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Bipolar Network News

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More Evidence That Lithium Prevents Manic and Depressive Episodes

There is a large body of research showing that lithium is better than placebo and a variety of comparison drugs at preventing manic episodes in people with bipolar disorder. It has been less clear whether lithium is as effective in preventing depressions in bipolar patients. In a 2014 meta-analysis in the *International Journal of Bipolar Disorders*, Emanuel Severus and colleagues confirmed that **lithium was more effective than placebo at preventing mood episodes overall and manic episodes. In a fixed effect statistical analysis, lithium was also better at preventing depressive episodes**.

The portion of the meta-analysis comparing lithium to placebo included seven randomized controlled trials that included a total of 1,580 patients. Lithium was more likely than placebo to lead to patients dropping out of a study for reasons other than a mood episode (for example, side effects), but patients who received lithium were more likely to complete their clinical trials.

Another part of the meta-analysis compared lithium to anticonvulsant drugs. Seven trials were included totaling 1,305 patients. Lithium was better than anticonvulsants at preventing manic episodes, but equally effective at preventing mood episodes overall and depressive episodes specifically. There was also no difference in patients dropping out of the trials or completing the trials.

Severus and colleagues concluded that lithium remains the most valuable treatment option for bipolar disorder, because no other drug has such consistent efficacy in preventing manias and depressions and mood episodes in general.

Also in this issue:

Combination of Lamotrigine and Quetiapine Superior to Quetiapine Alone

At a recent scientific meeting, researcher John Geddes and colleagues reported that compared to adding placebo to the treatment of **bipolar depressed patients already receiving the atypical antipsychotic quetiapine, adding the mood stabilizing drug lamotrigine led to significant improvements in their illness**. Lamotrigine was slowly titrated to doses of 200mg/day. (Slowly increasing dosage is important because a serious rash is a possible side effect of lamotrigine that occurs in about one in 5,000 individuals exposed to the drug.)

Researcher Charles Bowden found in 2000 that adding lamotrigine to valproate improved its effectiveness, as Marc van der Loos found in 2008 with lamotrigine and lithium. Thus it appears that adding lamotrigine to a mood stabilizer or to an atypical antipsychotic like quetiapine is a good second-line option in the treatment of bipolar depression. While lamotrigine is not FDA-approved for the acute treatment of depression, this approach is worthy of consideration, and could be of immediate clinical use. It provides an alternative to adding a unimodal antidepressant, which recent meta-analyses have indicated is not effective and may increase switches into mania, cycle acceleration, or treatment resistance in patients with bipolar disorder.

ECT Versus Drug Therapy for Bipolar Depression

Electroconvulsive therapy is often considered a primary treatment option for patients with severe bipolar disorder that has resisted pharmacological treatment. Researcher Helle K. Schoeyen and colleagues recently published the first randomized controlled trial comparing ECT (in this case right unilateral brief pulse ECT) with algorithm-based pharmacological treatment in 76 patients with treatment-resistant bipolar depression. The study is found in the *American Journal of Psychiatry*.

The response rate was significantly higher in the ECT group (73.9%) than in the patients who received drug treatment (35.0%). However, the two treatment groups had similarly low remission rates (34.8% for ECT and 30.0% for pharmacological treatment).

The algorithm-based pharmacological treatment used in the study was based on a sequence of treatments endorsed by researchers Frederick K. Goodwin and Kay Redfield Jamison in their 2007 book *Manic-Depressive Illness*. A selected treatment was chosen for each participant based on his or her medical history. If the first treatment was ineffective or intolerable, the patient would be switched to the next treatment option. Antipsychotics, antidepressants, anxiety-reducing drugs, and hypnotics were some of the other treatments included in the algorithms.

Patients in the study had previously showed a lack of response to at least two different antidepressants and/or mood stabilizers with documented efficacy in bipolar disorder (lithium, lamotrigine, quetiapine, or olanzapine) in adequate doses for a period of 6 weeks (or until they quit because of side effects).

Editor's Note: Even when ECT is effective, there is the issue of how to maintain that good response. We previously reported that in a 2013 study by Axel Nordenskjöld et al. in the Journal of ECT, *intensive followup treatment with right unilateral brief pulse ECT combined with pharmacotherapy was more effective than pharmacology alone at preventing relapses. Patients who improved after an acute series of ECT (three times/week) then received weekly ECT for six weeks and every two weeks thereafter, totaling 29 ECT treatments in one year.*

Other studies of more intermittent continuation ECT have not proved more effective than medication. Thus high intensity right unilateral brief pulse ECT is one option for extending the effects of successful ECT.

Bipolar Network News

Editor-in-Chief: Robert M. Post, MD
Managing Editor: Moira McCauley

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Send any comments or suggestions to:
mccauleybcn@gmail.com

BNN
5415 W. Cedar Lane
Suite 201B
Bethesda, MD 20814

To subscribe or unsubscribe, see our website or email us at:

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More Data on Memantine for Treatment-Resistant Depression

In 2012 we reported on an open study by Athanasios Koukopoulos and colleagues that explored whether the NMDA glutamate receptor antagonist memantine (Namenda), which is used to treat dementia, could be helpful to people with treatment-resistant bipolar disorder.

