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Bipolar Network News

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Vol. 17, Issue 3, 2013

Psychiatric Revolution: Changes in Behavior Associated with Dendritic Spine Shape, Number

New research shows that **cocaine, defeat stress, the rapid-acting antidepressant ketamine, and learning and memory can change the size, shape, or number of spines on the dendrites of neurons**. Dendrites conduct electrical impulses into the cell body from neighboring neurons.

Cocaine

Several researchers, including Peter Kalivas at the Medical University of South Carolina, have reported that cocaine increases the size of the spines on the dendrites of a certain kind of neurons (GABAergic medium spiny neurons) in the nucleus accumbens (the reward center in the brain). This occurs through a dopamine D1 selective mechanism. N-acetylcysteine, a drug that can be found in health food stores, decreases cocaine intake in animals and humans, and also normalizes the size of dendritic spines.

Depression

Depression in animals and humans is associated with decreases in Rac1, a protein in the dendritic spines of GABA neurons in the nucleus accumbens. Rac1 regulates actin and other molecules that alter the shape of the spines.

In an animal model of depression called defeat stress, rodents are stressed by repeatedly being placed in a larger animal's territory. Their subsequent behavior mimics clinical depression. This kind of social defeat stress decreases Rac1 and causes spines to become thin and lose some function. Replacing Rac1 returns the spines to a more mature mushroom shape and reverses the depressive behavior of these socially defeated animals. Researcher Scott Russo has also found Rac1 deficits in the nucleus accumbens of depressed patients who committed suicide. Russo suggests that decreases in Rac1 are responsible for the manifestation of social avoidance and other depressive behaviors in the defeat stress animal model, and that finding ways to increase Rac1 in humans would be an important new target for antidepressant drug development.

Another animal model of depression called chronic intermittent stress (in which the animals are exposed to a series of unexpected stressors like sounds or mild shocks) also induces depression-like behavior and makes the dendritic spines thin and stubby. The drug ketamine, which can bring about antidepressant effects in humans in as short a time as 2 hours, rapidly reverses the depressive behavior in animals and converts the spines back to the larger, more mature mushroom-shape they typically have.

Learning and Extinction of Fear

Researcher Wenbiao Gan has reported that fear conditioning can change the number of dendritic spines. When animals hear a tone paired with an electrical shock, they begin to exhibit a fear response to the tone. In layer 5 of the prefrontal cortex, spines are eliminated when conditioned fear develops, and are reformed (near where the eliminated spines were) during extinction training, when animals hear the tones without receiving the shock and learn not to fear the tone. However, in the primary auditory cortex the changes are opposite: new spines are formed with learning, and spines are eliminated with extinction.

Editor's Note: It appears that we have arrived at a new milestone in psychiatry. In the field of neurology, changes seen in the brains of patients with strokes or Alzheimer's dementia have been considered "real" because cells were obviously lost or dead. Psychiatry, in comparison, has been considered a soft science because neuronal changes have been more difficult to see and illnesses were and still are called "mental." Now that new technologies have made a deeper level of precision, observation, and analysis possible, we know that the brain's 12 billion neurons and 4 times as many glial cells are exquisitely plastic--capable of biochemical and structural changes that can be reversed using appropriate therapeutic maneuvers.

The changes associated with abnormal behaviors, addictions, and even normal processes of learning and memory now have clearly been shown to correspond with the size, shape, and biochemistry of dendritic spines. These subtle, reproducible changes in the brain and body are amenable to therapeutic intervention, and are now even more demanding of sophisticated medical attention.◊

Also in this issue:

New Findings On IV Ketamine For Treatment-Resistant Depression

We've written before about the rapid-onset antidepressant effects of ketamine, an anesthetic that is used in human and veterinary medicine. At lower doses, **intravenous (IV) ketamine can induce antidepressant effects in both unipolar and bipolar depressed patients**.

When doses of 0.5mg/kg are infused over a period of 40 minutes, antidepressant effects appear within two hours but are short-lived, typically lasting only three to five days. Results have been consistent across studies at Yale University, the Icahn School of Medicine at Mount Sinai, and the National Institute of Mental Health. So far, clinical use has been limited by the short duration of the effects and the required presence of an anesthesiologist, which can be prohibitively expensive for many patients.

In a cover story in the January 2013 issue of *Psychiatric Times*, Arline Kaplan reviewed new findings about ketamine. The drug is a high-affinity, noncompetitive NMDA-glutamate receptor antagonist. It is not yet FDA-approved for use in depression.

According to a recent article by Murrough and Charney, response rates to ketamine are around 54% and the drug "appears to be effective at reducing the range of depressive symptoms, including sadness, anhedonia [the loss of ability to experience pleasure], low energy, impaired concentration, negative cognitions, and suicidal ideation."

David Feifel, Director of the Neuropsychiatry and Behavioral Medicine Program at the University of California at San Diego (UCSD), instituted a program there in which patients can receive treatment with ketamine for clinical purposes (rather than for research) after signing detailed informed consent forms and being warned that the treatment is not yet approved for depression and that its effects may be temporary. **The UCSD Medical Center's Pharmacy and Therapeutics Committee, with the support of the anesthesiology department, agreed that nurses may administer the ketamine in an outpatient setting, making the procedure more affordable.**

There is still the question of how to make ketamine's effects last. In a study of 24 patients with treatment-resistant depression by Murrough et al., six IV infusions of ketamine administered over 12 days led to relapses of depression after an average of 18 days following the last infusion among the 70% of patients who responded.

Feifel decided to try a different approach, giving maintenance infusions every two weeks to patients whose response to a first IV ketamine infusion lasted a week or more, and is apparently having some success.

There are other ways of administering ketamine, including oral, nasal, and intramuscular methods, and Feifel thinks that among these, only the intramuscular method shows promise. He has shifted some IV ketamine patients to intramuscular administration, which is even more practical and cost-effective.

Another UCSD clinician, Scott Irwin, is evaluating ketamine's effectiveness when taken orally by clinically depressed patients at San Diego Hospice and the Institute for Palliative Medicine. Irwin says that psychomotor stimulants are the first-line treatment for the approximately 15% of patients in hospice care who are depressed. However, for those patients with significant anxiety, oral ketamine is prescribed instead.

Irwin has seen about a 70% response rate to oral ketamine in depression and a 100% response rate in anxiety. The ketamine is administered once per day, usually at night, with the primary side effect being sleepiness. About 50 patients have received ketamine so far, and Irwin expects to publish an open-label trial in the first 14 patients soon.

Editor's Note: It is not clear why oral ketamine appears to be effective in Irwin's hospice setting but not in Feifel's treatment-resistant depressed patients, but the discrepancy could relate to depression severity or the patients' degree of prior treatment resistance.

In an accompanying editorial, *Psychiatric Times* editor Ronald Pies urges caution in the use of ketamine. He suggests waiting for the results of a controlled trial wherein ketamine is compared to another IV drug that, like ketamine, causes an alteration in consciousness (he suggests midazolam, a benzodiazepine that causes some

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Bipolar Network News

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

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New Drug GLYX-13 Produces Rapid-Onset Antidepressant Effects

We have previously summarized studies on ketamine, which when given intravenously can bring about rapid-onset antidepressant effects that last for days at a time. Ketamine is a full antagonist (or a blocker) of the glutamate NMDA receptors. Another drug currently in development may work in a related way.

At a recent scientific meeting, researcher Sheldon Preskorn showed that the compound **GLYX-13, a partial agonist at the glycine binding site of the NMDA receptor (meaning it allows partial function of the glycine receptors that aid NMDA receptor function), exerts rapid antidepressant effects like the full antagonist ketamine** when administered intravenously compared to placebo. GLYX-13 allows about 25% of the receptor activity of the full agonists glycine or D-serine, and thus might result in a 75% inhibition of NMDA receptor function.

