploma or GED. **Living in a state with medical marijuana was also linked to a 1.84 percentage point increase in the probability of not enrolling in college**, and a 0.85 percentage point increase in the probability of not getting a college degree.

While medical marijuana is not prescribed to minors, Plunk and colleagues believe it is easier for adolescents in states where medical marijuana is available to access marijuana that has been prescribed to adults.

Editor's Note: Heavy marijuana use comes with risks such as doubling of the likelihood of psychosis, hastening the onset of schizophrenia and bipolar disorder, increasing cognitive impairment, and changing brain structure.

Risks of Synthetic Marijuana Use

Several states have reported upticks in overdoses from synthetic marijuana over the past few years. Synthetic marijuana, sometimes called "spice" and sold under descriptors such as "botanical incense," consists of man-made chemicals that are sprayed on plant matter and smoked, or sold as liquids to be consumed via e-cigarettes. Monitoring the Future, an ongoing survey of teen drug use in the US, reported in 2016 that 3.5% of high school seniors had used synthetic marijuana in the past year. The risks of the drug are not yet well known, since the chemicals used may vary from batch to batch.

A case series published in the *Western Journal of Emergency Medicine* in 2016 described 11 cases of patients who received emergency room treatment for an overdose of the synthetic cannabinoid MAB-CHMINACA. According to the Drug Enforcement Agency, MAB-CHMINACA can cause severe toxicity, seizures, excited delirium, cardiotoxicity and death.

Kenneth D. Katz and colleagues reported that all 11 patients required sedation, while nine required intubation to provide respiratory support. Three of the 11 patients had seizures, and one suffered from hyperthermia (increased body temperature). One patient died as a result of decreased oxygen to the brain and rhabdomyolysis, a condition in which muscles break down and release toxins, shutting down the kidneys. Many of the 11 were children or adolescents.

Katz and colleageus stress that synthetic cannabinoid use is a public health crisis, and that emergency rooms should be prepared to provide aggressive sedation and respiratory support to people overdosing on MAB-CHMINACA.

Editor's Note: 'Spice' is not only more potent than marijuana but also lacks cannabidiol, a cannabinoid thought to be responsible for some of the beneficial effects of marijuana.

Chronic Fatigue Linked to Low Metabolism

A 2016 article in the journal *PNAS* suggests that people with chronic fatigue syndrome, also known as myalgic encephalopathy, share a low metabolic profile.

In the study, researcher Robert K. Naviaux and colleagues measured 612 different metabolites in 63 metabolic pathways. They found abnormalities in 20 of these pathways in people with chronic fatigue. Eighty percent of the abnormal measurements were low.

The low metabolic profile resembled a stage of development some worm larvae go through when environmental conditions are harsh. The phase, called dauer, can be brought on by harsh temperatures, low food supply, or pheromones that indicate high population density. It resembles hibernation in some ways, including changes to mitochondrial function. Dauer allows larvae to live for 4 months rather than their normal lifespan of 3 weeks. They can resume normal development when conditions improve.

The authors suggest that chronic fatigue is a metabolic response to environmental stress, and hope to clarify the link between mitochondrial function and the illness.

Disrupting Memories of Cocaine Use Might Prevent Relapse

Cocaine users who want to abstain from the drug may find that encountering people or places who remind them of past cocaine use can increase their cravings for the drug and lead to relapse. **Researchers are studying animals to see if disrupting the link between an environmental cue and the memory of cocaine's effects could reduce cravings for the drug.**

In a 2016 article in the journal *Neuropsychopharmacology*, researcher Melissa S. Monsey and colleagues reported that in rats, the amnesia-causing natural compound garcinol can weaken the cues that lead to a cocaine-seeking. Garcinol is derived from the rind of kokum (or Garcinia indica) fruit, which is native to the west coast of India.

Monsey and colleagues delivered the garcinol during a period when the rats' brains were reconsolidating memories that linked an environmental cue with the pleasurable effects of cocaine.

For 12 days, the rats in the study could press a lever and receive an intravenous infusion of cocaine that was paired with a light and a sound. Then the lever stopped working for 8 days. Next, the researchers observed how the rats behaved when the light and sound returned.