In an update of that study, the researchers, led by Giulia Serra, compared patients' symptoms during three years of treatment as usual, followed by three years with memantine added to their stable medication regime (at doses of 20–30 mg/day). **Patients improved progressively over the three years of taking memantine.**

Improvements in symptoms included decreased time ill, decreased severity of symptoms, decreased duration of new episodes, and fewer episodes per year. Memantine was particularly helpful for those patients who had had rapid or continuous cycling. Side effects were minimal.

Given the success of this open study, randomized controlled trials are needed to explore this much-needed option for people with treatment-resistant bipolar disorder.

Employment Rights for People with Bipolar Disorder

Attorney Katharine Gordon has provided some information on the legal rights of people with bipolar disorder under the ADA.

When we think of the Americans with Disabilities Act (ADA), we might think of physical modifications to buildings, expensive lawyers, and complicated trials. But this law also gives people with bipolar ways to get fair treatment in the workplace. By learning a bit about your employment rights under this law, you can focus on excelling in your chosen career, rather than being sidetracked by ignorance, stereotypes, and stigma.

Here are a few things that you may not know about bipolar disorder and the ADA:

It is now clear that people with bipolar disorder are protected under the ADA in employment. Prior to 2008, there was often a battle of the experts to prove that a person with bipolar disorder had a severe enough impairment to be protected. This discouraged many from asking for their rights to be respected under this law in the first place. Unfortunately, companies would fire people for having bipolar disorder and then, in next breath, argue that bipolar wasn't a real disability therefore it was legal to fire people for reasons related to their bipolar disorder.

This changed with the passage of the Americans with Disabilities Act Amendments Act of 2008, which made it easier to establish disability. The Equal Employment Opportunity Commission, the agency responsible for enforcing this law, has made it clear in official regulations that **bipolar disorder should generally be covered as a disability for the purposes of protection in employment**: "It should easily be concluded that the following types of impairments will, at a minimum, substantially limit the major life activities indicated:…major depressive disorder, bipolar disorder, post-traumatic stress disorder, obsessive compulsive disorder, and schizophrenia substantially limit brain function."

Job applicants should never be asked whether they have bipolar disorder (or any other disability) until a conditional offer has been made. Rather, employers are only allowed to ask these types of questions after everything else has been done, including interviews, character investigations, and reference checks. Then they can ask disability-related questions, but only if they ask this information of all people hired for this position, and if they keep the answers to these questions separate from the rest of the employee's file. For more information, see the Job Accommodations Network's resources for job seekers and the EEOC's guidance on Job Applicants and the Americans with Disabilities Act.

> "Society's accumulated myths and fears about disability and disease are as handicapping as the… limitations that flow from actual impairment."
>
> —US Supreme Court

It is usually your choice as to whether you disclose your condition once you are on the job. If you have found successful treatment for your condition and it does not impact you in the workplace, then you might find it best not to reveal this, especially because of continuing stigma against people with bipolar disorder. However, there are some limited circumstances in which disclosure may be helpful or required. This includes if your employer has a reasonable belief based on objective evidence that a disability will interfere with your ability to safely or fully perform your job. You can read more about issues of disclosure in the EEOC's *Enforcement Guidance on the Americans with Disabilities Act and Psychiatric Disabilities and Questions and Answers: Enforcement Guidance on Disability-Related Inquiries and Medical Examinations of Employees under the Americans with Disabilities Act.*

You can ask for reasonable accommodations if you think you need them. However, in this case, you will generally need to provide documentation from a health care provider about your condition. You should work with your health provider to provide documentation that emphasizes your ability to do your job fully and safely rather than inadvertently raise concerns.

The Job Accommodations Network has a very helpful guide *Employees' Practical Guide to Negotiating and Requesting Reasonable Accommodations under the Americans with Disabilities Act (ADA)*, which includes sample documentation. Its *Accommodation and Compliance Series: Employees with Bipolar Disorder* provides suggestions for accommodations that might help people with bipolar disorder maintain stamina and attention throughout the workday, stay organized, work effectively with supervisors, and handle stress and change. Medical professionals may be interested in a *Journal of the American Medical Association* article, "The Americans with Disabilities Act: Shattered Aspirations and New Hope."

Psychotherapy of Childhood and Adolescent Bipolar Disorder

At the 2014 meeting of the American Academy of Child and Adolescent Psychiatry, there was an excellent symposium on different psychotherapeutic approaches for children and adolescents with bipolar disorder and related illnesses.

Amy West of the University of Illinois at Chicago started off this symposium by describing the effectiveness of child-and family-focused cognitive-behavior therapy or what is sometimes called RAINBOW therapy. Rainbow stands for Routine, Affect regulation, I can do it, No negative thinking, Be a good friend and balance life stressors, Oh how can we solve problems, and Ways to find support.