GLYX-13 did not induce any psychotomimetic effects (like delusion or delirium), which are possible with the full NMDA antagonist ketamine. The effects of GLYX-13 appeared within 24 hours, lasted at least 6 days, but were gone by day 14.

Editor's Note: In addition to ketamine's short duration of effects and potential psychotomimetic effects, it can also be abused. Whether GLYX-13 may be easier to use, longer-lasting, or safer for longer-term clinical effectiveness remains a key question.

IV Ketamine For Treatment-Resistant Depression

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sedation and amnesia) rather than just IV saline. (Apparently, in a recent study like this, ketamine was successful.) Pies also encourages psychotherapy for patients with treatment-resistant depression and suggests that these patients should be informed about other specific treatments that have demonstrated efficacy, such as T3 (a thyroid hormone), lithium, and electro-convulsive therapy (ECT).

Editor's Note: Pies' cautions are appropriate, but Sackeim and colleagues at Columbia University found that 40% of ECT responders relapsed within the first month after their last ECT treatment, so it appears that the effects of ECT may also be short-term. Moreover, ECT carries other risks including memory loss.

What is new with the ketamine story:

1. IV Ketamine is being given without an anesthesiologist present, at least at UCSD.
2. Orally administered ketamine is being used in hospice settings for rapid onset of antidepressant and anti-anxiety effects.
3. Intranasal ketamine is being explored in children with bipolar disorder.

Intranasal Ketamine Helps Some Youth with Bipolar Disorder

The anesthetic ketamine given intranasally may help children with a certain type of bipolar disorder. In an article published in the *Journal of Affective Disorders* in 2013, Demetri Papolos et al. reported seeing marked improvement in a subgroup of 12 children aged 6 to 19 years of age who were nonresponsive to the usual treatment regimens of lithium, mood stabilizers, and antipsychotics. **In addition to having typical mood swings, these children also have a fear of aggression, separation anxiety, sleep and circadian rhythm disorders, nightmares, thermoregulatory problems, and carbohydrate craving.** Papolos has described these children as having the "fear of harm (FOH) subtype."

Ketamine was given as an intranasal spray using an inhaler in 10mg doses. Doses were increased until the targeted symptoms remitted. **Average doses ranged from 30mg to 120mg, given every 3 to 7 days.** All symptom areas including depression and mania improved markedly, usually within a few hours, and this improvement lasted 3 to 4 days. Four types of aggression (measured on the Overt Aggression Scale) decreased significantly.

There were some dissociative side effects that were usually mild to moderate, but occasionally severe. They resolved spontaneously, usually within the first hour after treatment, and there appeared to be tolerance to them following repeated administration.

The authors urged caution until findings from these cases are confirmed by more controlled studies, but they concluded that the magnitude and rapidity of effects in these children with treatment resistant bipolar disorder suggested effectiveness and safety.

Blockade of NMDA Receptors Helps in Obsessive-Compulsive Disorder

At a recent scientific meeting, researcher Carolyn Rodriguez presented a randomized controlled crossover trial of ketamine in obsessive-compulsive disorder (OCD). In contrast to a previous negative study by Block and associates at the National Institute of Mental Health (NIMH), these investigators found that **intravenous (IV) infusion of ketamine (0.5 mg/kg over 40 minutes) was associated with a larger reduction in obsessive-compulsive symptoms when compared with saline infusion**. These effects were rapid in onset and persisted for approximately one week in 50% of the patients with OCD who had constant intrusive thoughts.

This dose of ketamine had previously been shown to induce rapid-onset improvement in depression and suicidal ideation in those with unipolar and bipolar depression. However, the improvement in obsessive-compulsive disorder symptoms appeared unrelated to any antidepressant effect because the individuals with OCD had minimal depressive symptoms at baseline.

The traditional pharmacological treatments for OCD are selective serotonin reuptake inhibitor (SSRI) antidepressants, which require high doses and weeks to months before the onset of full effect. In contrast, Rodriguez et al. found a 90% response rate to IV ketamine within 3 hours.

Ketamine is a blocker of the glutamate NMDA receptors, and these data suggest that targeting these receptors can induce rapid onset of positive effects in OCD. However, as is the case with the acute antidepressant response to ketamine in those with depression, the best ways to extend this therapeutic effect long-term remain to be determined.

Another blocker of NMDA receptors, the anti-Alzheimer's drug memantine (Namenda), has been reported in open studies to show improvement in those with OCD as well. N-acetylcysteine, a substance found in health-food stores, likewise appears to re-regulate a hyper-responsive glutamatergic system in the nucleus accumbens by other mechanisms, and was also shown to have efficacy as an augmenting treatment in OCD in those who are inadequately responsive to SSRIs in a 2012 article by Afshaw et al.

Editor's Note: Taken together, the data with ketamine, memantine, and N-acetylcysteine suggest that glutamate-based mechanisms are involved in OCD and may provide an alternative target for therapeutics in addition to serotonin.

Family History Of Alcoholism Predicts Ketamine Response

The drug ketamine can bring about antidepressant effects rapidly when given intravenously, but these effects last only a few days. In a recent study, **bipolar depressed patients with alcoholism or a family history of alcoholism in first-degree relatives had a more extended positive antidepressant response to IV ketamine than those without this history, and fewer adverse effects from the treatment**. The study, published by David Luckenbaugh et al. from the National Institute of Mental Health in the jo*urnal Bipolar Disorders* in December 2012, replicates similar findings in patients with unipolar depression, where positive family history of alcoholism also predicted better response and fewer adverse effects from IV ketamine.

Alcohol and ketamine have a common mechanism of action. They are both antagonists of the glutamate NMDA receptor, meaning they limit the effects of glutamate, the major excitatory neurotransmitter in the brain. This suggests a theoretical explanation for why a history of alcoholism might relate to ketamine response.

Editor's Note: Family history appears to be linked to how patients respond to different mood stabilizers. Lithium works best in those patients with a positive family history of mood disorders (especially bipolar disorder). Carbamazepine works best in those without a family history of bipolar disorder among first-degree relatives. Lamotrigine works best in those with a positive family history of anxiety disorders or alcoholism.

Drugs that are effective in patients with a family history of alcoholism all target glutamate in the brain. Lamotrigine decreases glutamate release, while ketamine reduces glutamate's effects at the receptor. Both decrease glutamate function or activity. Like lamotrigine, carbamazepine also decreases glutamate release and has good effects in those with a history of alcoholism.

Memantine is another mood-stabilizing drug that is an antagonist of the NMDA receptor, like ketamine and alcohol. It will be interesting to see whether memantine will also be successful in those with a personal or family history of alcoholism.

Youth at High Risk for Bipolar Disorder Show White Matter Tract Abnormalities

At a recent scientific conference, researcher Donna Roybal presented research showing that children at high risk of developing bipolar disorder due to a positive family history of the illness had some abnormalities in important white matter tracts in the brain. **Prior to illness onset, there was increased fractional anisotropy (FA), a sign of white matter integrity, but following the onset of full-blown bipolar illness there were decreases in FA.**

Roybal postulated that these findings show an increased connectivity of brain areas prior to illness onset, but some erosion of the white matter tracts with illness progression.

Editor's Note: It will be critical to replicate these findings in order to better define who is at highest risk for bipolar disorder so that attempts at prevention can be explored.

