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Intranasal Ketamine Has Long-Lasting Antidepressant Effects

It has been known for years that ketamine, an anesthetic at higher doses, can quickly produce antidepressant effects when delivered intravenously. However, these effects typically last only a few days. New research is exploring how to extend the antidepressant effects of ketamine.

Researcher Ella Daly and colleagues recently compared a form of ketamine called esketamine, this time delivered intranasally, to placebo in people with tough-to-treat depression that had resisted other treatments. Daly and colleagues randomized participants to receive one of three different doses of intranasal esketamine (28mg, 56mg, or 84mg) or placebo twice a week.

All of the doses improved participants' depression compared to placebo, with higher doses producing more sustained improvement. After the 2-week double-blind study, participants could choose to continue (or begin) taking esketamine for another nine weeks, tapering dosage slowly from twice a week to once every other week by the end. The participants were then monitored for another eight weeks. The intranasal esketamine doses they received led to sustained improvements in depression that lasted, in some cases, through the eight weeks following their final dose.

Side effects were not severe. Ketamine can produce dissociative sensations, but these tended to dissipate with two hours of administration.

Johnson and Johnson Pharmaceuticals funded this research, which was presented at a scientific meeting in 2015, and they plan to continue researching intranasal esketamine in the hopes of getting Food and Drug Administration approval for the drug.

Diabetes Drug Pioglitazone May Improve Depression

Researchers believe there is a link between diabetes and depression. Some drugs used to treat type II diabetes and its associated inflammatory symptoms have been found to improve depression as well. These include metformin, rosiglitazone, and pioglitazone. A recent study by Natalie Rasgon and colleagues explored the effects of pioglitazone treatment on people with insulin resistance, insulin sensitivity and/or pre-diabetes and ongoing depression. The researchers hoped to find that adding pioglitazone to the patients' regular antidepressant regimen might improve depression by reducing inflammation.

The study also touched on the role of telomere length in mental and metabolic disorders. Telomeres are repeated DNA sequences that sit at the end of chromosomes and protect them during cell replication. Telomeres get shorter with aging and with psychiatric illnesses. In the study, telomere length was used to predict whether patients' depression would improve.

Rasgon and colleagues found that **in those patients taking both pioglitazone and antidepressant treatments (compared to those who received a placebo in addition to their antidepressants), longer telomeres predicted better antidepressant response.** This suggests that telomere length could be used as a biomarker—that is, measuring a patient's telomere length could reveal whether that patient's depression is likely to respond to an anti-inflammatory treatment such as pioglitazone. The research was presented at a 2015 scientific meeting.

Also In This Issue:

In Mice, Ketamine Prevents Stress From Turning Into Depression

Stress increases the risk of psychiatric illnesses such as major depression and post-traumatic stress disorder. Not everyone who experiences stress goes on to develop these illnesses, though. Researchers are currently trying to find out why, exploring treatments that might increase resilience and prevent mental illnesses.

Animal research is often used to study depression. Mice exposed to certain stressors behave in ways that resemble human depression—like giving up faster when they're forced to tread water, or withdrawing from activities they once enjoyed, like eating sucrose. In a recent study by researcher Christine Denny and colleagues, mice were injected with either saline or ketamine, a rapid-acting antidepressant, and one week later they were exposed to triggers that typically produce a depressive response. Mice who received the saline injection still got depressed when, for example, they were repeatedly forced to confront a dominant mouse. But **mice who received ketamine injections did better, maintaining their motivation and not showing signs of depressive behavior following the stress. The researchers concluded that ketamine may have a protective effect against stress.**

Editor's Note: These results are remarkable because ketamine's effects are typically short-lived.

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Nutritional Supplement NAC Reduces Skin-Picking

The antioxidant N-acetylcysteine (NAC) has been found to be an effective treatment for a variety of habit-based behaviors—substance abuse, including cocaine, alcohol, marijuana, and nicotine; gambling; obsessive-compulsive behaviors; trichotillomania (compulsive hair-pulling), and repetitive behaviors among people with autism. Recent research by researcher Jon Grant and colleagues revealed that NAC can also treat skin-picking disorder.

At a 2015 scientific meeting, Grant reported that **1200–3000mg of NAC per day led to improvement in 47.1% of patients with a skin-picking disorder, compared to 19.2% improvement in patients who received placebo.**

In addition to its positive effects in people with addictions and habit-based behaviors, NAC has also improved mood and anxiety in bipolar disorder and treated negative symptoms of schizophrenia, such as withdrawal and lack of motivation.

Editor's Note: Given NAC's effectiveness in such a wide range of disorders and behaviors, it could be a particularly useful treatment for people with major psychiatric disorders, such as bipolar disorder or schizophrenia, with co-occurring substance abuse.

