

Bipolar Network News

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New Research on Ketamine

The drug ketamine can produce antidepressant effects within hours when administered intravenously.

Finding an Appropriate Control

Comparing ketamine to placebo has challenges because ketamine produces mild dissociative effects (such as a feeling of distance from reality) that are noticeable to patients. At the 2013 meeting of the Society of Biological Psychiatry, James W. Murrough and collaborators at the Mount Sinai School of Medicine reported their findings from the first controlled trial of intravenous ketamine in depression that uses an active control, the short-acting benzodiazepine midazolam, which has sedative effects and decreases anxiety, but is not known as an antidepressant. On virtually all measures intravenous ketamine was a more effective antidepressant following 2 infusions per week.

These data help dispel one of the criticisms of intravenous ketamine, that studies of the drug have not been sufficiently blinded (when patients and medical staff are kept from knowing which patients receive an active treatment and which are in the placebo control group) and that the lack of an appropriate active placebo contributed to the dramatic findings about ketamine's antidepressant effects. It now appears that these criticisms have been appropriately answered and that intravenous ketamine is highly effective not only in comparison to placebo but also to an active comparator.

This research was presented as a poster at the meeting and published

as abstract #442 in the meeting supplement to the journal *Biological Psychiatry*, Volume 73, Number 9S, and was also published in the *Archives of General Psychiatry* in 2013.

Slowing Down Ketamine Infusions to Reduce Side Effects

Ketamine is commonly given in 40-minute intravenous infusions. Timothy Lineberry from the Mayo Clinic reported in Abstract #313 from the meeting that slower infusions of ketamine over 100 minutes were also effective in producing antidepressant effects in patients with treatment-resistant depression. Lineberry's research group used the slower infusion in order to increase safety and decrease side effects, such as the dissociative effects discussed above. In the 10 patients the group studied, they observed a response rate of 80% and a remission rate of 50% (similar to ketamine's effects with 40-minute infusions).

Ketamine Acts on Monoamines in Addition to Glutamate

Ketamine's primary action in the nervous system is to block glutamate NMDA receptors in the brain. In addition to its effects on glutamate, it may also affect the monoamines norepinephrine and dopamine. Kareem S. El Iskandarani et al. reported in Abstract #333 that in a study of rats, ketamine increased the firing rate of norepinephrine neurons in a part of the brain called the locus coeruleus

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and also increased the number of spontaneous firing dopamine cells in the ventral tegmental area of the brain.

Editor's Note: These data showing that ketamine increased the activity of two monoamines could help explain ketamine's ability to induce rapid onset of antidepressant effects, in addition to its ability to immediately increase brain-derived neurotrophic factor (BDNF, important for long-term memory and the creation of new synapses) and to restore healthy mushroom-shaped spines on the dendrites of neurons in the prefrontal cortex.

Family or Personal History of Alcohol Dependence Predicts Positive Response to Ketamine in Depression

Mark J. Niciu and collaborators at the National Institute of Mental Health reported in Abstract #326 that a personal or family history of alcohol dependence predicted a positive response to IV ketamine in patients with unipolar depression.

Drugs that Antagonize the Glutamate NMDA Receptor are a New Approach to Antidepressant Treatment

Several antidepressant drugs work by blocking activity at the NMDA receptor for the excitatory neurotransmitter glutamate. These drugs include intravenous ketamine, a potent NMDA receptor blocker that can produce antidepressant effects within 2 hours of administration, and memantine (Namenda), which is less potent, acts more slowly, and can potentiate the antidepressant effects of lamotrigine and help stabilize mood in patients with treatment-resistant

bipolar disorder. Now a drug with a related mechanism, D-cycloserine, has been shown to have antidepressant effects. **High doses of D-cycloserine act as an antagonist at the glycine site of the NMDA receptor, blocking glycine's ability to facilitate glutamate transmission through the receptor.**

Glutamate is the major excitatory neurotransmitter in the brain and is important for the development of long-term memory. However, glutamate overactivity may contribute to depression. Decreasing this overactivity with the drugs noted above appears to produce antidepressant effects.