Routine

West emphasized the importance of routine in sleep, diet, medications, and homework, and indicated that frequent soothing is necessary. Posted reminders are also helpful.

Affect regulation

Affect regulation can be encouraged by promoting coping skills, particularly around identifying what triggers mood swings and rage attacks and creating plans for dealing with them.

I can do it

This is a reminder to parents and children to focus on strengths, successes, positive feedback, and the ability to call for help.

No negative thinking

Try positive restructuring and reframing of negative perspectives. Part of this includes mindfulness training for children and parents, who are taught to focus on breathing and accepting thoughts and emotions.

Be a good friend

Focus on listening, engaging friends, and enhancing communication.

Oh, how can we solve problems?

This is a reminder to families to cultivate an attitude of problem solving.

Ways to find support

Remembering ways to find support reminds parents to connect with relevant resources, and also coaches parents to be advocates for their children.

In a randomized study of 12 sessions of child and family focused cognitive behavior therapy, the children did much better than those receiving treatment as usual and showed greater improvement in mania and depression as well as overall functioning.

The second presentation was given by Mary Fristad of Ohio State University. She treated children with bipolar disorder not otherwise specified (BP-NOS) with psychotherapy and omega-3 fatty acids. Some research had suggested the efficacy of omega-3 fatty acids in childhood mood disorders and a much larger literature was positive in adult mood disorders. Given the safety of the manipulation, she felt it was worth trying in young children and those with BP-NOS who are rarely studied formally.

Fristad also cited a 2010 study by Amminger et al. in children who were at ultra high risk for schizophrenia. In that study, patients were randomized to 12 weeks of omega-3 fatty acids or placebo, and omega-3 fatty acids were associated with a very low conversion rate to full-blown psychosis, 4.9%, compared to 27.5% for those receiving placebo.

Fristad's therapy emphasizes education, support, and skill building in order to enhance understanding of the illness and its treatment. This helps ensure better compliance and better treatment outcome. Her formal treatment manual is available at www.moodychildtherapy.com.

Fristad randomized children with bipolar not otherwise specified, average age 10.2 +/- 0.2 years to either her psychotherapy plus omega-3 fatty acids or therapy plus placebo. Therapy plus omega-3 was much more effective on most outcome measures.

Editor's Note: Given the safety of omega-3 fatty acids, even these limited data would appear to justify their use in children with BP-NOS in the context of psychotherapy and psychoeducation.

The third presenter was David Miklowitz of UCLA who discussed family focused therapy. This approach has proven effective in studies of both adults and adolescents with bipolar disorder, and as well for those with prodromal symptoms. That is, if a parent had bipolar disorder and their offspring had depression, cyclothymia, or BP-NOS, family focused therapy was more effective in treating these symptoms than treatment as usual. Family focused therapy was particularly effective in children from families with high expressed negative emotion.

Miklowitz highlighted the technical strategies useful in clinical practice in order to assist children and families to understand what precipitated the most recent symptoms or phase of illness, track moods and identify early warning signs and symptoms over time, promote consistent daily routines and sleep-wake habits, address issues relative to medication consistency including psychoeducation about the illness and the need for treatment with psychopharmacology, distinguish mood swings from developmentally-appropriate mood instability, and address difficulties in coming to accept the difficult realities of pediatric mood disorders and the functional limitations they impose.

Miklowitz also indicated that it is crucial to enhance communication within the family and to decrease levels of negative expressed emotion.

Continued on Page 5

Treating Bipolar Disorder in Children and Adolescents

Continued from Page 4

Problem-solving strategies for all of these issues are a key to success.

The last talk was given by Tina Goldstein of Pittsburgh on the use of dialectical behavior therapy for adolescents with bipolar disorder. This therapy focuses on skill building, particularly mindfulness. Skills training is also offered the areas of psychoeducation, distress tolerance, emotion regulation, and taking the middle road (looking for alternative options to either extreme).

Goldstein randomized adolescents on a two to one ratio to dialectical behavior therapy or standard psychotherapeutic treatment. All of the participants also received pharmacotherapy. **Goldstein found a much higher rate of compliance and staying in treatment in those with dialectical behavior therapy compared to routine psychotherapy. There was also a significant decrease in depressive symptoms, a doubling of time euthymic, a threefold decrease in suicidal ideation, and an improvement in behavior regulation.**

Goldstein gave some examples of how to encourage stress tolerance and help adolescents use self-soothing techniques by associating images, sounds, and smells with positive feelings and building a toolbox for using these techniques. All of these approaches were delivered in the context of 16 weeks of multifamily group treatment.

Researcher Eric Youngstrom was the discussant of the symposium and highlighted the excellence of the talks and the effectiveness of all of the psychotherapeutic approaches presented. However, he described the need to enhance availability of these techniques to the general public, noting that in his hometown of Chapel Hill, North Carolina, there were no experts who were able to deliver these techniques. He raised the issue of how delivery of these treatments could be scaled up so that they are much more widely available to the general community.