NAC Reduces Alcohol Cravings, If Not Use

The antioxidant N-acetylcysteine (NAC) has been found to reduce many types of habitual behavior, from gambling to drug use to compulsive hair-pulling. In a recent study, while NAC and placebo reduced days of heavy drinking by about the same rates, **NAC significantly reduced alcohol cravings and improved quality of life compared to placebo among participants with alcohol dependence.**

In the 8-week study presented by researcher Gihyun Yoon and colleagues at a 2015 scientific meeting, 44 participants aged 18–65 received either 3600mg/day of NAC or a placebo. This dose of NAC was higher than the 600mg–2400mg doses that have typically been used in research settings, and there were few side effects, confirming that NAC is a safe treatment.

The authors are not sure how NAC produces this effect, but it may be by regulating the neurotransmitter glutamate.

Modafinil May Help Cocaine Users Prevent Relapse

There is currently no Food and Drug Administration–approved treatment for cocaine addiction. One reason may be that in studies of treatments for cocaine use, participants may have a wide variety of exposure to cocaine. Some may be regularly using cocaine, while others may have gone some time without using the drug. A recent study by Margaret Haney and colleagues addressed some of these challenges by comparing the addiction treatment modafinil to placebo in different scenarios—such as when cocaine users have access to cheap cocaine versus expensive cocaine—and determining under which circumstances modafinil reduces the use of smoked cocaine.

In the study, presented at a scientific meeting in 2015, Haney and colleagues reported that among people who were not currently smoking cocaine, modafinil reduced cocaine use compared to placebo, but modafinil did not reduce cocaine use among people who had recently smoked cocaine. Modafinil also reduced cocaine use when the drug was expensive, but not when participants had access to cheap $5 cocaine. According to the researchers, these findings suggest that **modafinil may be more useful at preventing relapse than at helping current users of cocaine achieve abstinence.**

Editor's Note: While they are not FDA-approved, two other treatments can reduce cocaine use, according to placebo-controlled studies: the antioxidant N-acetylcysteine (NAC) and the anticonvulsant topiramate.

RTMS May Reduce Cocaine Craving

At a recent scientific meeting, researcher Antonello Bonci of the National Institute on Drug Abuse reported that treatment with repeated transcranial magnetic stimulation (rTMS) reduced cocaine craving among chronic users. RTMS is delivered via a magnetic coil placed near the scalp, which transmits electrical signals to the brain. In Bonci's study, rTMS targeted the left dorsolateral prefrontal cortex. The treatment can increase blood flow and brain activity in this area, in addition to increasing production of brain-derived neurotrophic factor (BDNF), which protects neurons. Frontal cortical brain activity and BDNF in the cortex and hippocampus are typically reduced among chronic cocaine users.

RTMS may have a double benefit for people who are addicted to cocaine, decreasing depression and reducing cocaine craving.

RTMS May Treat Cocaine Addictions

In a pilot study, repeated transcranial magnetic stimulation (rTMS) reduced cocaine cravings and usage among people with cocaine addiction.

RTMS is a non-invasive treatment in which a magnetic coil placed near the skull transmits electrical signals to the brain. It is an effective treatment for depression, and there is growing evidence that it may also be able to treat addictions.

Participants in the pilot study by researcher Antonello Bonci and colleagues received rTMS directed at their dorsolateral prefrontal cortex or pharmacological treatments (including medications to manage depression, anxiety, and sleep problems) over a 29-day study period. **Among the rTMS recipients, 69% remained cocaine-free during the study period, compared to only 19% of those treated with medications.** Those who received rTMS also reported fewer cravings.

There were few side effects among those who received rTMS, and there was a 100% compliance rate among the 32 participants, meaning they all showed up for each of their sessions.

Bonci and colleagues are working on a larger study that will compare rTMS treatment to a sham procedure rather than to a medication regime.

Medications that Regulate Glutamate Can Reduce Cocaine Craving

Glia are brain cells that surround neurons and synapses, protecting and insulating them. Chronic cocaine use and withdrawal changes the way certain glial cells, called astrocytes, interact with neurons. In particular, chronic cocaine use and withdrawal can shrink astrocytes and cause them to pull away from neurons. Cocaine use and withdrawal also interfere with the way the neurotransmitter glutamate is cleared from synapses and transported into astrocytes.

New research shows that certain medications that regulate and increase the movement of glutamate from the synapse into glial cells can reduce cravings for cocaine.

In studies of rats chronically exposed to cocaine and then denied access to it, treatment with these glutamate-targeting medications reduces the rats' cocaine-seeking behaviors. The medications include N-acetylcysteine (NAC), a nutritional supplement that can reduce habitual behaviors, including addictive behaviors; riluzole, a treatment for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease; the antibiotic ceftriaxone; and propentofylline, which has been explored as a possible treatment for dementia and stroke.