Uriel Heresco-Levy et al. reported in a 2013 article in the *Journal of Neuropsychopharmacology* that high

doses of D-cycloserine (1000mg/day) had substantially greater antidepressant effects than placebo in a study of 26 patients with treatment-resistant depression. The drug was well tolerated.

Interestingly, low doses of the same drug have a different effect, acting as a partial agonist at the same site, facilitating glutamate transmission and enhancing the new learning that is necessary in cognitive behavioral therapy for anxiety disorders.

Editor's Note: D-cycloserine requires further study in larger controlled trials, but this small study suggests promise. While ketamine's effects are rapid in onset, they are also difficult to sustain. This study suggests a possible route to a slower onset with longer-lasting antidepressant effects.

Bipolar Network News

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

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.

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

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

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

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

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Psychotherapy Prevents Recurrence of Unipolar Depression

New research shows that **psychotherapy lowers the risk of relapse in unipolar major depression more than "treatment as usual" does, and also heads off depression in children at high risk.**

At the 2013 meeting of the American Psychiatric Association, researcher Pim Cuijpers reviewed 32 trials of cognitive behavior therapy, intensive behavioral therapy, and problem solving therapy used for the prevention of depression and found that these therapies were associated with a 21% lower risk of relapse compared to treatment as usual.

There were five critical elements that made these therapies useful: they supported coping with depression, and they included exercise, mindfulness, internet-based cognitive behavior therapy, and problem solving.

Among those who presented at the meeting, Greg Clarke of Kaiser

Permanente, Oregon discussed an 8-week course on coping with stress given to a group of adolescents (aged 14 to 16) who had four times the normal risk of developing depression because each had a parent with depression. Clarke found a significant reduction in depression among the adolescents who received therapy compared to controls.

Insomnia can be a precursor to a first depression or to recurrent depression. Cognitive behavior therapy was more effective in improving sleep than a comparative sleep hygiene course.

Researcher Judy Garber presented data showing that cognitive behavior therapy was effective in 13- to 17-year-olds who had a parent with depression and had themselves had a prior depression or were currently sub-syndromal. The effect of the therapy was only significant if the parent was not depressed at intake.

FDA Approves Lurasidone for Bipolar Depression

Last year the *BNN* summarized two presentations from the 2012 meeting of the American Psychiatric Association showing the antidepressant efficacy of the atypical antipsychotic lurasidone (Latuda) in bipolar depression. Lurasidone was more effective than placebo both when prescribed alone (monotherapy) and when prescribed as an add-on to the mood stabilizers lithium or valproate.

In June 2013, the Federal Drug Administration (FDA) approved lurasidone as both a monotherapy and as an adjunctive therapy with lithium or valproate for bipolar depression. Previously the only FDA-approved agents for bipolar depression were the atypical antipsychotic quetiapine (Seroquel) and the combination of the atypical antipsychotic olanzapine and fluoxetine.

Lurasidone's precise role in therapeutics remains to be explored, but its side effects profile is of particular interest, as it appears to be less sedating than the other atypical antipsychotics noted above. It also appears to have fewer side effects in the realm of weight gain, cholesterol or triglyceride increases, and increases in blood sugar and insulin resistance.

New Drug for Insomnia Shows Promise

The Federal Drug Administration (FDA) review committee suggested that a new type of drug for the treatment of insomnia might be approved in the future if the company who produces the drug, Merck, begins manufacturing it in smaller doses.

The drug, suvorexant, works differently from most sleep medications. Instead of creating sleepiness, it blocks a type of neurotransmitters called orexins, which are responsible for wakefulness. (Suvorexant is a selective antagonist of orexin receptors OX1R and OX2R and

More Evidence That Regular Antidepressants Do Not Work in Bipolar Depression

Psychiatrists most commonly prescribe antidepressants for bipolar depression, but mounting evidence shows that the traditional antidepressants are not effective in bipolar disorder. At the 2013 meeting of the American Psychiatric Association, researcher Jessica Lynn Warner reported that among 377 patients with Bipolar I Disorder who were discharged from a hospital, **those who were prescribed an antidepressant at discharge were just as likely to be remitted for a new depression than those not given an antidepressant.**

The average time to readmission also did not differ across the two groups and was 205 +/- 152 days. Those patients prescribed the serotonin and norepinephrine reuptake inhibitor (SNRI) drug venlafaxine (Effexor) were three times more likely to be readmitted than those not prescribed antidepressants.