Armodafinil: Antidepressant Effects In Bipolar I Depression

At a recent scientific meeting, researcher Joe Calabrese reported that **armodafinil (Neuvigil), a drug that is FDA-approved for the treatment of narcolepsy, performed significantly better than placebo at producing antidepressant effects in bipolar depression when added to treatment with mood stabilizers.** At a dose of 150mg, the drug behaved less like a psychomotor stimulant and more like a traditional antidepressant in that the antidepressant effects were delayed in onset. Stimulants have a rapid onset of action. Armodafinil was well-tolerated, not seeming to produce weight gain or switches into mania.

Editor's Note: At the moment, quetiapine (Seroquel) is the only FDA-approved monotherapy for the treatment of bipolar depression. Lurasidone (Latuda) may soon be approved, as we reported in BNN Volume 16, Issue 2 from 2013. It now looks as though armodafinil could become the third approved agent for bipolar depression.

Quetiapine has efficacy in preventing depressive and manic recurrences both alone in monotherapy and in combination therapy with lithium or valproate. So far only the combination therapy is FDA-approved for preventative purposes. The data on the long-term effects of armodafinil and lurasidone are eagerly awaited, as they are a critical component of the treatment of bipolar depression.

Mindfulness Training Improves Mood and White Matter Integrity

New research shows that regular meditation in the form of mindfulness training improves both mood and measures of white matter (axon tract) integrity and plasticity in the anterior cingulate cortex (a key node in the brain network modulating self-regulation).

This research by Tang et al. published in the *Proceedings of the National Academy of Sciences* in 2012 was a continuation of the same research group's investigation of integrative mind-body training (IMBT), a type of mindfulness training that incorporates increased awareness of body, breathing, and attention to external instructions meant to induce a state of balanced relaxation and focused attention.

In a previous Tang et al. study comparing participants who received IMBT training with a control group who spent the same amount of time doing relaxation training, **the participants who practiced IMBT for five days (20 minutes/day) had better scores on measures of attention, anxiety, depression, anger, fatigue, and energy**.

In another study the researchers found that four weeks of IMBT (30 minutes/day) increased fractional anisotrophy (FA) in white matter areas involving the anterior cingulate cortex, while four weeks of relaxation training did not bring about any effect on white matter. Decrease in FA is a part of aging. **The four weeks of IMBT also decreased axial and radial diffusivity, suggesting better alignment of axons along white matter tracts.**

In the most recent study, two weeks of IMBT (30 minutes/day) produced a reduction in axial diffusivity, but no effects on fractional anisotrophy or radial diffusivity, suggesting that the reduced axial diffusivity leads to the other changes seen with longer IMBT.

Editor's Note: In those with unresolved problems with anxiety and depression, regular 20-30 minutes/day mindfulness practice may have beneficial effects not only on mood, but also on central nervous system structures. Mindfulness training involves focused attention on sequentially different parts of the body leading to exclusive focus on the physical aspects of breathing in and out. Intruding thoughts are recognized, but let go as passing interruptions, and focus is returned to the body and breathing. The aim is to clear the mind of its usual ideas, thoughts, and worries by continually refocusing on breathing. It takes practice to achieve, but regular mindfulness training can be a helpful addition to pharmaco- and psychotherapy.

It is also noteworthy that mindfulness training is one of the processes that helps elongate the ends of each strand of DNA, called telomeres. Telomeres shorten with aging, stress, and episodes of depression, and short telomeres lead to a variety of adverse medical consequences.

Lithium Treatment Reduces Suicide Rate and Increases Longevity

Suicide is an unfortunate consequence of bipolar disorder in 10-15% of patients. A study by Manchia et al. published in the journal *Bipolar Disorders* in 2013 examined suicidal behavior in 737 families of bipolar patients, including 4,919 first-degree relatives. Suicidal behavior ran in families and was more prevalent in those with an early age of onset and a shorter duration of illness. The good news: **lithium treatment decreased suicide risk independent of its degree of effectiveness in treating bipolar disorder**. Those on lithium also had a longer median age of survival (73 versus 65 years).

Editor's Note: These data are consistent with a variety of other studies and raise the question why lithium is used less frequently in the US than in many European countries and Canada. Given its neuroprotective effects, its prevention of suicide and dementia, and its positive effects on longevity, it is hard to see why lithium is not included in the treatment regimens of more patients (at whatever dosage is well-tolerated), even if it alone is not sufficient for treating their manic and depressive episodes.

*Research (by this editor Robert Post and colleagues) shows that bipolar disorder is a more pernicious illness in almost all respects in the US compared to the Netherlands and Germany (*International Journal of Neuropsychopharmacology, *2011). Whether bipolar illness would be less severe in the US if it were more often treated with lithium is an unanswered question. The field cannot provide an answer with systematic prospective controlled data, as most study designs would be unethical (i.e. would deny useful treatment to suffering patients), although one large randomized comparative study called BALANCE did show the superiority of lithium over valproate. However, individual patients in consultation with their physician could evaluate the evidence and request that lithium be considered in their treatment regimen.*

If a patient has some clinical predictors of a good response to lithium, the decision to include the drug could be even more straightforward. Some of these predictors include: a positive family history of mood disorder, especially bipolar disorder; a classic course with distinct episodes and clear periods of wellness; manic episodes that are euphoric as opposed to dysphoric (i.e. anxious/irritable); lack of an anxiety disorder or substance abuse comorbidity; the absence of mood-incongruent delusions; and a sequence of episodes of mania followed by a depression and then a well interval (MDI) rather than the sequence of DMI.

Lithium Increases Length of Telomeres

Telomeres sit at the ends of strands of DNA at each chromosome. Various events make telomeres decrease in length: cell division/replication, stress, aging, and depressive episodes in Bipolar II disorder.

Martin Schalling, a professor of medical genetics at the Karolinska Institutet in Sweden, has found that lithium treatment lengthens telomeres.

Editor's Note: This finding by Schalling, which will soon be published, adds to the list of beneficial neurobiological effects of lithium, including increasing cell survival factors BDNF and Bcl-2, decreasing cell death factors BAX and p53, increasing marker of neuronal integrity NAA, and possibly increasing hippocampal and cortical grey matter volumes.

Clinically, lithium decreases recurrence of manic and depressive episodes (mania more than depression), decreases suicidality, and may slow cognitive deterioration in those with mild cognitive impairment.

These clinical and neurobiological benefits to lithium treatment should be factored in to calculations of the risk/benefit ratio for lithium use in long-term preventative treatment of bipolar disorder.

Lithium in Public Water Supply Decreases Suicide

Blüml et al. reported in the *Journal of Psychiatric Research* in 2013 that among 226 counties in Texas, the ones with higher trace levels of lithium in the public water supply had lower rates of completed suicide in the general population than did the counties with lower lithium levels. The naturally occurring lithium levels in public water supplies in the geographic regions described in this study ranged from 2.8 to 219 µg/l or 0.00043 to 0.0315 mmol/l (much lower than the levels used to treat bipolar disorder).

This is the fourth positive study describing this effect, including two in Texas, one in Japan, and one in Austria. (One study from part of England failed to show this relationship, though levels measured in that study had a much lower and restricted range, from less than 1 to 21 µg/l.) The most recent studies have collected more water samples and used more sophisticated statistical analyses to control for socioeconomic and a variety of other demographic effects on suicide.

Editor's Note: Why higher trace levels of lithium occurring naturally in the water supply should have this anti-suicide effect in the general population is unknown, but it is a fascinating finding. It also gives indirect credence to the clinical findings in patients with unipolar and bipolar disorder that lithium (albeit in the much higher levels achieved with medication) has anti-suicide effects.