Antidepressant Effects of Sleep Deprivation are Associated with Increases in BDNF

Brain-derived neurotrophic factor (BDNF) is a protein that protects neurons and aids with learning and memory. BDNF levels are low in people with depression, and every type of antidepressant treatment increases BDNF, including different types of medications, electro-convulsive therapy, repeated transcranial magnetic stimulation (rTMS), exercise, atypical antipsychotic drugs used to treat bipolar depression, omega-3 fatty acids, and ketamine. New research shows that sleep deprivation, which is sometimes used to rapidly improve depression, also increases BDNF.

A study by researcher Anne Eckert and colleagues found that **partial sleep deprivation (preventing sleep only during the second half of one night) increased BDNF levels in the blood the following day.** Those participants who responded well to the sleep deprivation were found to have BDNF levels that fluctuated more throughout the day before the sleep deprivation compared to participants who did not respond well to the sleep deprivation, whose BDNF levels were relatively stable.

The research, which was presented at a scientific meeting in 2015, suggests that sleep deprivation in depressed patients increases BDNF, and that such increases are an important function of any antidepressant treatment.

Lurisadone is Effective in Mixed Depression

Lurasidone (Latuda) has been approved by the US Food and Drug Administration (FDA) for the treatment of bipolar depression. A new study indicates that it is also effective in those with unipolar depression complicated by a few manic features, i.e. mixed depression, which is often more severe and less responsive to traditional antidepressants than traditional unipolar depression.

At a 2015 scientific meeting, Andrew Nierenberg and colleagues presented the results of a six-week study comparing lurasidone to placebo. In about 200 depressed patients who had some manic symptoms, **20–60 mg of lurasidone significantly improved unipolar depressive symptoms in addition to the mixed manic symptoms.**

At baseline, the patients' manic symptoms included: flight of ideas/racing thoughts in 66.8% of the participants, pressured speech in 61.1%, decreased need for sleep in 40.8%, increased energy or activity in 28.0%, elevated or expansive mood in 18.0%, increased or excessive involvement in pleasurable activities in 15.6%, and inflated self-esteem or grandiosity in 6.6%.

Thiamine (Vitamin B1) May Increase Effectiveness of Antidepressants

A new study suggests that the nutritional supplement vitamin B1, also known as thiamine, can improve symptoms of depression when taken with an antidepressant. Edith Holsboer-Trachsler and colleagues presented the research from their randomized, double-blind, placebo-controlled study at a recent scientific meeting. In a 12-week study, about 50 adults (averaging 35 years of age) with major depression were prescribed a selective-serotonin reuptake inhibitor (SSRI) antidepressant. In addition, half received thiamine supplements while the other half were given placebos. Starting at six weeks, **those receiving thiamine with their antidepressant showed more improvement in their depressive symptoms than those receiving the antidepressant alone.**

Thiamine is an essential nutrient for humans. It is found in foods such as yeast, pork, cereal grains, and certain vegetables. Thiamine deficiency has been linked to irritability and symptoms of depression, while thiamine supplementation can improve mood and reduce feelings of stress. No side effects were reported in the study.

Holsboer-Trachsler and colleagues hope that thiamine supplementation may help patients adhere to their antidepressant regimens by decreasing the time it takes until their moods begin to lift.

Lithium Lessens Likelihood of Several Medical Conditions

Lithium is one of the most effective medications for bipolar disorder, but it has other benefits as well. At a 2015 scientific meeting, Ronald Fieve reported that among 1021 psychiatric outpatients, 570 who received long-term lithium treatment for their psychiatric illnesses had a significantly lower likelihood of certain medical conditions compared to the other outpatients who did not receive lithium therapy. **The medical conditions that lithium seemed to reduce were seizures, amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease, dementia, and heart attack.**

It is not yet know how lithium might reduce these medical conditions. It may be by increasing the length of telomeres. Telomeres are repeated DNA sequences that sit at the end of chromosomes and protect them during cell replication. Telomeres get shorter with aging and with stressors or psychiatric illnesses. Lithium directly increases the enzyme telomerase, which maintains telomere length. This may be one reason lithium use provides some protection from seizures, heart attacks, and other conditions.

Poverty Early in Life Decreases White Matter Integrity in the Brain

One-fifth of children in America grow up in poor families. Poverty can affect development, health, and achievement, and new evidence shows it even affects brain structure.

New unpublished research suggests that early poverty can affect the brain's structure into adulthood. At a 2015 scientific meeting, researcher James Swain reported that **socio-economic status at age 9 was associated with the integrity of white matter in several regions of the brain, including the hippocampus, parahippocampal gyrus, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, corpus collosum, and thalamus at age 23–25, regardless of income at that time.**

The brain regions affected by childhood poverty support executive function (planning and implementation skills), social cognition, memory, and language processing. White matter provides the physical connections between parts of the brain, so damage to white matter may lead to problems with functional connectivity of the brain.