Editor's Note: At this point, parents should be aware that there are specialized types of highly effective psychotherapy for children and adolescents with full-blown bipolar disorder, its spectrum including bipolar not otherwise specified, and disorders that may develop into bipolar disorder, such as depression and cyclothymia. Appropriate therapies can be accessed through the research groups described in this article and their trainees at UCLA, Pittsburgh, Ohio State University, as well as the University of Illinois at Chicago and perhaps at other academic centers of excellence in other cities.

If families are unable to access these locations, they should continue to seek expert treatment that includes some of the core components of the psychotherapies described above. In particular, education about the illness and its treatments is crucial, as is recognizing early signs and symptoms and developing plans to address these before a major mood episode develops. In this regard, charting mood on a regular basis may be invaluable, not only to recognize mood, behavior, and sleep fluctuations, but also to evaluate the effectiveness of treatment approaches.

Mood charts can be downloaded from our website. Go to www.bipolarnews.org and click on the tab for mood charting.

Keith O'Neil: A Hero in Football and in Public Health

Keith O'Neil is a former Super Bowl champion and the founder of the Forever Foundation, an organization whose mission is to educate the public about bipolar disorder and to de-stigmatize the illness. In September he spoke at the Brain and Behavior Research Foundation (formerly NARSAD) meeting in Washington, DC.

O'Neil's life story holds many important lessons—not only about the difficulties of bipolar illness, but also about the hope of recovery. He described being six years old and experiencing high levels of anxiety and fear, and an inability to get to sleep. His mind raced and he was so irritable that he was nicknamed "The Bear."

The anxiety and the racing thoughts continued, and O'Neil became increasingly depressed. When he was 10 or 12 years old, he began to experience suicidal thoughts and searched his parents' medicine cabinet for pills he could use to commit suicide. Anxiety and depression became more prominent even though he was an "A" student, one of the most popular kids at school, and an extraordinary athlete, and had a loving family and many friends. He began to use alcohol excessively, had conduct problems, was impulsive and was always in trouble.

O'Neil excelled in football in high school, started college at Northern Arizona University, and quickly became an All-American linebacker at Penn State. He was a first-round draft pick for the New York Giants. His teammates would nap between workouts for coach Bill Parcells, but instead, O'Neil would sit and cry over his inability to sleep. When he was later picked up by the Dallas Cowboys as a free agent, he was unable to sleep for five nights.

O'Neil moved on to the Indianapolis Colts. He did not sleep for four nights before his first game, and told coach Tony Dungy that he needed help, as he did not think he could play the next day. Dungy took him seriously and had him meet with the general manager, the team doctor, and the trainer. O'Neil felt extraordinarily relieved to be able to talk about his anxiety for the first time and took some clonazepam (Klonopin) for sleep and anxiety. Although he missed his first game, he became increasingly successful and the captain of the team that three years later would go on to win the Super Bowl.

Even though he was a standout player, O'Neil was so anxious that he would get confused about the playbook and have to rehearse it over and over in order to remember. He dealt with his racing mind and his anxiety in part by funneling it into "controlled recklessness" as a football player.

O'Neil returned to the Giants for five seasons. While in New York, his wife miscarried, triggering O'Neil's first major manic episode. He felt super human, spent excessive amounts of money (bought a Rolex watch and three diamond earrings), did not need sleep, and was generally out of control. In 2010, O'Neil was diagnosed with bipolar disorder by Steven Dubovsky, one of the pioneers in the development of calcium channel blockers for the treatment of bipolar disorder.

After his manic episode, O'Neil swung into a severe 18 month–long depression, which he described as "the depths of hell." He gradually improved and started on a regimen that included medications, exercise, and relying on his family for comfort and support. He then moved to Phoenix, Arizona to start his foundation—the Forever Foundation.

The foundation provides information about the illness and promotes de-stigmatization. O'Neil visits high schools to teach students about bipolar illness and the importance of talking about anxiety and depression and getting help.

In the question and answer period following his talk, O'Neil discussed his own treatment. His early experiences with antidepressants were somewhat positive for his depression and anxiety, but may have been influential in his first manic episode. He said he is now well, and described his current medication regimen, which includes lithium, the mood stabilizing anticonvulsant oxcarbazepine (called Trileptal, which is structurally similar to carbamazepine or Tegretol), and the atypical antipsychotic aripiprazole (Abilify), which works extraordinarily well for him and which he called his savior. O'Neil occasionally uses Ambien (zolpidem) or Seroquel (quetiapine) for sleep.

O'Neil talked about the importance of confronting his own illness and adopting a positive attitude about getting treatment and doing everything he could to get well. He had a family history of mood disorders including depression in his paternal grandfather and bipolar disorder in an uncle.