The light and sound were meant to remind the rats of the previous times they received cocaine, prompting their brains to reconsolidate the memory linking the light/sound with the pleasurable effects of cocaine.

Half of the rats were given an injection of garcinol during this memory reconsolidation period. **While all of the rats continued to seek out cocaine, in the garcinol-treated rats, the light/sound was no longer linked to cocaine.** Their cocaine-seeking behavior from then on was unrelated to the light/sound, and the link between the light/sound and cocaine could not be reinstated in these rats.

This research on rats may help clarify how cravings are produced in the brain, and how they might be prevented or treated.

Editor's Note: In 2012, Yan-Xue Xue and colleagues reported in the journal Science *that in humans, psychological techniques can be used to help a patient unlearn the association between an environmental cue and the effects of a drug, using the same theory of the memory reconsolidation period.*

When patients in recovery from heroin addiction were prompted to revisit memories of heroin use 10 minutes before extinction training (in which they looked at heroin or heroin paraphernalia without receiving the drug), they ended up with fewer cravings for heroin 1, 30, and 180 days later compared to patients who did extinction training without revisiting memories of past heroin use (and thus without opening the memory reconsolidation window, which researchers believe opens 5 minutes to an hour after someone engages in active recall).

Weight Loss Drug Lorcaserin Cuts Opiate Use in Rats

Lorcaserin is a drug approved for weight loss in very obese patients. It stimulates serotonin 5 HT-2c receptors thought to control appetite by inducing the secretion of the polypeptide pro-opiomelanocortin. In a 2017 article in the journal *ACS Chemical Neuroscience*, researcher Kathryn Cunningham and colleagues reported that the drug had reduced opiate use and craving in rats. Previous research by Cunningham showed that lorcaserin reduced cocaine seeking in rats.

Most treatments for opiate addiction work by occupying opiate receptors so that opiates are prevented from stimulating them, thus reducing the pleasurable effects of the opiates. It is not yet well understood how drugs like lorcaserin that target serotonin 5 HT-2c receptors affect the brain's reward system.

In the study, rats were trained to self-administer oxycodone. They were also trained to associate certain lights and sounds with oxycodone availability. **Lorcaserin reduced the rats' drug-seeking behavior and also weakened the link between the light and sound cues and the drug-seeking behavior.**

Future research may explore whether drugs like lorcaserin can reduce opiate use in people.

Currently, there are a few options to treat opiate addiction. N-acetylcysteine (NAC) is an over-the- counter (nonprescription) drug that has been shown to decrease opiate use in both animals and humans. NAC also decreases use or craving for many other drugs of abuse including cocaine, alcohol, nicotine, and marijuana. NAC reduces the excitatory glutamate signal in the reward area of the brain (the nucleus accumbens) by increasing the number of transporters carrying glutamate out of the synapse and into glial cells. It has an excellent side effects profile and can readily be used in opiate-addicted patients.

Opiate replacement therapy with methadone or the partial opiate agonist buprenorphine is one treatment option for opiate addiction. Buprenorphine is also combined with the opiate antagonist naloxone in a drug called Suboxone, which can reduce opiate use. Naloxone is a pure opiate antagonist that can rapidly reverse the respiratory-suppressing effects of an overdose of opiates.

Antidepressant Use in Pregnancy Does Not Increase Autism Risk

Two large observational studies published in the journal *JAMA* in 2017 find no link between antidepressant use during pregnancy and risk of an autism spectrum disorder. Previous studies had suggested a link between the two, but may not have sufficiently accounted for confounding factors. In both new studies, autism rates did not differ between siblings exposed to antidepressants in utero and those who were not exposed.

One of the studies, by researcher Ayesha C. Sujan and colleagues, analyzed **exposure to antidepressants in the first trimester and neurodevelopmental outcomes in almost 1.6 million Swedish children. Antidepressant use did slightly increase the chance of a preterm birth, but was not linked to autism spectrum disorder**, attention-deficit hyperactivity disorder (ADHD), or small size of the fetus.

The researchers suggested that doctors and patients work together to decide how depression should be treated during pregnancy, based on severity of the depression, treatment history, and access to services.

The other study, by researcher Hilary K. Brown and colleagues, analyzed 36,000 births in Ontario, Canada and found no increased risk of autism spectrum disorder based on antidepressant exposure in utero. The study controlled for 500 characteristics such as mother's education, age, and health history.