Perinatal Choline Supplements May Reduce Risk of Schizophrenia

Many psychiatric illnesses, including bipolar disorder, schizophrenia, autism, attention deficit hyperactivity disorder (ADHD), and anxiety disorders may stem from abnormalities in brain development that begin before birth. Researchers are trying to determine whether dietary supplements taken by pregnant mothers or infants can reduce the risk of such illnesses. At a recent scientific meeting, researcher Randal Ross and colleagues reported that **compared to placebo, choline supplements reduced problems with a brain process called sensory gating in one-month-old infants and also improved the children's attention span and social skills at age 3.**

Sensory gating is the process by which the brain filters out unimportant information, to avoid flooding higher cortical centers with irrelevant stimuli. Deficits in the way the brain inhibits response to this type of irrelevant information are associated with mental illnesses such as schizophrenia.

In Ross's study, healthy pregnant mothers received either a placebo or 6300 mg of choline, a nutrient found in liver, egg yolks, and meat. After delivery, the infants also received 700 mg of supplemental choline per day. In children who carried CHRNA7, a risk gene for schizophrenia discovered by Ross's colleague Robert Freedman, choline reversed the associated risk of sensory gating problems and normalized their behavior at age 3.

Crack Cocaine Use and Early Life Stressors Shorten Telomeres

Telomeres are repeated DNA sequences that sit at the end of chromosomes and protect them during cell replication. Shorter telomeres are associated with aging and an increase in multiple medical and psychiatric disorders, while some healthy behaviors including exercising, eating healthy, meditating, and avoiding smoking can help maintain telomere length. Lithium treatment also increases telomere length.

Recent research by Mateus Levandowski and colleagues found that **people who were dependent on crack cocaine had shorter telomeres than elderly women without psychiatric illnesses, particularly if the crack cocaine users had also experienced stress early in life, such as maltreatment or neglect.**

Since short telomeres are associated with a variety of medical and psychiatric problems and premature aging, the combined effects of drug use and early life stressors are likely to have an adverse impact on people who have experienced both.

Low Vitamin D Linked to Small Hippocampus & Schizophrenia

Low levels of vitamin D have been linked to schizophrenia in several studies. In one, infants with low vitamin D were more likely to develop schizophrenia in adulthood, but supplementation reduced this risk. A 2015 article by Venkataram Shivakumar and colleagues in the journal *Psychiatry Research: Neuroimaging* found that among patients with schizophrenia who were not currently taking (or in some cases, had never taken) antipsychotic medication, **low levels of vitamin D were linked to smaller gray matter volume in the right hippocampus, an area involved in schizophrenia.**

Vitamin D has neuroprotective effects and is important to normal brain development and function. Vitamin D is essential to the production of brain-derived neurotrophic factor (BDNF), a protein that is important for learning and memory, and vitamin D also reduces oxidative stress. BDNF deficiency and oxidative stress have both been linked to schizophrenia, and they both can cause abnormalities in the hippocampus.

Learn about the Child Network study: See page 11

Therapies Improve Symptoms and Brain Connectivity and Function

Mindfulness Therapy Improves Anxiety in Children with a Bipolar Parent

Children of parents with bipolar disorder are prone to anxiety and emotional dysregulation, but treating these symptoms with antidepressants can provoke symptoms of mania. Thus, non-pharmacological treatements for anxiety and depression are needed. A recent study by Melissa DelBello found that **12 weeks of mindfulness-based cognitive therapy improved symptoms of anxiety and mood dysregulation in 20 youth with a bipolar parent.** DelBello used functional magnetic resonance imaging (fMRI) to observe that the therapy increased activation of brain structures related to emotion and sensing. Amygdala activation differed between those with anxiety and those with mood dysregulation, suggesting that the therapy's effect was on regions that modulate the amygdala, including prefrontal and insular regions, rather than on the amygdala itself.

Cognitive Behavioral Therapy Improves Depression, PTSD by Improving Brain Connectivity

A recent study clarified how cognitive behavioral therapy improves symptoms of depression and post-traumatic stress disorder. The participants were 62 adult women. One group had depression, one had PTSD, and the third was made up of healthy volunteers. None were taking medication at the time of the study. The researchers, led by Yvette Shelive, used functional magnetic resonance imaging (fMRI) to analyze participants' amygdala connectivity.

At the start of the study, participants with depression or PTSD showed diminished connectivity between the amygdala and brain areas related to cognitive control, the process by which the brain can vary behavior and how it processes information in the moment based on current goals. The lack of connectivity reflected the severity of the participants' depression. Twelve weeks of cognitive behavioral therapy improved mood and connectivity between the amygdala and these control regions, including the dorsolateral prefrontal cortex and the inferior frontal cortex. These regions also allow for executive functioning, which includes planning, implementation, and focus.