O'Neil remembered that in his days as a professional football player, even though he was a standout player, he was so anxious that he would get confused about the playbook and have to rehearse it over and over in order to remember. He felt that he dealt with

Continued on Page 7

Lessons from Keith O'Neil's Struggle and Recovery from Bipolar Disorder

Continued from Page 6

his racing mind and his anxiety in part by funneling it into "controlled recklessness" as a football player.

Keith O'Neil received a standing ovation from the gathering of scientists and approximately 150 supporters of the Brain and Behavior Research Foundation .

It is noteworthy that after Keith's presentation, many of the scientific presenters speaking about the latest advances in the understanding and treatment of anxiety disorders in children, depression, and bipolar disorder directly referred to his life story and the important messages embedded in it.

One example is the high family burden of illness. In the United States, first episodes of bipolar disorder begin in childhood (before age 13) a quarter of the time and in adolescence (before age 19) two-thirds of the time. More patients in the US compared to Europe have a family history that includes not only bipolar disorder but also many other psychiatric illnesses such as depression and substance abuse comorbidity. Grandparents of US versus European patients also have more mood and other disorders. The total family history burden of disorders in parents and grandparents is directly related to an earlier age of onset in patients with bipolar disorder.

Another example is O'Neil's early experience of the illness and his personal traits. High levels of anxiety and insomnia are often early precursors to bipolar disorder. Individuals with bipolar disorder are often extremely smart, "A" students in school, and creative. The illness in adolescents and children is often not recognized or diagnosed for 10 to 15 years or more.

Another example is O's'Neil symptoms. Suicidal ideation is common, and suicide attempts occur in about 40% of individuals with bipolar disorder. Use of alcohol and other substances of abuse is very common. Getting help for these addictions is important to getting well and staying well. Racing thoughts in an otherwise classical depression is often associated with either non-response to antidepressants or an increased risk of switching into mania on them. Severe unrelenting depression often follows a manic episode. Depression and anxiety can impair learning and memory.

O'Neil's treatment also has similarities with many patients'. Recognizing the need for medications is a key to recovery. Requiring multiple drugs in combination in order to achieve and maintain remission is typical in the treatment of bipolar disorder. Eliciting and receiving support by family, friends, and others is an important component in fighting the illness. A positive approach to the illness, i.e. doing everything one can to ameliorate symptoms, is another key to getting well and staying well.

Being a role model, i.e. achieving great success in one's profession even with the extraordinary adversities of bipolar illness is a great personal accomplishment and important public health message. Active work to de-stigmatize the illness, and helping young people to recognize psychiatric illness, talk about it, and get help can be life saving.

Being attentive to risk factors, such as family members' histories of mood disorders, may heighten awareness of illness in childhood and shorten the time to first treatment.

Differences in Depressive Episodes Across Bipolar I, II, and Major Depression

In a recent retrospective study, people with bipolar I disorder, bipolar II disorder, and major depressive disorder were interviewed about a 14-year period of their illness, and several differences emerged.

People with bipolar I disorder described their illnesses as including more psychomotor retardation (slowing of movements) and more psychotic features. People with bipolar II disorder had more mixed states than both people with major depression and people with bipolar I disorder. They also had less psychomotor slowing than people with bipolar I disorder.

Another purpose of this study by Andrew Frankland and colleagues in the *Journal of Clinical Psychiatry*, was to determine the effectiveness of the Probabalistic Approach to Bipolar Disorder, a statistical method for differentiating diagnoses. The approach was successful in differentiating both bipolar subtypes from major depression, but not in differentiating between the bipolar subtypes.

Ambiguity in the Data on Omega-3 Fatty Acids for Depression

In a recent randomized, controlled clinical study comparing two types of omega-3 fatty acid supplements (one with EPA and one with DHA) with placebo in 196 adults with major depression, there were no statistically significant differences in outcomes across the three groups. The participants received the treatments for eight weeks, and response and remission rates were 40-50% in those receiving either omega-3 preparation (at doses of 1000mg/day) and 30% for placebo. The research was published by David Mischoulon and colleagues in the *Journal of Clinical Psychiatry*.

Transgenerational Transmission of Drug Exposure and Stress in Rodents

New data suggest that there can be transgenerational transmission of the effects of drug exposure and stress from a paternal rat to its offspring. The father mates with a female who was not exposed to drugs or stress, and the father has no more contact with the offspring. Consensus is now building that the effects of the father's drug exposure on the offspring occur via epigenetic alterations to his sperm.

Epigenetic alterations are those that are mediated by chemical changes in the structure of DNA and of the histones around which DNA is wrapped. These changes do not alter the inherited gene sequences but only alter how easy it is for genes encoded in the DNA to be activated (transcribed) or suppressed (inhibited).

There are three common types of epigenetic modifications. One involves the attachment of a methyl or acetyl group to the N-terminals of histones. Methylation typically inhibits transcription while acetylation activates transcription. Histones can also be altered by the addition of other compounds. The second major type of epigenetic change is when the DNA itself is methylated. This usually results in inhibition of the transcription of genes in that area. The third epigenetic mechanism is when microRNA (miRNA) binds to active RNA and changes the degree to which proteins are synthesized.