The journal *JAMA Pediatrics* also published a meta-analysis and review of 10 studies on the subject, finding that a woman's history of psychiatric disorders weakened any link between antidepressant use during pregnancy and risk of autism spectrum disorder in her children. This implies that the underlying illness, not its treatment, may be responsible if there is any link between depression and autism. The meta-analysis was carried out by researcher Antonia Mezzacappa and colleagues.

Birth Defects from Valproate Lower in Bipolar Disorder than in Epilepsy

The anticonvulsant valproate increases the risk of serious birth defects in fetuses exposed to it. However, a 2017 report by ANSM, France's agency for health and product safety, and its national insurance fund for employed workers shows that these risks are lower for women taking valproate for bipolar disorder than for women taking valproate for epilepsy.

In France, the risk of a major fetal malformation was 10.2 per 1000 women in the general population, about twice that (22.2 per 1000) in women taking valproate for bipolar disorder, and about 4 times higher (46.5 per 1000) in women taking valproate for epilepsy. The authors suggest that treatment for bipolar disorder may be more likely to be interrupted during pregnancy, and this could explain the different levels of risk by diagnosis.

Among the risks of defects in the fetuses of women being treated with valproate for epilepsy, the risk of a ventricular septal defect (a hole in the wall separating the lower heart chambers) was 11.2% compared to 2.7% in fetuses not exposed to valproate, while risk of an atrial septal defect (a hole in the wall separating the upper heart chambers) was 19.1% in the fetuses of those prescribed valproate for epilepsy compared to 1.9% in unexposed fetuses. Risk of hypospadias (placement of the urethra opening on the underside of the penis rather than its end) was 22.7% compared to 4.8% in the general population.

Risks of a major malformation were dose dependent in those with epilepsy (but interestingly, not in those with bipolar disorder), meaning the more valproate patients with epilepsy took, the higher their risk of a fetus with birth defects.

The only birth defects that were more common in the fetuses of women taking valproate for bipolar disorder than in fetuses not exposed to valproate were hypospadias (17.5% risk compared to 4.8% in the general population) and craniostenosis, a deformity of the skull (4.2% risk compared to 0.4% in the general population).

The relative safety of valproate in women being treated for bipolar disorder compared to those being treated for epilepsy is good news for some. However, fetal exposure to valproate has also been linked to deficits in cognitive development.

The risk of spina bifida, which causes lifetime paralysis, in a fetus may no longer be such a catastrophic issue for women taking valproate for bipolar disorder (where the risk did not exceed that of the general population), as was once assumed based on data from women with epilepsy (where the risk is usually 2-4%, but was 8% in this French study). This may be of some comfort to women with bipolar disorder who require valproate treatment to remain stable and wish to become pregnant or in those who experience an unplanned pregnancy.

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

Safety of Atypical Antipsychotics in Pregnancy

A 2017 article in the *Journal of Clinical Psychiatry* systematically reviewed data on the risks related to schizophrenia, bipolar disorder, and treatment with atypical antipsychotic medication during pregnancy. The article by researcher Sarah Tosato and colleagues suggests that **a mother's illness may be more harmful to a fetus than treatment for that illness is.**

The review analyzed 49 articles about illness-related and atypical antipsychotic–related risks in bipolar disorder and schizophrenia. Tosato and colleagues found that abrupt discontinuation of treatment led to a high risk of relapse in pregnant women with bipolar disorder or schizophrenia.

Schizophrenia was linked to a slight increase in obstetric complications for mothers, while both bipolar disorder and schizophrenia were linked to a slight increase in complications for newborns. Mothers ill with schizophrenia had the highest risk for serious complications, including stillbirth, neonatal or infant death, and intellectual disability in the child.

The researchers reported that **untreated bipolar disorder and schizophrenia are risk factors for birth defects, but use of atypical antipsychotics is not.** Children's neurodevelopment also does not seem to be affected by mothers' use of atypical antipsychotics during pregnancy.

The authors suggest that, given parents agree and understand any risks involved, the least harmful choice of action is to maintain treatment of women with bipolar disorder and schizophrenia during pregnancy at the safest minimum dosage to keep their illness at bay.