These naturalistic data (generated from observations of what doctors normally do and information in the hospital's clinical notes) resemble those from controlled studies. In the most recent meta-analysis of antidepressants in the treatment of bipolar depression (by researchers Sidor and MacQueen), there appeared to be no benefit to adding antidepressants to ongoing

treatment with a mood stabilizer over adding placebo. Randomized studies by this editor Post et al. and Vieta et al. have shown that venlafaxine is more likely to bring about switches into mania than other types of antidepressants such as bupropion or selective serotonin reuptake inhibitors (SSRIs).

In addition, a naturalistic study published by this editor Post et al. in the *Journal of Clinical Psychiatry* in 2012 showed that the number of times antidepressants were prescribed prior to a patient's entrance into a treatment network (the Bipolar Collaborative Network) at an average age of 40 was related to their failure to achieve a good response or a remission for a duration of at least six months during prospective treatment.

Editor's Note: Antidepressants are still the most widely used treatments for bipolar depression, and their popularity over more effective treatments (mood stabilizers and some atypical antipsychotics) probably contributes to the fact that patients with bipolar disorder receiving typical treatment in their communities spend three times as much time in depressions than in manic episodes. Using other treatments first before an antidepressant would appear to do more to prevent bipolar depression. These treatments include mood stabilizers (lithium, lamotrigine, carbamazepine, and valproate); the atypical antipsychotics that are FDA-approved for monotherapy in bipolar depression, lurasidone (Latuda) and quetiapine (Seroquel); and the combination of olanzapine and fluoxetine that goes by the trade name Symbiax.

Evidence from several sources suggests that the SNRI venlafaxine may be a risk factor for switches into mania and lead to re-hospitalizations. Other data suggest that in general, in bipolar depression, augmentation treated with antidepressants should be avoided in several cases: in childhood-onset bipolar depression, in mixed states, and in those with a history of rapid cycling (4 or more episodes per year).

Important Reminders from an APA Symposium on Bipolar Disorder

Our editor Robert M. Post served as discussant at a symposium on special topics in bipolar disorder at the 2013 meeting of the American Psychiatric Association. Here are some of the findings that were presented at the symposium.

Michael Gitlin of the University of California, Los Angeles (UCLA) emphasized the **importance of treating patients until remission** in order to achieve functional recovery and prevent cognitive impairment.

Michael Bauer of Dresden, Germany reviewed data showing that **early onset of the illness and long delays to first treatment are important predictors of poor response to treatment**.

Mark Frye of the Mayo Clinic discussed the promise of pharmacogenomics to aid in the selection of the best medicine for a given individual (i.e. **personalized medicine**). Currently the presence of one of a few relatively rare gene variations – HLA-B 1502 (in Asian populations) and HLA-A 3101 (in European populations) – can

predict that an individual may develop a severe rash when taking the anticonvulsant carbamazepine.

Researcher J. Rybakowski has found that a somewhat common variant in the gene responsible for producing brain-derived neurotrophic factor (the val-66-met allele for proBDNF) is associated with a good response to lithium. This may be explained by the fact that lithium increases BDNF, and this could be crucial in those with the val-66-met allele, which functions less efficiently than the more common and better functioning allele val-66-val.

David Miklowitz, also of UCLA, reviewed data that strongly indicates **psychotherapy is effective** in the treatment and prevention of bipolar depression. He and Kiki Chang of Stanford University found that family focused therapy (FFT) was effective in treating early syndromes that sometimes lead to bipolar disorder (including depression, anxiety, or BP-NOS) in children at high risk for bipolar disorder because of a family history that includes bipolar disorder in a first degree relative.

There are 8 key ingredients to family focused therapy (see box below).

In his own discussion, Post emphasized several points from each presentation. Among these was the recommendation by both Gitlin and Bauer that patients use a **personal calendar** to monitor symptoms and side effects. (We offer an easy download of a personal calendar on our website, www.bipolarnews.org.)