At a recent scientific meeting, researchers described the various ways epigenetic changes can be passed on to future generations.

Researcher Chris Pierce reported that chronic cocaine administration increased brain-derived neurotrophic factor (BDNF) in the medial prefrontal cortex of rats. (BDNF is important for learning and memory.) The cocaine administration led to acetylation of the promoter for BDNF.

This exposure to cocaine in male rats who then fathered offspring led to two changes in the offspring, presumably conveyed by epigenetic changes to the fathers' sperm. The first change was a decrease in cocaine reinforcement. The offspring took longer to acquire a cocaine self-administration habit. The second change was long-lasting learning deficits in the male offspring, specifically recognition of novel objects. The deficit was associated with a reduction in long-term potentiation in the offspring. Long-term potentiation is the strengthening of synapses that occurs through repeated patterns of activity. Surprisingly, the following generation also showed deficits in learning and memory, but did not show a loss of long-term potentiation.

Editor's Note: These data indicate that alterations in sensitivity to cocaine (in this case slower acquisition of cocaine self-administration) can be transferred to a later generation, as can learning deficits in males. These data suggest that fathers' experience of drugs can influence cocaine responsiveness and learning via epigenetic mechanisms likely mediated via epigenetic changes to the father's sperm.

This research suggests the possibility that, in a human clinical situation, there would be three ways that a father's drug abuse could affect his child's DNA. First, there is the traditional genetic inheritance, where, for example, an increased risk for drug abuse is passed on to the child via the father's genetic code. Next, drug abuse brings about epigenetic changes to the father's sperm. (His genetic code remains the same, but acetyl groups attach to the BDNF promoter section of his DNA, changing how those proteins get produced.) Lastly, if the father's drug abuse added stress to the family environment, this stress could have epigenetic effects on the child's DNA.

Researcher Alison Rodgers described how epigenetic changes involving miRNA in paternal rats influence endocrine responsivity to stress in their offspring. Rodgers put rats under stress and observed a decrease in hormonal corticosterone response to stress. When a father rat was stressed, nine different miRNAs were altered in its sperm. To prove that this stress response could be passed on transgenerationally via miRNAs, the researchers took sperm from an unstressed father, loaded it with one or all nine miRNAs from the stressed animal, and artificially inseminated female rats. Rodgers found that the sperm containing all nine miRNAs, but not the sperm carrying one randomly selected miRNA, resulted in offspring with a blunted corticosterone response to stress.

Researcher Eric Nestler showed that when a rodent goes through 10 days of defeat stress (being defeated repeatedly by a larger animal), they begin to exhibit behaviors resembling those seen in depression. Social avoidance was the most robust change, and continued for the rest of the animal's life. Animals did not have to be physically attacked by the bigger animal to show the depression-like effects of defeat stress. Just witnessing the repeated defeats of another rat was sufficient to produce the syndrome. Again, father rats that experienced defeat stress or witnessed it passed this susceptibility to defeat stress on to their offspring (with whom they never had any contact), likely by epigenetic changes to sperm.

Editor's Note: People take genetic vulnerability seriously, and doctors counsel families with bipolar disorder to be on the lookout for symptoms and engage in preventive measures as necessary (just as a family with a history of heart disease or breast cancer might increase vigilance and preventative measures). The risks of psychiatric illness through epigenetic mechanisms should be taken equally seriously, and families should consider preventive interventions as needed.

Continued on Page 9

Transgenerational Transmission of Drug Exposure and Stress in Rodents

Continued from Page 8

The evidence for epigenetic inheritance has profound clinical implications, if it is found that similar epigenetic mechanisms occur in humans. Earlier research indicates that maternal behavior can bring about long-term changes in offspring behavior and biology. Anxiety and stressors in a mother can bring about epigenetic changes to eggs, and can also affect a fetus in utero. Now it appears that a father's sperm can also convey information about the fathers' drug use or experience of stress to subsequent generations.

Now we know that life experiences of parents can also affect their offspring through epigenetic changes to genetic material.

In the US, the parents and grandparents of patients with bipolar disorder are more ill than the parents and grandparents of patients with bipolar disorder from the Netherlands and Germany. Family histories in the US include more unipolar depression, bipolar disorder, alcohol and substance abuse, suicide attempts, and other psychiatric illnesses, and a family history that includes these illnesses is associated with an earlier age of onset of bipolar disorder and a more difficult course of illness. Patients with bipolar illness in the US also reported more of these difficulties (excepting suicide attempts) in their children than patients with bipolar disorder in the Netherlands and Germany reported about their children.

Thus, we have seen four generations (patients plus their grandparents, parents, and children) with more cases of bipolar illness and more severe illness in those from the US compared to the Netherlands and Germany. It is likely that that this illness burden is conveyed through both genetic and epigenetic mechanisms.