Use of Hormonal Contraceptives May Increase Depression Risk in Young Women

Women, particularly adolescent women, are at increased risk of developing depression if they use hormonal contraceptives, according to a 2016 study in the journal *JAMA Psychiatry*. The study by Charlotte Wessel Skovlund and colleagues used data from a Danish registry of more than one million women between the ages of 15 and 34 who had no history of depression or other psychiatric disorders. During follow-up (which lasted an average of 6.4 years), **55% of the women were using or had recently used hormonal contraceptives. These women were more likely to be prescribed an antidepressant for the first time, and more likely to be diagnosed with depression compared to women who did not use hormonal contraceptives.**

The increased risk of being prescribed an antidepressant varied by contraceptive type. The norgestrolmin patch increased risk by 2.0 times, and the etonogestrel vaginal ring did so by 1.6 times. The levonorgestrel intrauterine device (IUD) made an antidepressant prescription 1.4 times more likely. Progestin-only pills increased risk by 1.34 times and combined oral contraceptive pills increased it by 1.23 times compared to women who did not use oral contraceptives.

The relative risk peaked at around six months after starting hormonal contraceptives.

Patients aged 15–19 were particularly vulnerable to depression. The likelihood of receiving an antidepressant prescription was 1.8 times higher in teens taking combined pills, 2.2 times higher in those taking progestin-only pills, and 3 times higher in teens using hormonal methods of birth control that are not delivered orally compared to those who did not use hormonal contraceptives at all.

Women with History of Depression 20 Times More Likely To Have Postpartum Depression

A study of almost all women who gave birth in Sweden between 1997 and 2008 reports that **women with a history of depression are 21.03 times more likely to suffer from postpartum depression than those without such a history.** The 2017 article by Michael E. Silverman and colleagues in the journal *Depression and Anxiety* reports that advanced age and gestational diabetes also increased the likelihood of postpartum depression.

Whether a woman had gone through a depression in the past also affected her other risk factors for postpartum depression. Among women who had been depressed before, having diabetes before pregnancy and having a "mild" pre-term delivery were risk factors for postpartum depression. In contrast, among women with no history of depression, young age, having an instrument-assisted or caesarean delivery, and "moderate" pre-term delivery were risk factors for postpartum depression.

Rates of postpartum depression decreased one month after delivery.

Editor's Note: About one in five women in the general population experience postpartum depression. All new mothers should be screened for postpartum depression, but especially those with a history of depression. Instituting supportive measures may help prevent an episode.

Hormone Replacement With Estrogen/Progestogen Combo Increases Breast Cancer Risk More Than Once Thought

A 2016 article in the B*ritish Journal of Cancer* suggests that previous studies underestimated breast cancer risk in women who received hormone replacement therapy with the combination of estrogen and progestogen. The article by researcher Michael E. Jones and colleagues reported that **combined hormone replacement therapy could increase the risk of breast cancer by more than three times, depending on how long a woman is exposed to the therapy. The longer the duration of use, the greater the risk of breast cancer.** In the study, women who used other types of hormone replacement therapy, such as estrogen only or tibolone, did not have drastically higher rates of breast cancer than had been reported before.

Jones and colleagues suggest that previous studies did not use long enough follow-up periods to track whether women developed breast cancer while using hormone replacement. Their own study is based on a United Kingdom dataset known as the Breakthrough Generations Study. Study participants completed questionnaires at 2.5 years after recruitment, again at around 6 years, and again around 9.5 years. At the time of recruitment, women using combination hormone replacement therapy had been doing so for a median of 5.5 years.

Women who used combination hormone replacement therapy for 5.4 years were 2.74 times likelier to have breast cancer than those who didn't receive hormone replacement. Using the combined therapy for more than 15 years increased risk 3.27 times compared to non-users.

The study also reported that as body mass index increased, breast cancer risk increased, regardless of hormone use.

While the study by Jones and colleagues was large (39,183 participants), the number of women who took combined hormone replacement and developed breast cancer was still fairly small (52). Seven of the 52 had taken the combined pill for more than 15 years. One limitation of this study is that these seven women may have skewed the risk assessments somewhat.