Yoga Therapy Improves Depression and Inflammation

Drug treatment for major depression can produce remission in 35–50% or patients. The others may need additional interventions, and some mind-body techniques have been successful. A recent randomized study by Anup Sharma and colleagues found that **Sudarshan Kriya Yoga (SKY) decreased depression at one and two months when added to participants' regular treatments.** Participants who received the yoga treatment also showed reductions in inflammation in the blood, including lower levels of the inflammatory proteins TNF-alpha, IL-10, and CRP.

Lithium Treatment Reduces Inflammation, Mania-Like Behavior in Rats

Patients with bipolar disorder often show increases in signs of inflammation, including levels of the proteins IL-2, IL-4, Il-6, IL-10 and tumor necrosis factor in their blood. Lithium is the most effective treatment for bipolar disorder, but it is not yet clear how it works. A recent study by researcher Joao de Quevado and colleagues determined that lithium can reduce the same inflammatory markers in rats.

Rats were treated with amphetamine to induce mania-like behavior, which was accompanied by increases in some of the same inflammatory markers in the blood and brain that are increased in people with bipolar disorder. **Lithium treatment reduced both the manic behavior and levels of these inflammatory proteins in the rats.**

The researchers concluded that lithium may treat mania by reducing inflammation.

Easier Vagal Nerve Stimulation Via the Ear

Vagal nerve stimulation (VNS) is an FDA-approved treatment for seizures and treatment-resistant depression. It typically requires an operation to insert a stimulator in a patient's chest wall that delivers electrical impulses to their left vagus nerve via electrodes placed on the patient's neck. New research by Bashar W. Badran and colleagues may have identified **a less invasive and less expensive way to stimulate the vagal nerve—via electrodes placed on the ear.**

The researchers tested different parameters for vagal nerve stimulation via the ear on 15 healthy volunteers and found that this type of VNS was feasible, tolerable, and reasonably safe. Among the different parameters tested, a stimulation pulse width of 500 microseconds at 25Hz had the greatest effect on heart rate, slowing it by about 4.25 beats per minute compared to a sham treatment.

Next Badran and colleagues plan to study the effects of this type of VNS on brain activity using functional magnetic resonance imaging (fMRI).

In Small Open Study, Dietary Supplement Improves Post-Partum Blues

Post-partum depression affects 13% of new mothers, but little is known about how to prevent it. Doctors are researching ways of reducing post-partum blues, which can occur 4–6 days after delivery, when levels of the enzyme monoamine oxidase-A are high. At a 2015 scientific meeting, researchers led by Yekta Dowlati of the Centre for Addiction and Mental Health at the University of Toronto reported that a nutritional supplement designed to counteract the high levels of monoamine oxidase-A improved depression among 17 healthy women who had recently given birth, compared to 16 new mothers who did not receive the supplement. **The supplement contained 2g of tryptophan and 10g of tyrosine, both amino acids found in protein-rich foods, plus blueberry juice and a blueberry extract.**

In Rats, Dad's Cocaine Use Affects Son's Spatial Memory

Evidence is mounting that certain behaviors by parents can leave marks on their sperm or eggs that are passed on to their offspring in a process called epigenetics. In a recent study by researcher Mathieu Wimmer and colleagues, **male rats that were exposed to cocaine for 60 days (the time it takes for sperm to develop fully) had male offspring who showed diminished short- and long-term spatial memory compared to the offspring of male rats that were not exposed to cocaine.** Female offspring were not affected in this way.

The spatial tasks the offspring rats completed depended heavily on the hippocampus. Wimmer and colleagues believe that cocaine use in the fathers decreased the amount of a brain chemical called d-serine in the offspring. D-serine plays a role in memory formation and the brain's ability to form synaptic connections. Injecting the offspring of rats who were exposed to cocaine with d-serine before the spatial memory tasks normalized the rats' performance.

Multiple Risks of Benzodiazepine Use

Benzodiazepines are a class of drugs that became widely used in the 1970s for their ability to reduce panic, anxiety, and insomnia. Some also functioned as anticonvulsants, reducing seizures. They are considered "downers," with sedating qualities.

New research shows that benzodiazepine use, particularly long-term use, comes with risks such as increased mortality and mood instability.

At a 2015 scientific meeting, researcher Jari Tiihonen reported that among 21,492 patients with schizophrenia in Sweden, benzodiazepine use was associated with increased mortality, while antidepressant and antipsychotic use decreased mortality.

At the same meeting, researcher Cristina Albott reported that benzodiazepines may interfere with the rapid onset of antidepressant effects usually brought about by intravenous treatment with the drug ketamine.

In 2010, researcher Roy Perlis reported in the *Journal of Clinical Psychiatry* that in STEP-BD, a large study of people with bipolar disorder, benzodiazepine use was associated with an increased risk of recurrence of mood episodes.