Post also endorsed Bauer's emphasis on the need for **early intervention**, since delay to first treatment is an independent risk factor for a poor outcome in adulthood. (This finding has been replicated in three studies -- Franchini et al. in 1999, Post et al. in 2010, and Drancourt et al. in 2012.

Each of these factors and family focused therapy need greater attention in the US, since Post noted that **all aspects of bipolar disorder are more difficult for patients in the US compared to those in Germany, the Netherlands, and many other European countries**. About two-thirds of the adults with bipolar disorder in the US had onset of the illness before age 19, while in most European countries, only about one-third of adult patients had an early onset.

These data are also consistent with the low incidence of bipolar disorder in children at high risk for the disorder because of a parent with bipolar disorder in studies from the Netherlands, Switzerland, and Germany. In contrast, similar studies of children with at least one parent diagnosed with bipolar disorder in the US (by Chang et al., Nurnberger et al., Wozniak et al., and Birmaher et al.) show a higher incidence of the illness. Canadian studies by Duffy et al. and studies of an isolated Amish community in

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Components of Family Focused Therapy

For treating depression, anxiety, and bipolar disorder not otherwise specified (NOS) in children who have a first-degree relative with bipolar disorder)

1. Consistent monitoring of the illness and developing an early warning system with a plan for responding if early symptoms emerge
2. Stress management
3. Development of a relapse prevention plan
4. Emphasis on sleep hygiene and the importance of regular sleep patterns
5. Work on medication adherence
6. Development of self-regulatory skills
7. Improvement of family relationships
8. Avoidance of substances of abuse.

Treating Bipolar Disorder As A Family Illness

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Pennsylvania by Egeland et al. show a low incidence much like in Europe.

Given the great need for care of children with signs of bipolar disorder in the US and the shortage of child psychiatrists and pediatricians knowledgeable about bipolar disorder, Post recommended that in the absence of other alternatives, adult psychiatrists of parents with bipolar disorder who have children with the disorder should fill this gap by treating the children themselves. If the child has only early symptoms, family focused therapy as described by Miklowitz above would be recommended.

See the two tables on this page for some options for physicians treating families affected by bipolar disorder.

Possible Interventions for At-Risk Children in Addition to Family Focused Therapy

Our editor Robert M. Post recommends that in the absence of good care in the community for children at high risk for bipolar disorder because a parent has the disorder, adult psychiatrists of parents with bipolar disorder who have children with the disorder should fill this gap by treating the children themselves. If the child has only early symptoms, family focused therapy as developed by David Miklowitz would be recommended.

Here are some other suggestions in addition to family focused therapy:

1. Good Diet, Exercise, Sleep Hygiene
2. Omega-3 Fatty Acids
3. Check Vitamin D3 levels and Add Supplement if Needed
4. Melatonin for Insomnia
5. N-acetylcysteine (NAC) for Irritability (as in studies of children with autism spectrum disorders)
6. Folate for Depression and/or Elevated Homocysteine
7. Check for Evidence of Inflammation (Increased IL-6 or CRP)

An Option with Some Side Effects:

- Minocycline (an anti-inflammatory neuroprotective antibiotic)

Physicians Treating Parents with Bipolar Disorder: Ask About Their Children

1. Support Pregnant Women with Bipolar Disorder
 - A. Depression during pregnancy is more common among women with bipolar disorder than among controls--consider cognitive behavioral therapy, omega-3 fatty acids, folate, & rTMS
 - B. 52% incidence of post-partum depression (3x higher than controls)--Monitor closely and treat accordingly
2. Ask Your Affectively Ill Patients About Their Children
3. Encourage Good Diet and Exercise in These Children
4. Encourage Watchful Waiting in Families with Children at High Risk
5. If a Child becomes Symptomatic, Suggest:
 - A. Family Focused Therapy (FFT), or other Family-Based Treatment
 - B. Low-Risk Interventions Like Nutrition and Sleep Hygiene
6. If a Child Develops BP-NOS, Encourage:
 - A. Mainstream Pharmacotherapy
 - B. Increased Social Support (Family, Friends, Advocacy)
7. If a Child Develops BP-I, Encourage Ongoing Monitoring & Medication
8. If an Adolescent Becomes Manic, Educate About Substance Abuse and Attempt Primary Prevention of a Substance Abuse Disorder