Telomeres

Elizabeth H. Blackburn, who won the Nobel Prize for Medicine in 2009, has said that stress, aging, poor diet, depressive episodes, and anger have been associated with telomere shortening, while exercise, good diet, mindfulness training, and a commitment to positive life goals counter this shortening.

Treating the Two Forms of Acquired Lithium Resistance

Lithium is one of the most important treatments available for bipolar disorder. Unfortunately, a small percentage of patients who initially respond well to lithium may develop resistance to the drug over time. **Some develop tolerance to the drug's therapeutic effects over a period of years, seen as a gradual breaking through of manic or depressive episodes that increase in severity or frequency. Others who are good long-term responders to lithium but stop taking the drug and then suffer relapses fail to respond as well as they had before.** In a few instances, the drug no longer helps at all. This latter form of acquired lithium resistance is called **lithium discontinuation-induced refractoriness**.

In a review article published in the *Journal of Affective Disorders* in 2011, this editor (Robert Post) analyzed case series and case reports that depicted these two different types of acquired lithium resistance and reported that each must be addressed in a different way.

In the case of tolerance development, a temporary break from lithium may theoretically restore its effectiveness, but the typical way to treat this situation is to add additional drugs with different mechanisms of action that are not affected by the tolerance.

Editor's Note: In those who stop effective lithium treatment and experience relapses that are no longer responsive when lithium is re-instituted, it is not clear what the best treatment approaches are. The most conservative approach to preventive treatment with lithium is to avoid discontinuing the drug. This is a generally sound principle for the treatment of recurrent unipolar or bipolar illness. When things are going well, do not change the regimen; leave well-enough alone. Conversely, when treatment is not optimal, as in the case of loss of drug responsiveness via tolerance, a more aggressive exploration of treatment options would be warranted.

Patients should be aware of the multiple dangers of stopping effective treatment with lithium. These include: likely relapse, perhaps the necessity of hospitalization, an increased risk of suicide, and the loss of responsiveness to lithium that appears to occur in approximately 15% of patients who stop lithium when it is working effectively.

Lithium Increases the Volume of the Prefrontal Cortex in Responders

Studies have indicated that lithium increases gray matter and the volume of the cortex and hippocampus in patients with bipolar I disorder. A poster presented by S. Selek et al. at the 5th Biennial Conference of the International Society for Bipolar Disorders described a longitudinal study of fronto-limbic brain structures in patients with bipolar I disorder during lithium treatment.

This study reported that patients whose illness failed to respond to lithium had smaller right amygdalas than euthymic bipolar I patients or healthy controls. After treatment with lithium, those who responded well to the drug showed significant enlargement of the left prefrontal cortex and the left dorsolateral prefrontal cortex, while those who responded poorly to lithium showed decreases in the volume of their left hippocampus and right anterior cingulate cortex.

Editor's Note: This is one of several studies that suggest a relationship between volume of brain regions and degree of response to lithium. These data add to the remarkably consistent literature suggesting that lithium may have neurotrophic and neuro-protective effects, potentially because of the drug's ability to increase neuroprotective factors such as BDNF and Bcl-2 while decreasing cell death factors such as BAX and p53.

Lithium Discontinuation Results in Only Modest Improvement in Renal Function

Lithium is important in the long-term maintenance treatment of bipolar disorder. Unfortunately long-term use can be complicated by renal (kidney) dysfunction and, in rare cases, renal failure. A 2012 study by Rej et al. of geriatric patients with a history of lithium use and symptoms of chronic renal failure found that after two years, differences in outcomes for patients who continued lithium use versus stopping this treatment were not significantly different, though the lithium continuers had slightly less renal function after 60 months.

Editor's Note: This study addresses one of the important unanswered questions about what to do when kidney function starts to diminish (observed as high levels of creatinine (Cr) or low Cr clearance) in patients on chronic lithium treatment.

The findings of Rej et al. suggest that the advantages of discontinuing lithium are not huge. Renal function may deteriorate a bit less (or not at all) in those who stop lithium. However, if someone is highly responsive to lithium and the "creatinine creep" upwards is slow, that patient might be able to proceed with careful monitoring and lithium continuation. Where other treatment options are readily available, the discontinuation route might be a good choice.

This study brings some much-needed randomized longitudinal data (if not a definitive recommendation) to bear on a difficult clinical decision that may have to be addressed in some patients with bipolar disorder.

Glial, Not Neuronal, Deficits May Be Responsible For Depression

The brain consists of 12 billions neurons and four times as many glial cells. Neurons conduct electrical activity, and it is thought that changes in neural activity and synaptic activity (where neurons meet) underlie most behaviors. It was once thought that glia were just fluff, but new research shows that they may play a role in depression.

There are three types of glia: astrocytes, oligodendrocytes, and mico-glia. Researcher Mounira Banasr had previously shown that neuronal lesions in the prefrontal cortex of mice did not produce depressive-like behaviors, but glial lesions did.

In a new study presented at a recent scientific meeting, Banasr reported that destroying astrocytes in the prefrontal cortex of mice induced depressive- and anxiety-like deficits. Using a virus that specifically targeted astrocytes, the researchers documented that the depressive behavior was specifically related to loss of astrocytes and not loss of other glial cell types, such as oligodendrocytes or micro-glia.

Editor's Note: There is evidence of glial abnormalities in patients with mood disorders. Banasr's research raises the possibility that glial deficits (rather than neuronal alterations) could be crucially involved in depression. In this study, the depressive- and anxiety-like behaviors persisted for 8 days following the astrocyte ablation, but by day 14 the animals had recovered, possibly with the production of a new supply of astrocytes. These data also raise the possibility that targeting the mechanisms of glial dysfunction could be a new avenue to pursue in the therapeutic approaches to depression.

Lamotrigine Not Helpful as Add-on to Lithium and Valproate in Rapid Cycling Bipolar Disorder

A 2012 study by Kemp et al. in the journal *Bipolar Disorders* found that lamotrigine added to combination treatment with lithium and valproate was no more effective than placebo in patients with rapid cycling bipolar disorder. Only 14% (19 out of 133) of rapid cycling patients stabilized upon initial treatment with the open combination of lithium and valproate, a startlingly low rate. In the next phase of the study, 49 patients who were not stabilized were given adjunctive treatment with either lamotrigine (n=23) or placebo (n=26) on a double-blind basis, but no significant difference was observed.

Editor's Note: This study has two pieces of not-so-good news. The first is that it was so difficult to stabilize these patients with rapid cycling bipolar disorder. The second is that the add-on of lamotrigine, which is highly effective in the prevention of depressions in bipolar disorder, was in this case no more effective than placebo.

This study again demonstrates that rapid cycling bipolar disorder is difficult to treat, and even the use of three proven mood stabilizers in combination is not always effective. Many doctors would recommend an atypical antipsychotic as the next clinical option.

Lithium

Lithium treatment deserves a new look in light of studies that suggest it decreases suicide rates and increases longevity even in those in whom it has not been particularly effective as a mood stabilizer.

Lithium-Induced Hypercalcemia

In a poster at the 5th Biennial Conference of the International Society for Bipolar Disorders, researchers from the Netherlands including E.J. Regeer described the prevalence of hypercalcemia (high calcium levels) in patients with bipolar disorder who are treated with lithium. **In a study of 314 patients taking lithium, Regeer and colleagues found that calcium levels were elevated in 15.6% of the patients, and the length of time patients had been treated with lithium was significantly related to the degree of hypercalcemia.** It is recommended that blood levels of calcium be monitored in patients on lithium.