Editor's Note: Benzodiazepines can also exacerbate symptoms of post-traumatic stress disorder (PTSD) and regular use can lead to a decrease in lifespan. It now seems as though there are many reasons to exercise caution in the use of these drugs.

Anti-Inflammatory Treatments May Improve Depressive Symptoms

Studies have found that inflammatory molecules play a role in depression. A recent study by researcher Yu Sun and colleagues used data from clinical trials of anti-inflammatory drugs to show that these drugs also reduced depressive symptoms. The two drugs, which are administered either by a shot or injection into the skin, each consist of antibodies that target the inflammatory molecule IL-6. Sirukumab is being looked at as a possible treatment for rheumatoid arthritis, while siltuximab is a potential treatment for Castleman's disease, an illness characterized by enlarged lymph nodes. As part of the clinical trials for these drugs, patients with these illnesses responded to survey questions that assessed symptoms of depression and fatigue.

Among patients who reported that they have at least one depressive symptom most of the time and another symptom at least part of the time, the anti-inflammatory drugs significantly improved depressive symptoms compared to placebo. Even when the patients' inflammatory illnesses did not respond to the anti-inflammatory treatments, their depressive symptoms did improve (symptoms of fatigue did not). **An improvement in depressive symptoms was observed after 6 weeks in patients with Castleman's disease taking siltuximab, and after 12 weeks in patients with rheumatoid arthritis taking sirukumab.**

In the sirukumab study, the level of the inflammatory molecule IL-6 in participants' blood before the study was linked to the magnitude of improvement in their depressive symptoms during the study. IL-6 is elevated in many patients with unipolar and bipolar depression. It is possible that antibodies that target IL-6 could be used to treat primary depression (in the absence of other inflammatory disorders).

Brain Inflammation in Depression

Many studies have found links between levels of inflammatory molecules in the blood and depression or depressive symptoms. There has been less research about inflammation in the brain and its possible role in depressive illness. Improvements in positron emission topography (PET) scan technology now allow for better brain imaging that can reveal when microglia are activated. (Microglia serve as the main immune responders in the central nervous system.)

A study by researcher Jeffrey Meyer found **evidence of microglial activation in several brain regions (including the prefrontal cortex, the anterior cingulate cortex, and the insula) in people in an episode of depression who were not receiving any treatments.** Participants with more microglial activation in the anterior cingulate cortex and insula had more severe depression and lower body mass indexes.

Meyer, who presented this research at a scientific meeting in December, called it strong evidence for brain inflammation in depressive episodes, and suggested that treatments that target microglial activation would be promising for depression.

However, at the same meeting, researcher Erica Richards reported that she had not been able to replicate Meyer's results. Her research, which included depressed participants both on and off medication and non-depressed participants, found that depressed participants did show more inflammation in the two brain regions she targeted, the anterior cingulate and the subgenual cortices, but this difference did not reach statistical significance, particularly when patients taking antidepressants were included in the calculations. Richards hopes that with a greater sample size, the data may show a significant difference in brain inflammation between depressed and non-depressed participants.

Inflammation Plays a Role in Fear

People with post-traumatic stress disorder (PTSD) often experience fearful memories of the trauma they witnessed. Researchers are working to determine the neurobiological basis for these persistent fear memories in order to better treat PTSD. Current treatments mainly target the central nervous system. Because many people with PTSD have elevated levels of pro-inflammatory immune molecules in their blood, there has been a recent push to determine whether targeting that inflammation may be another way of treating PTSD.

A recent study by researchers Matthew Young and Leonard Howell used an animal model to learn more about the link between trauma, inflammation, and fear memories. **The researchers exposed mice to a trauma that produced both a persistent fear response and an increase in inflammatory molecules in the blood. Some of the mice were also given antibodies to neutralize the inflammatory immune response.** When the mice were exposed to a cue meant to remind them of the trauma, levels of the inflammatory molecule IL-6 spiked again. When the mice were given antibodies to neutralize IL-6 just before being exposed to the cue, they produced less of a fear reaction.

The researchers, who presented their work at a scientific meeting in December, concluded that traumatic experiences produce not only persistent fearful memories, but also an immune reaction. They believe that the spike in IL-6 following trauma plays a role in the persistence of those memories, and that elevated IL-6 in the blood may explain symptoms of PTSD and other disorders that involve fear learning (such as phobias).

DNA Repair Plays Role in Brain Development, Cancer, and Aging

DNA has several ways of repairing itself. Serious damage, including breaks to both strands of the double helix and problems with replication, prompt a process known as DNA damage repair, or DDR. Researcher Stephen J. Elledge of Harvard Medical School won the 2015 Albert Lasker Basic Medical Research Award for his findings about DDR. He summarized these findings in a September article in the journal JAMA.