Right Unilateral ECT Plus Pharmacotherapy Better Than Pharmacotherapy Alone After Successful ECT

A new study is one of the first to find that after successful electroconvulsive therapy (ECT) treatment for depression, continuation of ECT together with pharmacotherapy was superior to continuation with pharmacotherapy alone. ECT produces a seizure while a patient is under anesthesia. The treatment has been successful in acutely treating many patients with severe depression who have not responded to other treatments. The question remains how to maintain the positive acute effects of ECT for a longer duration.

The new research was published in the *Journal of ECT* in 2013 by Axel Nordenskjöld et al. Patients with unipolar or bipolar depression who improved after an acute series of ECT (usually given 3 times per week) were randomized to receive either continuing ECT plus pharmacotherapy or pharmacotherapy alone. The ECT continuation group received weekly ECT for 6

weeks and every 2 weeks thereafter for a total of 29 ECT treatments in one year. The pharmacotherapy consisted of antidepressants (98%), lithium (56%), and antipsychotics (30%). Venlafaxine (Effexor) was considered the first choice for medication, and lithium augmentation was offered to all patients (not just those with bipolar depression). Of the participants, 64% had recurrent unipolar depression, while less than 20% had bipolar depression.

Among all the patients who were randomized at the beginning of the study (the intent-to-treat cohort), **the one-year relapse rate was 61% for patients treated with pharmacotherapy alone and 32% for patients treated with the ECT plus pharmacotherapy** ($p=0.036$). Relapse rates at 6 months were 54% for the pharmacotherapy alone group and 29% for the group receiving ECT plus pharmacotherapy. Some patients required inpatient care

during the trial—36% of the patients in the pharmacotherapy alone group and 20% of those in the pharmacotherapy plus ECT group. There was no evidence of a differential effect on cognition across the two groups. (There is concern that bilateral ECT can adversely affect cognition, especially autobiographical memory, but this is not a concern with right unilateral ECT.)

Various parameters for ECT have been studied. This research used unilateral ultrabrief pulse ECT. These parameters are standard in Sweden, where the study took place, and these results are of particular interest as they differ from a US study that used bilateral ECT with treatments given more intermittently. In that study, in which response to ECT with pharmacotherapy did not differ from response to pharmacotherapy alone, ECT continuation was given in the form of 4 weekly treatments, 4 biweekly treatments and then 2 monthly treatments, and this regimen resulted in a relapse rate of 37% within 6 months (Kellner et al. 2006).

Only one other study in geriatric patients who were psychotically depressed showed superiority of continuation ECT.

Editor's Note: The take-home message from this study may be that for patients with recurrent unipolar depression who respond positively to a course of right unilateral ultrabrief pulse ECT, continuation of regular ECT plus pharmacotherapy is worth considering over pharmacotherapy alone. While direct comparative studies have not been performed, it would appear reasonable to use weekly ECT for 6 weeks and then every 2 weeks thereafter for the continuation ECT treatment rather than a more intermittent series of treatments as in the studies of Kellner et al. Previous studies have shown that the addition of lithium to antidepressants is superior to antidepressants alone in the continuation phase of ECT (Sackeim et al. 2001), so having lithium in the regimen would also appear useful.

Relapse After Electro-Convulsive Therapy

While ECT is effective for patients with treatment-resistant depression, many still relapse after the treatment. Medications can prolong the period of remission, but even so, relapse rates have increased in recent decades (probably at least partly because ECT was once a standard initial treatment but is now only used with those patients with the most difficult-to-treat illnesses.) A 2013 meta-analysis by Jelovac et al. in *Neuropsychopharmacology* reviewed existing research on relapse and which medications might be able to best prolong remission after ECT.