The researchers recommended testing for parathyroid hormone in blood in order to exclude other causes of hypercalcemia. They also suggested that when lithium cannot safely be discontinued or when its discontinuation does not resolve the hypercalcemia, other treatment for high blood calcium, including removal of the parathyroid, may be necessary.

Long-term Response in Bipolar Illness

Willem Nolen, a researcher who spent 40 years studying unipolar and bipolar disorder, recently retired from his position at Groningen Hospital in the Netherlands. In February, his retirement was celebrated with a symposium where he and other researchers discussed some of their important findings from the last several decades.

Nolen recently published a double-blind randomized study showing that **in patients who were initially responsive to monotherapy with quetiapine (Seroquel), continuing the drug (at doses of 300-800mg/night) or switching to lithium were both more effective than switching to placebo over 72 weeks of long-term follow-up**.

This study shows that quetiapine, which is only FDA-approved for long-term preventative treatment when used in combination with lithium or valproate (Depakote), also has efficacy when used as monotherapy.

Lithium is Highly Effective in Long-term Prevention

Nolen's work also adds to an impressive amount of literature showing that lithium is highly effective in long-term prevention. This case is especially noteworthy because lithium was effective even in patients who had initially been selected for their response to quetiapine. (Studies that use this kind of "enriched sample" can only claim that quetiapine has long-term efficacy in those patients who initially respond well to the drug.) The data on lithium are even more impressive since the patients in this study were not enriched for lithium response.

Nolen has also conducted multiple studies of lithium, but optimal doses and target blood levels of the drug remain controversial. The therapeutic range of lithium is usually considered to be 0.6 to 1.2 meq/L, but some have argued that lower levels may still be effective. In a new analysis of those patients in the quetiapine study who were switched to lithium treatment, **Nolen found that only lithium levels above 0.6 meq/L produced better results than placebo in long-term prophylaxis.**

These data are also consistent with a recent study in the US known as Litmus. Patients who had only partially responded to their usual treatment received an addition of either low-dose lithium (600mg/day) or placebo. These low doses of lithium did not enhance treatment outcomes better than placebo. However, this dose of lithium did reduce the dose of antipsychotics needed to prevent symptoms from breaking through.

Editor's Note: For good therapeutic effects in bipolar disorder prevention, it appears wise to aim for lithium doses that produce blood levels of at least 0.6meq/L. If a patient cannot achieve this goal because side effects emerge, an argument can still be made for continuing to use lithium even at lower blood levels. In addition to Nolen's study in which lithium reduced the necessary dose of antipsychotics, there is evidence that low levels of lithium might have positive effects on both cognitive deterioration and suicide. In animals, even blood levels of lithium as low as 0.38 meq/L increased neuroprotective factors such as Bcl-2 in the brain.

Another important message of Nolen's study was that long-term maintenance treatment is absolutely necessary, as about 90% of patients who were initially successfully treated with quetiapine and then switched to placebo relapsed by the end of the study, and almost all did so within a year. These data parallel the high rate of relapse in patients who stop effective lithium treatment reported by Suppes et al. in 1995.

Stopping effective treatment can lead to episode recurrence, hospitalization, or suicide. Among those who stop effective preventative treatment with lithium, relapse, and begin lithium treatment again, 10 to 15% fail to re-respond as well as they had previously, and some fail to respond at all.

Childhood Onset Illness More Difficult Than Adult Onset

There is more evidence that childhood onset of bipolar illness means a more difficult course of illness. In a study published in *World Psychiatry* in 2012, Baldessarini et al. pooled data from 1,665 adult patients with bipolar I disorder at seven international sites and compared their family history of bipolar disorder, outcomes, and age of onset. Among these patients, 5% had onset in childhood (age <12 years), 28% during adolescence (12-18), and 53% during a peak period from age 15-25.

Patients who were younger at onset had more episodes per year, more co-morbidities, and a greater likelihood of a family history of the illness. Patients who were older at onset were more likely to have positive functional outcomes in adulthood, like being employed, living independently, and having a family.

Nolen's Findings:

1. Lithium levels should be above 0.6 meq/L for a good prophylactic response in bipolar disorder, although lower levels of lithium may have other benefits.

2. Quetiapine monotherapy is also effective in prophylaxis (although it is only FDA-approved as an adjunct to lithium or valproate).

3. Consistent, persistent long-term maintenance treatment is required in bipolar disorder. This may sometimes require complicated treatment regimens.

Aspirin added to Regular Treatment Reduces Symptoms of Schizophrenia

Most drugs used to treat schizophrenia target dopamine and serotonin receptors in the brain. While these are effective in many patients, relapse is common and side effects can be severe. Researchers are looking for ways to target other mechanisms that cause schizophrenia, and inflammation seems to be one of these. There is evidence that a treatment as simple as aspirin, when added to regular treatment with antipsychotics, can improve schizophrenia by targeting inflammation.

In a 2010 study by Laan et al. published in the *Journal of Clinical Psychiatry*, patients with moderate or severe schizophrenia were given either placebo or aspirin (acetylsalicylic acid, 1000mg) in addition to their regular treatments every day for three months. **The patients who received aspirin showed a significant reduction in the positive symptoms of schizophrenia, and to a lesser extent the negative symptoms, compared to those who received placebo.** Cognitive function was not improved. The effect size (Cohen d) for the total scale score was 0.5, which is considered a "medium" effect and one that is clinically relevant.

The reductions in symptoms were greater in those patients who had more altered immune function.

Oxytocin Improves Some Aspects of Social Cognition In Schizophrenia

Researcher Josh Woolley and colleagues at the University of California, San Francisco have found that intranasal oxytocin (at doses of 40 IU) improved social cognition in patients with schizophrenia when compared with placebo. Oxytocin is a hormone that facilitates social bonding. Social cognition refers to the way we understand what emotions other people are communicating through facial expression, voice, etc.

Interestingly, less complicated aspects of social cognition like recognizing affect and distinguishing between sincerity and sarcasm were not affected by the oxytocin treatment. However, **more complex types of social inference (such as decoding whether an actor intended sarcasm versus telling a white lie) were substantially improved.**

These tasks evaluate "theory of mind," the ability to attribute mental states to oneself and others, and to recognize that another person's mental state may be different from one's own. These abilities are sometimes lacking in those with schizophrenia and other disorders, such as autism. Given that these abilities have been related to real world social functioning, Woolley and colleagues suggest that oxytocin could, for example, help these individuals to make more friends.

RTMS Improves Working Memory In Patients With Schizophrenia

Repetitive transcranial magnetic stimulation (rTMS) may improve working memory in patients with schizophrenia, according to a small study published by Zafiris J. Daskalakis and colleagues in *Biological Psychiatry* in 2013. Patients with schizophrenia received either 20 Hz rTMS over the left and right prefrontal cortex or a sham treatment, and the rTMS improved working memory on a particular task, the n-back task, wherein patients are asked to recall whether a stimulus they're currently viewing is the same as the previous one they viewed, or one they viewed several times back. **Twenty sessions of rTMS over a period of 4 weeks brought memory back to the levels seen in normal controls.**

Editor's Note: Since many patients with bipolar disorder also have deficits in prefrontal-based memory and performance even when euthymic, it will be important to see if rTMS would also be helpful in these patients. RTMS at 20 Hz increases neuronal activity as measured by PET scan of the prefrontal cortex and other regions of the brain, and this lasts for at least 48 hours after each treatment.

Since many patients with schizophrenia and bipolar disorder show deficits in prefrontal activity at baseline, the normalization of these alterations could relate to the memory improvement. This proposition could be tested relatively easily.