These data also suggest that future generations in the US are at increased risk for illness complexity, and that we should take these clinical findings seriously and try to head off the early development of bipolar disorder with new approaches to treatment and prevention. This is a clinical and public health necessity, and one with a sense of immediacy.

On a more speculative and preliminary note, the conveyance of information transgenerationally via epigenetic marks in sperm raises a potential ameliorative approach for consideration. Should people consider harvesting and freezing their sperm when they are young adults?

The offspring of older fathers are at greater risk for some illnesses such as autism and bipolar disorder. It has long been though that mutations in sperm increase as a result of the aging process, but the current data raise the possibility that an accumulation of environmental factors (such as stressors) causing epigenetic alterations could also play a role.

Women who want to delay childbearing sometimes freeze their eggs when they are young (and eggs are more plentiful and likely to be viable). Perhaps younger men should also consider storage of their sperm for later use. In this way, the number of mutations from aging would be reduced, but so might the influence of epigenetic alterations. This might also be particularly appropriate for consideration in men who will undergo the pernicious effects of chemotherapy for cancer or even in those who will be deployed to high risk war zones where they could be exposed to traumatic experiences resulting in PTSD (which also conveys an increased risk for alcohol and substance abuse). Preserving sperm for later use might help prevent not only mutations that occur with aging, but also adverse epigenetic marks that could accumulate over time.

HDAC Inhibitors Treat Mania-Like Symptoms in Mice

Mice with a particular genetic mutation affecting circadian rhythms exhibit symptoms that resemble those of human mania: disruption of sleep and wake cycles, hyperactivity, and reduced anxiety and depression. It has been found that these behaviors can be normalized by inhibiting a type of enzyme called histone deacetylases (HDACs). **HDACs bring about epigenetic changes to gene transcription by removing acetyl groups from histones, the structures around which DNA is wrapped**. Removal of the acetyl group tightens the structure of the DNA, making it more difficult to transcribe. The drug valproate (trade name Depakote) is one type of HDAC inhibitor. It prevents the removal of the acetyl groups, loosening the structure of the DNA, making it easier to transcribe.

A recent study by Ryan Logan and colleagues compared the effects of valproate and other HDAC inhibitors on mice with a mutation in the Clock delta 19 gene, which causes mania-like symptoms. Valproate and the HDAC inhibitor SAHA both normalized the mice behavior. MS275, another HDAC inhibitor that targets only class I HDACs, also normalized the behaviors. The researchers were able to determine that all of these treatments targeted a specific class I HDAC called HDAC2, which has been implicated in schizoaffective and bipolar disorders.

These data link epigenetic mechanisms (HDAC inhibition) to the antimanic effects of valproate in this animal model of mania. It appears that maintaining the presence of acetyl groups on histones has antimanic effects in mice with a mutation in the Clock delta 19 gene.

Lithium Extends Anti-Depressant Effects of Ketamine in Mice

While it can sometimes take weeks for the effects of antidepressant treatments to appear, intravenous ketamine can produce antidepressant effects in as little as two hours. However, ketamine's effects fade after three to five days. New animal research by Chi-Tso Chiu and colleagues explores whether adding lithium to ketamine treatment can produce more sustained antidepressant effects.

Mice who are restrained by being placed in a tube for several hours (chronic restraint stress) exhibit a behavioral and neurochemical profile that resembles human depression. **When Chiu and colleagues pretreated these stressed mice with sub-therapeutic doses of lithium (600 mg/L) in their drinking water for several weeks, a sub-therapeutic dose of ketamine (2.5 mg/kg of body weight) was enough to produce robust antidepressant effects in the mice, while neither drug alone was effective at these doses.**

The combination of ketamine and lithium also restored the density of spines on the dendrites of neurons in the medial prefrontal cortex. Post-treatment with lithium (1200 mg/L) for several weeks was also successful in extending the effects of a single (50 mg/kg) ketamine injection.

Both lithium and ketamine affect the intracellular signaling pathway mTOR. Ketamine activates the pathway, increasing levels of synaptic proteins and dendritic spine density. It also increases brain-derived neurotrophic factor (BDNF) and the BDNF receptor TrkB. BDNF is important for learning and memory.

When lithium was added to the treatment of the mice with ketamine, the mTOR and BNDF pathways were further activated. Lithium also inhibits the receptor GSK-3, supporting ketamine's rapid-acting antidepressant effects.

Ketamine treatment can produce oxidative stress, in which toxic free radicals can endanger cells, and the addition of low doses of lithium also completely prevented this neurochemical side effect.

Chiu and colleagues hope that the findings of this study in mice can eventually be applied to research in humans in the hopes of finding a clinical option that would sustain the rapid-onset antidepressant effects of ketamine for the long term.