DDR occurs because of DNA's remarkable self-awareness. **Through the DDR process, DNA can detect when it has been damaged and prompt the right kind of repair.** When damage occurs, DDR allows for the activation of enzymes that can remodel DNA to maintain the integrity of the genome.

When DDR pathways are activated, they can alter more than 1000 different proteins. DDR can affect immune function, blood and bone marrow, viral response, cancer, aging, and brain development.

Mutations in components of the DDR pathway can lead to problems with brain development, including Seckel syndrome (characterized by dwarfism, brain and facial abnormalities, and mental retardation) and ataxia telangiectasia (loss of control of bodily movements along with weakened immune system).

DDR is particularly relevant to cancer, since properly functioning DDR promotes a stable genome. Classic cancer treatments such as radiation and chemotherapy also rely on DDR to prompt cell death.

DDR also plays a role in aging. When we get older or have certain illnesses, telomeres, bits of material at the end of DNA strands that protect the DNA during replication, get shorter. This prompts DDR to engage in tumor prevention measures, either killing off the cells or changing them into what's called senescent cells. Senescent cells prevent tumors, but their accumulation is associated with chronic inflammation, aging, and age-related diseases.

Editor's Note: You can protect your telomeres and possibly hold off the age-related effects of DDR. Healthy diet, exercise, meditation, goal setting, and making positive contributions to society all help maintain telomere length. Lithium treatment also directly increases telomere length.

Liraglutide FDA-Approved for Obesity

The drug liraglutide (trade name Saxenda) has been approved by the Food and Drug Administration (FDA) as a treatment for obesity. It had previously been approved for the treatment of type 2 diabetes.

Liraglutide is taken as a daily injection and is meant to be used alongside a calorie-reduced diet and increased physical activity. Liraglutide works by mimicking a peptide (GLP-1) that regulates appetite and calorie intake.

Recommended dosage is 3 mg/day, but should begin at 0.6 mg/day for the first week and gradually increase by 0.6mg each week to reduce the likelihood of gastrointestinal side effects.

In three clinical trials, participants who were overweight or obese, some of whom had weight-related conditions such as high blood pressure, type 2 diabetes, or high cholesterol, either received training about following a reduced-calorie diet and increasing physical activity or had already lost up to 5% of their body weight by engaging in these practices.

Among those participants who did not have diabetes or a weight-related condition, 62% lost up to 5% of their body weight after a year of taking liraglutide, compared to 34% of those who were given a placebo injection.

Of the participants who had type 2 diabetes, 49% lost up to 5% of their body weight after a year of liraglutide, compared to 16% of those who received placebo.

Of those who had a weight-related condition other than diabetes, 42% lost up to 5% of their body weight compared to 21.7% who took placebo.

Repeated Sports Injuries Linked to Brain Inflammation

Professional football players face repeated mild traumatic brain injuries throughout their careers, and may face a variety of brain impairments, from depression to dementia, as a result.

A recent study by researcher Jennifer Coughlin and colleagues clarified how these impairments may be caused by repeated brain impacts. The researchers used positron emission tomography (PET) scans to observe the volume of translocator protein, a marker of brain injury and repair, in the brains of seven active or recently retired National Football League (NFL) players. Compared to healthy, athletic volunteers who were age-matched to the NFL players, **the NFL players showed greater volume of translocator protein in several brain regions, including the left and right thalamus, the left and right temporal poles, and the brainstem.**

It is not yet clear whether the increased volume of translocator protein is a sign of the brain's attempts to repair itself, or whether it shows deterioration toward chronic traumatic encephalopathy. Translocator protein is also considered a marker of microglial activation, which occurs with inflammation.

High levels of translocator protein have also been seen in patients with depression and schizophrenia.

Depression and Bipolar Disorder in Adolescence Linked to Early-Onset Cardiovascular Disease and Hardening of the Arteries

The link between mood disorders and cardiovascular illnesses has been clear for some time. Now there is evidence that this link begins early in life. In 2015, the American Heart Association issued a statement that adolescents with major depressive disorder and bipolar disorder are at increased risk for both accelerated atherosclerosis (narrowing and hardening of the arteries) and early-onset cardiovascular disease.

In the statement, the American Heart Association recommended that major depressive disorder and bipolar disorder be classified as "tier II" conditions (which also include HIV and chronic inflammatory disease) that confer a moderate risk of disease.

Until recently, it had been assumed that the increased risk of cardiovascular disease among people with depression or bipolar disorder was a result of behaviors linked to these illnesses, such as higher rates of smoking, obesity, or diabetes, which increases heart disease. Some psychiatric medication can also bring about risk factors for cardiovascular problems. It turns out that these types of factors could not fully explain the increased risk of atherosclerosis and cardiovascular disease among people who had depression or bipolar disorder in their teens.