The researchers analyzed 32 studies that each included at least 2 years of followup. In studies from the recent era in which patients received continuation treatment with medication following ECT, 51.1% of patients relapsed within a year, and the majority of those (37.7%) relapsed within the first 6 months after ECT. Among patients treated with

continuation ECT, a similar proportion (37.2%) also relapsed within 6 months of the initial ECT treatment. In randomized controlled trials, treatment with antidepressants with or without lithium following ECT halved the rate of relapse within 6 months compared to placebo.

Even with continuing intermittent ECT treatment, risk of relapse remains high, especially within the first 6 months. The authors concluded that maintenance of well being following ECT must be improved.

Editor's Note: One possibility for prolonging remission is the more intensive continuation regimen using right unilateral ultrabrief pulse ECT suggested by Nordenskjöld et al. in the Journal of ECT in 2013. Continuation treatment with a combination of ECT and medication resulted in 6-month relapse rates of 29% (compared to 54% with medication alone) and one-year relapse rates of 32% (compared to 61%).

RTMS Has Long-Term Effects in Depression

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive treatment that uses a rapidly changing magnetic field to target neurons, creating a weak electric current. It is used to treat depression, strokes, and other neurological and psychiatric conditions. At the 2013 meeting of the American Psychiatric Association (APA), researcher Linda L. Carpenter reported on new findings about the long-term effects of rTMS.

In the new research, which was led by Mark Andrew Demitrack, 307 patients with unipolar depression who had not responded well to previous antidepressant treatment were given rTMS. They were treated in 43 different

clinical practices and administered rTMS according to their evaluating physician, following Federal Drug Administration guidelines. Of the 307 patients who began the study, 264 benefited from initial treatments with rTMS, were tapered off rTMS, and agreed to participate in a one-year follow-up period, by the end of which **68% had improved and 40.4% had achieved complete remission** as measured by the Clinical Global Impressions scale for severity of illness.

However, some study participants (30.2%) had worsened by the first follow-up assessment at the 3-month mark, and rTMS had to be re-introduced.

Vagus Nerve Stimulation Covered by Medicare In Epilepsy But Not In Depression

The federal Centers for Medicare and Medicaid Services (CMS) appear to discriminate against people with psychiatric illness. They will not approve the use of VNS (Vagus Nerve Stimulation) for treatment resistant depression among Medicare beneficiaries but have approved it for refractory epilepsy.

Vagus nerve stimulation consists of electrical stimulation of the vagus, one of the cranial nerves. **The Federal Drug Administration (FDA) has already approved VNS for both illnesses, meaning that it has been judged to be effective and safe in both.**

The CMS decision will make it harder for poor patients to access this treatment because it means that Medicare will not reimburse the cost of the treatment.

Cyberonics, the company that manufactures the device used to provide VNS, applied for CMS approval of the use of VNS for depression in 2007 and was rejected, but hoped that the research collected in the intervening years that shows VNS's efficacy in treatment-resistant depression would be

enough to get eventual approval from CMS. They have been rejected again.

Editor's Note: The data supporting VNS's efficacy in epilepsy are skimpy and without a large effect size, so it cannot be argued that the quality of data supporting the coverage of VNS for depression is the reason it hasn't been approved for that purpose. Both epilepsy and depression can be devastating and life altering. To support the use and reimbursement for the same FDA-approved device for one but not the other illness seems worthy of protest.

This appears to be another example of the incongruous use of FDA approval status to deny coverage. Insurance companies and government agencies routinely use lack of FDA approval to deny reimbursement claims for many commonly used drugs and treatments, while at the same time, in cases such as the use of VNS, actual FDA approval is disregarded and considered an insufficient criterion. Having it both ways does not seem to bother the policy makers who appear to put the financial bottom line ahead of ethics, fairness, and good medical care.

A New Target for Deep Brain Stimulation (DBS) for Treatment-Resistant Depression

Deep brain stimulation (DBS) is a treatment for illnesses such as Parkinson's, chronic pain, and depression. In DBS, electrodes inserted in the brain produce electrical impulses. Different anatomical parts of the brain have been targeted successfully using DBS. These include the subgenual anterior cingulate (Area 25), the nucleus accumbens, and the habenula.