Adjunctive Topiramate Effective In Schizophrenia

Many patients with schizophrenia do not reach full remission on antipsychotic drugs alone. The anticonvulsant drug topiramate (Topamax) has shown some promise as an adjunctive treatment for schizophrenia. To clarify the results of studies of topiramate, researcher Christoph Correll and colleagues performed a meta-analysis of nine randomized, placebo-controlled clinical trials of the drug. They found that when topiramate was added to antipsychotic treatment, **it improved both positive and negative symptoms of schizophrenia, and it also led to reduced weight**.

Editor's Note: Topiramate might also be useful for patients with schizophrenia who have the common comorbidities of alcohol and cocaine abuse, since in other studies of patients with these primary disorders, topiramate was helpful.

Metformin Effective for Treating Antipsychotic-Induced Amenorrhea, Weight Gain, and Insulin Resistance in Women

Treatment with antipsychotics often has side effects such as amenorrhea (loss of the menstrual period) and weight gain that make sticking to a treatment regimen difficult for some patients. A 2012 study by Wu et al. in the *American Journal of Psychiatry* suggests that the drug metformin, often used to treat diabetes, can reverse these changes. The 84 female patients recruited for the study were being treated for a first episode schizophrenia, were on one antipsychotic, and had experienced amenorrhea for several months. They received either placebo or 1000mg/day of metformin in addition to their antipsychotic treatment for six months. Seventy-six women completed the trial.

Metformin was able to reverse the side effects in many of the women. **Menstruation returned in 28 of the patients taking metformin compared to only two patients taking placebo.** Among those on metformin, body mass index (BMI) decreased by a mean of 0.93, compared to a mean increase in those on placebo (0.85). Insulin resistance improved in the women on metformin as well.

Editor's Note: Metformin can also delay the onset of type II diabetes in those in the borderline diabetic range. The weight loss on metformin was not spectacular and other options include the combination of the antidepressant bupropion (Wellbutrin) and the opiate antagonist naltrexone (Revia, 50mg/day), monotherapy with topiramate (Topamax), the fixed combination of topiramate and phentermine (Qsymia), or monotherapy with zonisamide (Zonegran).

Ginkgo Biloba Improves Tardive Dyskinesia

Tardive dyskinesia is a sometimes irreversible side effect of antipsychotic treatment, and is characterized by uncontrollable, subtle and spontaneous motor movements, usually of the tongue, mouth, or fingers.

Extracts of the leaves of the gingko biloba tree contain potent antioxidants. In a study published by Zhang et al. in the journal *Biological Psychiatry* in 2012, treatment with ginkgo biloba (EGb-761) at 240mg/day for 12 weeks improved tardive dyskinesia more than placebo. **Patients with tardive dyskinesia had low levels of brain-derived neurotrophic factor (BDNF) at baseline, and gingko biloba increased these levels.** BDNF is important for the production and protection of neurons, and maintaining long-term memory.

The increase in BDNF was correlated with the degree of improvement achieved with gingko biloba in these patients. Different people have different variations in the gene for BDNF. As a result, some people's BDNF is transported to dendrites and synapses more efficiently than others'. Improvement was greatest in those patients with the most common and best-functioning variant of BDNF, Val66Val, and worst in those patients with the rare and poorest-functioning variant, Met66Met.

Editor's Note: These findings could be of great clinical importance. Tardive dyskinesia occurred in 20 to 40% of patients with bipolar disorder following treatment with the older "typical" antipsychotics. The incidence is much lower with the newer "atypical" antipsychotics, but having an effective and well-tolerated treatment for this disfiguring side effect is an extra bonus.

NAC Not Effective In Kids With Trichotillomania

N-acetylcysteine (NAC) is a drug available over-the-counter in health food stores that is effective in a variety of disorders, including trichotillomania (compulsive hair-pulling) in adults. Researcher Michael Block of Yale University reports that, in contrast to NAC's robust effects in adults, the drug was not effective in children with trichotillomania aged 8 to 17. However, behavior therapy has been reported to be effective in both adults and children.

Editor's Note: Why a drug that is so effective for trichotillomania in adults does not work well or at all in children is not clear. It is even more perplexing given that NAC has shown robust effects on some other childhood disorders, such as irritability and stereotypy in children with autism. However, if this discrepancy and other differences in pharmacological response across demographics are replicated, the reasons for differential response should be investigated.

As many researchers have emphasized, kids are not just shorter adults, but might have entirely different brains that are in a different stage of development. Extrapolating the therapeutic effects that occur in adults to children may not always be a valid strategy.

Cinnamon: A Dash is Good, But A Spoonful is Dangerous

Cinnamon seasoning is good for you; it sensitizes insulin receptors and helps prevent type 2 diabetes.

Attempting to swallow a whole spoonful—a stunt called the Cinnamon Challenge that was popularized by a viral YouTube video—can be dangerous. It induces violent coughing and a gag reflex that may lead to inhaling the spice into the lungs. Cinnamon is composed of cellulose fibers which do not dissolve or degrade in the lungs, and thus can cause scarring and other long-term lung complications. Details can be found in the May 2013 issue of the journal *Pediatrics*.

Clarifying the Mechanism of Action of NAC

N-acetylcysteine (NAC) is a drug available over-the-counter in health food stores that seems to be effective for a variety of disorders, including depression and many different habits and addictions. Preventing relapse of cocaine abuse is one of its uses. Researcher Kathryn Reissner at the Medical University of South Carolina found that **NAC increases the expression of a glial glutamate transporter (GLT-1) that helps clear excessive glutamate in the nucleus accumbens**, and that this mechanism is critical to preventing the reinstatement of cocaine self-administration in rodents.

As we have previously described in *BNN*, NAC also decreases cued release of glutamate in the nucleus accumbens by potentiating the cystine-glutamate exchanger. This initially increases extrasynaptic glutamate, but subsequently downregulates glutamate release in the nucleus accumbens through actions at an inhibitory presynaptic metabotropic glutamate receptor.

However, the new data indicate that this action at the cystine-glutamate exchanger is not required for NAC's effects on cocaine reinstatement, but the induction of GLT-1 is. Furthermore, another compound, propentofylline, which increases glutamate GLT-1, is also effective in suppressing cocaine reinstatement. Cocaine decreases a marker of glial activity, glial fibrillary acidic protein (GFAP), in the nucleus accumbens, suggesting that deficient glial functioning and uptake of glutamate could be another target of therapeutics in cocaine addiction.

Editor's Note: There are also glial deficits in depressed patients, so it is conceivable that NAC's effect on GLT-1 glutamate clearance is also involved in the antidepressant effects of NAC.

NAC Improves Irritability and Repetitive Behaviors in Children with Autism

The antioxidant N-acetylcysteine (NAC), which can be found in health food stores, seems to be effective for irritability and repetitive behaviors in children with autism. In a small controlled study that was published by Hardan et al. in the journal *Biological Psychiatry* in 2012, 33 mostly male children with autism (aged 3-12 years) received either placebo or NAC at doses of 900mg daily for 4 weeks, followed by 900mg twice daily for 4 weeks, then 900mg three times a day for 4 weeks. Beginning in week 4, the children receiving NAC showed significantly improved irritability scores, and a trend for improvement in repetitive behaviors.

Social responsiveness did not improve significantly, but the children receiving NAC did show some improvement in some areas of social behavior, such as social cognition and autism mannerisms.

There were few side effects associated with NAC. The most significant were gastrointestinal side effects, but these were mild, especially when compared with the side effects associated with FDA-approved treatments for autism, such as the atypical antipsychotics risperidone and aripiprazole.

The authors of the study plan to expand their research in a study of more than 100 children with autism.