It is not clear why depression and bipolar disorder make cardiovascular illness more likely, though it may be due to blood vessel damage resulting from inflammation or oxidative stress.

The American Heart Association recommends that pediatricians and cardiologists pay particular attention to this link by identifying and treating mental illness as early as possible and by making sure that their colleagues understand the role of mental illnesses in cardiovascular risk.

Inactivity in Young Adulthood May Worsen Cognition Later in Life

The couch potato lifestyle common in the US may have consequences later, in the form of deficits in memory, executive functioning (including planning and execution) and processing speed.

At the 2015 Alzheimer's Association International Conference, researcher Kristine Yaffe and colleagues reported that **low levels of physical activity and high rates of television viewing in young adulthood may reduce cognitive capabilities in midlife.**

The Centers for Disease Control report that less than 50% of adults aged 18–64 get the recommended minimum of physical activity each week. The guidelines recommend at least 150 minutes of moderate intensity aerobic activity (such as walking briskly) and two or more days of muscle-strengthening activities that work all major muscle groups.

Yaffe says that physical activity can protect against cognitive decline or dementia later on.

Participants in the long-term study who reported burning fewer than 300 calories per 50-minute session three times per week during two-thirds of their followup visits had worse cognition at year 25 than those participants who were more active. Those who watched more than four hours of television per day also had reduced cognition in midlife.

Yaffe stresses that exercising regularly is not just important in keeping weight down and protecting the heart, but also in protecting the brain. Regular physical activity may even prevent illnesses such as Alzheimer's disease.

Bad Habits May Reduce Brain Volumes, May Cause Dementia

Smoking, alcohol use, obesity, and diabetes aren't just harmful to the body. They may actually lead to dementia.

Behavioral risk factors for cardiovascular disease like those listed above have been linked to reduced volume in the brain as a whole and several brain regions, including the hippocampus, precuneous, and posterior cingulate cortex. A 2015 study by researcher Kevin King and colleagues found that these reduced brain volumes are early indicators of cognitive decline.

King and colleagues analyzed data on 1,629 participants in the long-term Dallas Heart Study. Their cardiovascular risk factors were assessed when they began the study, and their brain volume and cognitive function were measured seven years later.

Alcohol use and diabetes were associated with lower total brain volumes, while smoking and obesity were linked to low volumes in the posterior cingulate cortex.

Low hippocampal volume was linked to past alcohol use and smoking, while lower precuneous volume was linked to alcohol use, obesity, and blood glucose levels. King and colleagues suggested that subtle differences in brain volumes in midlife are the first sign of developing dementia in participants who were still younger than 50 years of age.

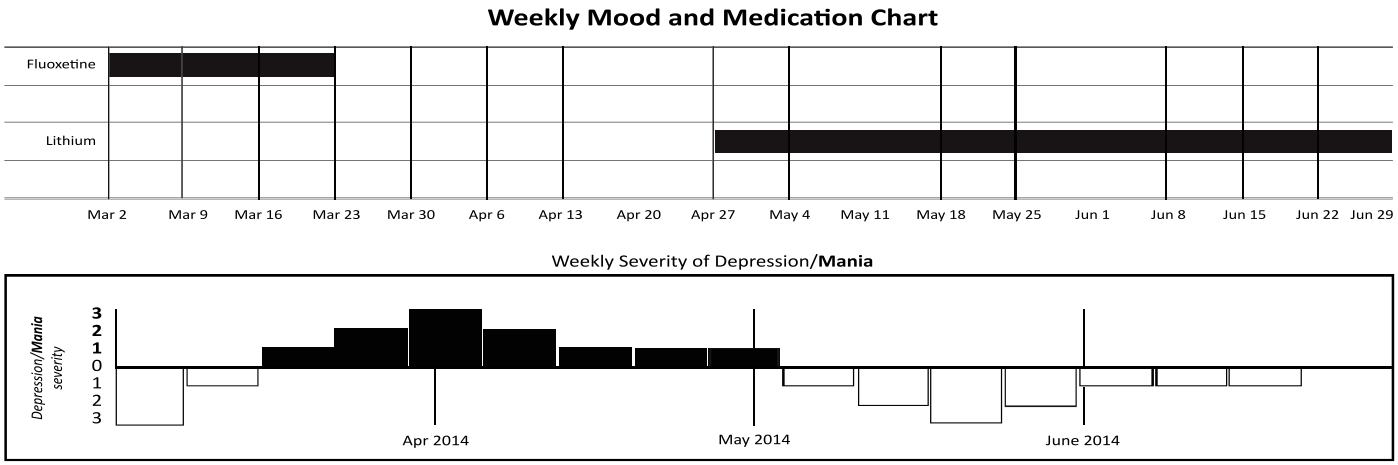
Is Your Child at Risk for a Mood Disorder? Join the Child Network

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

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

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

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



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

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

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

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