Now researcher Thomas E. Schlaepfer has found that inserting the n. accumbens electrode deeper and closer to the ventral tegmental area or the VTA (which contains dopamine cell bodies) produces more rapid onset of antidepressant effects (in a matter of days) in a high percentage of patients (7 out of 8 according to one of Schlaepfer's reports). Stimulation of the nucleus accumbens in the typical location resulted in 50% improvement in 5 out of 10 patients after one year of follow-up.

Schlaepfer believes that changing the position of the electrode places it in the medial forebrain bundle (MFB), which contains fibers going from the VTA to the nucleus accumbens. Interestingly, when animals are given the opportunity to self-stimulate this area (by pressing a lever that activates an electrode placed in the area), they will, indicating it is rewarding or pleasurable. The same animals will avoid self-stimulating certain other fiber tract sites in the brain.

Schlaepfer's research was presented at the 2013 meeting of the Society of Biological Psychiatry, and the abstract is available in the Convention Supplement to the journal *Biological Psychiatry*, Volume 73, Number 9S.

Loss of Appetite or Weight in Depressed Parents Predicts Depression in Children

Depression in a parent is one of the factors that best predicts whether a young person will develop depression. Since depression symptoms can vary greatly from person to person and some symptoms are known to be more heritable than others, new research is investigating whether a parent's profile of symptoms affects their child's likelihood of developing the illness. A 2013 study by Mars et al. in the *Journal of Clinical Psychiatry* suggests that **loss of appetite or weight in a parent with depression is the symptom that most strongly predicts new onset of depression and depressive symptoms in their offspring.**

The study observed 337 parent-child pairs. The parents (mostly mothers), who had a history of recurrent unipolar depression, ranged in age from 25–55 years, and their children ranged from 9–17 years. The study lasted four years, during which the families participated in three assessments. Parents' symptoms

were recorded and children were also assessed for symptoms or new development of depression. Thirty percent of the offspring whose parents reported weight loss or low appetite were found to have new onset of depression at followup, compared to nine percent of the offspring whose parents did not have these symptoms.

There are nine symptoms used to diagnose depression in the *Diagnostic and Statistical Manual for Mental Disorders*: low mood, loss of interest (anhedonia), loss of energy, change in appetite or weight, change in sleep, low self-esteem or guilt, suicidality, psychomotor slowing (retardation), and loss of concentration or indecisiveness. Of these, parental loss of appetite or weight was the only symptom that predicted depression in a child. Interestingly, the severity of parental depression or the presence of other health problems in the parent did not account for the emergence of illness in the children.

Adversity May Increase Risk of Mood Disorders

In adults with bipolar disorder, adversity in childhood has been associated with an earlier onset of bipolar disorder compared to those who did not experience some form of adversity such as verbal abuse, physical abuse, sexual abuse, loss of a parent, abandonment, or neglect. At the 2013 meeting of the Society of Biological Psychiatry, Nancy Low et al. reported that **the number of these stressful life events a child experienced was associated with the number of their anxiety symptoms, psychiatric disorders, and lifetime substance abuse.** Having experienced 3 or more types of adversity was associated with a 3.5-fold increased risk for developing a mood disorder and a 3-fold increase in anxiety disorders and alcohol or drug abuse.

While the study has not yet been published in a peer-reviewed journal, the abstract (#194) may be found in the meeting supplement, Volume 73, Number 9S of the journal *Biological Psychiatry*.

Editor's Note: Low's study is the first to report that childhood adversity is a risk factor for the onset of bipolar disorder in the general population.

Given the increasing evidence for the persistence of epigenetic marks on DNA and histones (which can't change the sequence of genes but can change their structure) in those who have experienced such stressors in childhood, this could provide a mechanism for the long-term vulnerability of these children to the development of mood disorders and a variety of physical illnesses.

Emotional Abuse in Childhood is a Risk Factor for Bipolar Disorder

Evidence is growing that stressful events in childhood are associated with an earlier onset of bipolar disorders and a more difficult course of illness than in those who did not experience this type of adversity. Monica Aas and colleagues in Norway have found for the first time that emotional abuse in childhood, especially before age five, also increases risk of bipolar disorder. This study indicates that while bipolar disorder has a genetic component, environmental factors also play a role.