Experts suggest that women balance the possible risks and benefits of hormone replacement therapy. The therapy can be helpful in reducing symptoms of menopause, particularly hot flashes.

Using the lowest effective dose for the shortest time possible may be the best option. The increased risk of breast cancer drops after a woman stops using hormone replacement.

Alterations in Amino Acids in Blood That Affect Metabolism May Help Explain Chronic Fatigue

Chronic fatigue syndrome, more recently known as myalgic encephalopathy, is a debilitating and somewhat mysterious illness. However, a 2016 article in the *Journal of Clinical Investigation Insight* suggests that low blood levels of amino acids related to oxidative metabolism, the process by which oxygen is used to make energy from sugars, may play a role in the illness. High levels of amino acids related to the breakdown of proteins were also seen.

The study by Øystein Fluge and colleagues compared blood concentrations of 20 amino acids in 200 patients with chronic fatigue and 102 healthy participants. **There were shortages in 6 amino acids that fuel oxidative metabolism in those with chronic fatigue, particularly women. Men with chronic fatigue had high levels of a different amino acid related to protein catabolism, the breaking down of complex molecules, a process that releases energy.**

The differences between men and women with the illness might be because men use muscle tissue as a source for amino acids, while women, who have less muscle mass, use amino acids from blood as fuel.=

The changes in both sexes suggest a functional impairment in pyruvate dehydrogenase (PDH), an enzyme that is important for the conversion of carbohydrates into energy. If PDH fails to work and cells turn elsewhere to create energy, muscles may suddenly weaken and lactate may build up, which patients experience as a burning in their muscles after the slightest exertion.

Fluge and colleagues are cancer researchers. They stumbled into chronic fatigue research when they noticed that people with chronic fatigue who were treated for cancer with the drug rituximab saw reductions in their fatigue. Rituximab, which is also used to treat some autoimmune diseases, is a monoclonal antibody directed at B cells. When it binds, it induces cell death. The researchers hope to clarify the link between the immune system and the problems with energy metabolism they have identified in people with chronic fatigue.

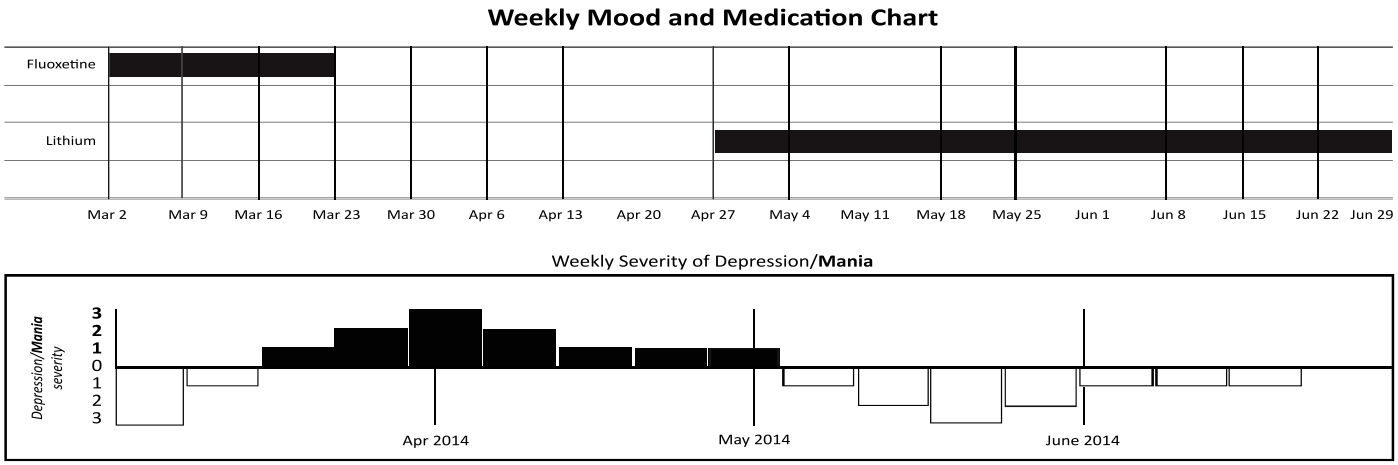
Is Your Child at Risk for a Mood Disorder? Join the Child Network

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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