Editor's Note: It should be noted that we previously summarized this study in the BNN based on research presented by Fung et al. at a meeting of the American Academy of Child and Adolescent Psychiatry two years ago. The study has now been published.

NAC Normalizes Glutamate Levels in Cocaine-Dependent People

Glutamate is the major excitatory neurotransmitter in the brain, while GABA is the main inhibitory neurotransmitter. Too much or too little of one or the other can lead to an imbalance in neuronal communication. In a 2012 study by Schmaal et al. published in the journal *Neuropsychopharmacology*, **cocaine-dependent patients were found to have high levels of glutamate in the dorsal anterior cingulate cortex. A single administration of N-acetylcysteine (NAC) at a dose of 2400mg lowered these levels**.

Healthy (non-addicted) participants who received the same administration of NAC did not show the same drop in glutamate levels.

The study also observed levels of impulsivity in the patients. Higher baseline levels of glutamate were associated with greater impulsivity, and both higher baseline level of glutamate and greater impulsivity were predictive of a larger drop in glutamate levels following NAC administration.

The researchers suggest that these findings may eventually be used in the treatment of cocaine-addicted people, since abnormal glutamate levels are related to risk of relapse. In drug-dependent rodents, NAC was found to normalize hyper-responsive glutamate release in the nucleus accumbens (the brain's reward center) and prevent cocaine-reinstatement or relapse.

Editor's Note: When these data from the lab of Peter Kalivas at the Medical University of South Carolina were initially collected, it was thought that NAC's effect on a cysteine-glutamate exchanger in the nucleus accumbens explained its treatment success, but new data suggest that NAC may actually facilitate glutamate clearance by increasing the number of glutamate transporters in glial cells.

The Amygdala Plays a Role in Habitual Cocaine Seeking

At a recent scientific meeting, Jennifer E. Murray et al. presented findings about the amygdala's role in habitual cocaine seeking. The amygdala is the part of the brain that makes associations between a stimulus and a response. When a person begins using cocaine, a signal between the amygdala and the ventral striatum (also known as the nucleus accumbens), the brain's reward center, creates a pleasurable feeling for the person. The researchers found that in mice who have learned to self-administer cocaine, **as an animal progresses from intermittent use to habitual use, the amygdala connections shift away from the ventral striatum toward the dorsal striatum, a site for motor and habit memory**. If amygdala connections to the dorsal striatum are severed, the pattern of compulsive cocaine abuse does not develop.

Editor's Note: These data indicate that the amygdala is involved in cocaine-related habit memory, and that the path of activity shifts from the ventral to the dorsal striatum as the cocaine use becomes more habit-based – automatic, compulsive, and outside of the user's awareness.

As we reviewed in BNN *Volume 16, Issue 5 from 2012, the amygdala also plays a role in context-dependent fear memories, such as those that occur in post-traumatic stress disorder (PTSD). The process of retraining a person with PTSD to view a stimulus without experiencing fear is called extinction training. A study by Agren et al. published in* Science *in 2012 demonstrated that when extinction training of a learned fear took place within the brain's memory reconsolidation window (five minutes to one hour after active memory recall), the training was sufficient to not only "erase the conditioned fear memory trace in the amygdala, but also decrease autonomic evidence of fear as revealed in skin conductance changes in volunteers."*

The preclinical data presented by Murray and colleagues suggest the possibility that amygdala-based habit memory traces could also be revealed via functional magnetic resonance imaging (fMRI) in subjects with cocaine addiction. Attempts at extinction of cocaine craving, if administered within the memory reconsolidation window, might likewise be able to erase the cocaine addiction/craving memory trace, as Xue et al. reported in Science *in 2012.*

Cocaine Memories Selectively Erased in Mice

At a recent scientific meeting, researcher Sheena Josselyn discussed attempts to erase cocaine-cue memories in mice.

Articles published in *Science* by Han et al. in 2007 and 2009 showed that about 20% of neurons in the lateral amygdala of mice were involved in the formation of a fear memory, and that selective deletion of these neurons could erase the fear memory.

Using the same methodology, Josh Sullivan et al. identified neurons that were active in the mouse brain during cocaine conditioning. Amygdala activity showed that the mice preferred an environment where they received cocaine to an environment where they didn't. The researchers noticed increased cyclic AMP, a messenger that led to increased production of calcium responsive element binding protein (CREB). When the researchers targeted the neurons in the lateral amygdala that were overexpressing CREB, they found that selective destruction of the overexpressing neurons disrupted the cocaine-induced place preference.

The research team further documented this effect by temporarily, rather than permanently, knocking out neuronal function. They could reversibly turn off neurons with an inert compound that promotes neuronal inhibition. Silencing the neurons that were overexpressing CREB before the conditioned place preference testing also limited cocaine-induced place preference memory.

Editor's Note: While this type of intervention is not feasible in humans with cocaine addiction, these data do shed more light on the mechanisms behind cocaine conditioning.

We have written before that if extinction training to break a cocaine habit or neutralize a learned fear is performed within the brain's memory reconsolidation window (five minutes to one hour after memory recall), it can induce long-lasting alterations in cocaine craving or conditioned fear.

It is possible that properly timed extinction of cocaine- or fear-conditioned memories might work similarly to the selective silencing of neurons that was carried out in the mice using a drug that inhibited CREB-activated neurons. Determining the commonalities between these ways of eliminating conditioned memories could lead to a whole new set of psychotherapeutic approaches to anxiety disorder, addictions, and other pathological habits.

Female Rodents More Sensitive to Defeat Stress, Cocaine Sensitization

Among rodents, being subjected to defeat stress (when an intruder mouse is threatened by a larger mouse defending its territory) can make an animal more susceptible to cocaine. This is referred to as cross-sensitization.

Researcher Elizabeth Holly and colleagues have found that compared to males, female rodents are more sensitive to defeat stress and have greater reactions to cocaine and cocaine sensitization following this type of stress. This is probably related to a neuropeptide called corticotropin releasing factor (CRF), which is associated with cross-sensitization. When the mice were exposed to cocaine, there were increases in CRF in a part of the brain called the ventral tegmental area (VTA), which contains cell bodies of dopamine neurons that travel to the nucleus accumbens, the brain's reward center. Blocking the CRF receptors in the VTA prevented the sensitization to cocaine from occurring in the mice.

Editor's Note: These data in animals resemble clinical observations in humans that women are more sensitive to stress and are more prone to depression, and can have an exceedingly difficult time stopping cocaine use if they become addicted.

'Bath Salts' Ingredient Worse than Cocaine, and 10 times More Powerful

Between 2010 and 2011, reports about the recreational drug commonly known as "bath salts" skyrocketed, and its use has been connected with a range of serious consequences including heart attack, liver failure, prolonged psychosis, suicide, violence, and even cannibalism. The drug, which is distinct from actual bath salts and sometimes goes by other names such as "plant food," contains synthetic cathinones, which have effects that resemble those of amphetamines and cocaine. (Natural cathinone is derived from the plant Khat, which some cultures, particularly in the Horn of Africa and the Arabian Peninsula, have used socially for its euphoric effects when chewed.)

Synthetic cathinones are not well understood, but a few studies published in the journal *Neuropsychopharmacology* this year provided some preliminary findings. The most common synthetic cathinone found in the blood and urine of patients admitted to emergency rooms in the US after taking bath salts is 3,4-methylenedioxypyrovalerone, or MDPV.