If You Are Depressed After a Heart Attack, Treat the Depression

Depression is common following heart attacks, and it can complicate recovery. A recent study by Jae-Min Kim and colleagues investigated the safety of treating depression with escitalopram in people recovering from acute coronary syndrome. In a 2015 article in the Journal of Clinical Psychiatry, they reported that 217 people with depression and acute coronary syndrome were randomized to receive either escitalopram (in flexible doses ranging from 5–20 mg/day) or placebo for 24 weeks. **Patients who received escitalopram saw more improvement in their depression on a variety of scales,** and also showed improvements in social and occupational functioning. There were no adverse cardiac effects from escitalopram, though some people taking it did experience dizziness.

Atypical Antipsychotic Lurasidone Normalizes a Gene Important in Circadian Rhythms

Disruptions to circadian rhythms are common in mood disorders, leading some researchers to believe that normalizing these daily rhythms may improve the illnesses. Several genes, called CLOCK genes, are implicated in circadian rhythms. In animal studies, researcher Marco Riva and colleagues are examining the expression of CLOCK genes in different brain regions as a result of chronic stress that is meant to produce behaviors resembling human depression.

Male rats were exposed to chronic mild stress for two weeks, and divided into those that were susceptible to stress (identified by their loss of interest in sucrose) and those who were not. Then the rats were randomized to receive either a placebo treatment or 3 mg/kg/day of the atypical antipsychotic lurasidone (trade name Latuda), which has been effective in bipolar depression, during five more weeks of the stress procedure.

The researchers observed the expression of CLOCK genes Clock/Bmal1, Per1, Per2, Cry1, and Cry2. In susceptible rats, the chronic mild stress decreased the clock genes Per1, Per2, and Cry2 in the prefrontal cortex. **Lurasidone reversed these CLOCK gene abnormalities and the rats' depression-like behaviors**, which may explain some of the drug's efficacy in bipolar depression.

Editor's Note: Lurasidone is also a potent inhibitor of 5HT7 serotonin receptors, an effect that has been linked to antidepressant efficacy. Lurasidone also increases brain-derived neurotrophic factor (BDNF), which is important for learning and memory, and prevents stress from decreasing BDNF. Now it seems that lurasidone's normalization of CLOCK genes may be another mechanism that explains the drug's antidepressant effects.

To Investigators or Clinicians in Bipolar Disorder,

We are reaching out to you to let you know about a new study that the Bipolar Collaborative Network is implementing called the Child Network. Our goal is to **foster collective knowledge about childhood bipolar and other disorders by acquiring data about children who have or may be vulnerable to childhood-onset mood and bipolar disorders and associated conditions**. Depressive, oppositional, and bipolar disorders as well as anxiety in very young children have not been well studied for their course and for treatment effectiveness and tolerability. Our goal is to compile and analyze the varied treatments for children with these disorders. How well a child responds to a specific treatment may provide new preliminary information of use to others, and assist parents and physicians in assessing treatment options.

The Child Network is specifically for parents of children ages 2 to 12 who have few symptoms, minor (prodromal) symptoms, or the full onset of their illness, including bipolar disorder, prior to age 13. We also seek parents who have been diagnosed with a bipolar disorder to rate their own children who are genetically at higher risk for a mood disorder but as yet display no symptoms. A small percent of these children may eventually develop an anxiety, depressive, or bipolar disorder in childhood. It is estimated from several studies that more than ¼ of adults in the United States with a confirmed diagnosis of bipolar disorder experienced a very early onset in childhood (before age 13). However, many of these individuals did not receive treatment for their illness for 10-15 years following initial onset of the illness, and this delay was associated with a more difficult course of illness.

Participating in the Child Network will primarily involve a weekly ten-minute parental assessment of their child, as well as confidential disclosure of medications and other treatments and any side effects that occur in the prior week. There will also be a short demographics questionnaire and a once a year more detailed symptom checklist. This study does not involve treatment. The network is only meant to document what is currently being done in the community. The child of participating parents will continue to be treated according the child's physician's preferences. Studies in this network will not involve randomized or controlled clinical trials or use of placebo, but rather will examine what agents and their combinations that children are already taking are effective, and for which children.

We believe that this network will also benefit its participants. Parents will be able to print out results of the ongoing brief weekly ratings in a graphic form so that the course of the child's symptoms can easily be visualized. Also, although family members already have access to general information provided in the Bipolar Network News (BNN), participation in this study may help attune parents to the complexities of treatment and engender more careful reading of the BNN and other literature.

We hope that this brief description of the Child Network study helps to orient you to its purpose and that your organization will pass on our introductory remarks to your members. We also encourage you and parents to visit www.bipolarnews.org and click on the tab for Child Network to learn more about the Child Network and to access the informed consent documents.

Thank you for your time.

Robert M. Post, MD and Michael Rowe, PhD
Bipolar Collaborative Network , and
Robert L. Findling, MD, MBA, Principal Investigator

This research study is IRB approved by the Johns Hopkins University School of Medicine
Principal Investigator: Robert L. Findling, MD, MBA IRB Study #00026940

BNN
PO Box 18
Beltsville, MD 20704-0018

ADDRESS SERVICE REQUESTED