In a study of rats by Baumann et al., MDPV was found to have a strong blocking effect on uptake of the neurotransmitters dopamine and norepinephrine, while having only weak effects on uptake of serotonin. MDPV's ability to inhibit the clearance of dopamine from the synapse is similar to cocaine's actions, but MDPV is much more potent and effective at this. MDPV was also 10 times more potent than cocaine at producing physical symptoms in the rats, such as motor activation, tachycardia (irregular heart beat), and hypertension (high blood pressure).

Another study of rats by Fantegrossi et al. found that rats that received MDPV experienced motor stimulation that was potentiated by being in a warm environment. When the rats received relatively high doses in heated cages, they engaged in profound stereotypy (repetitive movement) and self-injurious behavior such as skin-picking or chest-biting. This study also found similarities in the internal effects of MDPV and MDMA (ecstasy) and methamphetamine.◊

Even Short-Term Recreational Use Of Ecstasy Causes Deficits In Visual Memory

German researchers have found that MDMA (ecstasy) users who took more than 10 pills in a one-year period showed deficits in visual memory. Wagner et al. published the study in the journal *Addiction* in 2012.

In tests where participants were trained to associate certain words with certain images and then recall one in response to the other, those who had taken ecstasy at least ten times the previous year showed deterioration in both their immediate and delayed recall skills.

Given the role of the hippocampus in relational memory, the researchers suspect that there is a relationship between ecstasy use and hippocampal dysfunction.

Editor's Note: This is the most definitive study on this subject so far because it observed new users before and after they had used ecstasy for at least 10 times in one year (unlike many retrospective studies that observed participants only after they had been using the drug for some time, so it was impossible to know if they had pre-existing memory problems).

Other data in animals and humans suggest that ecstasy burns out the terminals of serotonergic neurons and thus causes brain damage. It now appears this damage to the brain and memory can occur even during short-term or casual ecstasy use.◊

Bath Salts, Continued

Ecstasy Use Increases Serotonin Receptors in Women

MDMA, better known as the drug ecstasy, has been found to reduce serotonin terminals in animals. A small study by Di Iorio et al. published in the *Archives of General Psychiatry* in 2012 suggests that the drug also has detrimental effects on serotonin signaling in humans.

The researchers used positron emission tomography (PET) scans to identify serotonin receptors in the brains of 10 women who had never used ecstasy and 14 who had used the drug at least five times before and then abstained for at least 90 days. The team found significantly greater cortical serotonin2A receptor nondisplaceable binding potential (serotonin2ABPND, an indicator of serotonin receptors) in abstaining MDMA users than in those women who had never used the drug.

The increase in serotonin receptors observed in these ecstasy users could be a sign of chronic serotonin neurotoxicity. Loss of serotonin nerve terminals decreases serotonin levels and secondarily results in the production of more serotonin receptors. Thus, one explanation for the receptor increase is that it is prompted by the decrease in serotonin transmission that MDMA is known to cause.

The higher levels of serotonin2ABPND were found in several regions of the MDMA users' brains: occipital-parietal, temporal, occipito-temporal-parietal, frontal, and frontoparietal. Lifetime use of the drug was associated with serotonin2ABPND in the frontoparietal, occipitotemporal, frontolimbic, and frontal regions. There were no regions in which the MDMA users had lower levels of receptors than women in the control group. The duration of the ecstasy users' abstinence from using the drug had no effect on levels of serotonin$_{2A}$BP$_{ND}$

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ECT Update: Some good news and some not-so-good news

A 2013 study by Prudic et al. in the *Journal of Electro-convulsive Therapy* reveals some good and some not-so-good news about ECT. The good news about ECT is that it produced moderate acute remission rates. In this randomized study of ECT treatment, improvement rates were better when patients received right unilateral (RUL) ultra-brief pulse at high doses (6 times a patient's seizure threshold) than with bilateral (BL) pulse at low doses (1.5 times the patient's seizure threshold). RUL also has fewer cognitive side effects than BL.

Prudic also found that these acute remission rates were best when antidepressant treatment was begun at the same time as ECT rather than after the end of ECT treatment.

Unfortunately, a previous study by Prudic et al. showed that relapse rates after ECT remain high. Two-thirds of patients relapse in the first six months after ECT. Half of patients who receive antidepressant treatment following ECT relapse within the first six months after their last ECT treatment. Twenty to forty percent relapse in the first month after their last ECT treatment.

In the current study, timing and likelihood of relapse was independent of whether antidepressant treatment was started at the outset of ECT or after the end of ECT. Relapse also did not depend on which pharmacological treatments are used (nortriptyine plus lithium versus venlafaxine plus lithium).

Older patients (average age 55) did better—they relapsed less often than patients with an average age of 45. Patients with unipolar and bipolar depression did not differ in relapse rates.

Previous history of illness did affect relapse. The number of prior antidepressant trials a patient had tried for a current depressive episode (a measure of treatment resistance) was related to how fast they relapsed on follow-up pharmacotherapy after receiving ECT (more antidepressant trials was associated with faster relapse).

Researchers Kellner et al. showed that continuation of ECT treatment is not superior to continued treatment with drugs following ECT treatment.

Editor's Note: ECT works acutely, but too often its effects do not last long, even with intensive continuation treatment with an antidepressant and lithium. Therefore for patients with highly recurrent illness, its usefulness is largely limited to acute emergencies, such as high risk of suicide or medical deterioration.

There are currently no good controlled studies showing how to prevent depressive relapse after remission with ECT using either drug continuation therapy or maintenance ECT. Greater degrees of treatment resistance are associated with lower rates of both acute remission and faster relapse during follow-up pharmacotherapy.

If a patient is going to have ECT, RUL would be recommended over bilateral, because bilateral ECT is associated with decreases in autobiographical memory even after six months, and these deficits are in proportion to the number of bilateral ECT treatments received.

Alternatives to ECT

Other types of brain stimulation treatments could potentially serve as alternatives to ECT.

Unlike ECT, whose effects rapidly wane, the therapeutic effects of vagal nerve stimulation (VNS) are unique in that they appear to increase over time, while side effects (such as hoarseness) decrease.

Repeated transcranial magnetic stimulation (rTMS) has fewer side effects (especially cognitive ones) than ECT, but like ECT there are no definitive procedures for dealing with maintaining its effectiveness for the long term.

Given the large number of potential pharmacoprophylactic approaches for recurrent unipolar and bipolar disorders, in non-emergency situations this editor prefers to explore drug options in depth in the hopes of both achieving remission and maintaining it with continuation of that same regimen.

The number of prior depressions a patient has had is a risk factor not only for treatment resistance, but also for cognitive dysfunction. Therefore it appears prudent to institute long-term preventative treatment with antidepressants after a second or third unipolar depressive episode (as recommended in most treatment guidelines) or with lithium, mood stabilizers, or atypical antipsychotics after a first or second manic episode in bipolar disorder in order to prevent the accumulation of mood episodes, which have deleterious effects on a patient's medical and psychiatric health, cognitive function, and longevity. It has not yet been definitively proven, but there is much to suggest the wisdom of the mantra: "Prevent Episodes, Protect The Brain."

Instituting and maintaining early and long-term prophylaxis will likely require patients to take an active role in ensuring that episodes are treated to remission and in maintaining this remission with careful long-term preventive treatment and monitoring.

The duration of time well on preventive treatment is not a good predictor of likely continued wellness if effective drug treatment is discontinued. So until there are data to the contrary, the safest approach is long-term continuation of what is working well.◊

Ecstasy and Serotonin

Continued from Page 14

observed, suggesting that the effects might be long-lasting, if not permanent.

Editor's Note: Given serotonin's importance in brain function and the drug's popularity for recreational use, this finding has implications both for ecstasy users and for research on serotonin signaling.◊

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