In Norway and France, the research group surveyed patients with bipolar disorder and people in the general population about childhood trauma, including emotional abuse, sexual abuse, physical abuse, emotional neglect, and physical neglect. Among the almost 800 participants, **patients with bipolar disorder were twice as likely as control participants to have experienced multiple types of trauma.** However, emotional abuse was the only factor specifically linked to bipolar disorder. People who were emotionally abused in childhood were more than twice as likely to develop bipolar disorder in adulthood. Moreover, the more severe the emotional abuse, the more likely it was that a child would go on to develop bipolar disorder.

Among the adults with bipolar disorder, emotional abuse and sexual abuse in childhood predicted younger age of illness onset, more suicide attempts, more rapid cycling, and greater proneness to depression. Emotional or sexual abuse were linked to the most suicide attempts, and sexual abuse was linked to rapid cycling.

More trauma in childhood was also linked to affective instability in adults. Aas' research was presented at the 14th International Congress on Schizophrenia Research.

Jules Angst on the Long-Term Progressive Course of Mood Disorders

At a symposium celebrating the retirement of Willem Nolen, a researcher who spent 40 years studying unipolar and bipolar disorder, from his position at Groningen Hospital in the Netherlands, his colleague Jules Angst discussed some recent findings. Angst is perhaps the world's leading authority on the long-term course of unipolar and bipolar disorders based on his multiple prospective follow-up studies, some lasting 20-30 years.

Poverty Impacts Kids' Brain Development

In a 2013 study of children by Luby et al. in the *Journal of the American Medical Association Pediatrics*, poverty in early childhood was associated with smaller white and gray matter in the cortex and with smaller volume of the amygdala and hippocampus when the children reached school age. The effects of poverty on hippocampal volume were mediated by whether the children experienced stressful life events and whether a caregiver was supportive or hostile.

The children were recruited from primary care and day care settings between the ages of three and six, and were studied for five to ten years. They were initially assessed annually for three to six years and information on psychosocial, behavioral, and developmental dimensions were collected. Then the children took part in a magnetic resonance imaging (MRI) scan and continued annual assessments that included information such as whether the children experienced stressful life events.

Previous research has shown that poverty affects children's psychosocial development and economic success in adulthood. This research shows that poverty also affects brain development. The findings suggest important targets for intervention that could help prevent these developmental deficits.

The Sensitization-Kindling Model

Angst described evidence that supports the sensitization-kindling model of recurrent mood disorders, which this editor (Robert Post) described in 1992. Episodes tend to recur faster over time, i.e. the well interval between episodes becomes progressively shorter. While stressors often precipitate initial episodes, after multiple occurrences, episodes also begin to occur spontaneously (in the absence of apparent stressors).

This type of progressive increase in response to repetition of the same stimulus was most clearly seen in animal studies, where repeated daily electrical stimulation of the amygdala eventually produced major motor seizures (i.e. amygdala kindling). Daily electrical stimulation of rodents' amygdala for one second initially produced no behavioral change, but eventually, minor and then full-blown seizures emerged. Once enough of the stimulated full-blown amygdala-kindled seizures had occurred, seizures began to occur spontaneously (i.e. in the absence of the triggering stimulation).

The analogy to human mood disorders is indirect, but kindling provides a model not only for how repeated triggers eventually result in full-blown depressive episodes, but also for how these triggered depressive episodes may eventually occur spontaneously as well.

Long-Term Treatment of Mood Disorders

Angst also discussed long-term treatment of mood disorders. He has found that long-term lithium treatment not only reduces suicides in patients with bipolar disorder, but also reduces the medical mortality that accompanies bipolar disorder.

Angst noted his previous surprising observations that in unipolar

disorder, long-term maintenance treatment, even with low doses of tricyclic antidepressants, prevents suicide. Previously, researchers Ellen Frank and David Kupfer of Western Psychiatric Institute and Clinic at the University of Pittsburgh Medical Center had found that when patients with recurrent unipolar depression who had been stable for 5 years on the tricyclic antidepressant nortriptyline were blindly switched to half their original dose, about 90% rapidly relapsed into a new episode of depression. Their data helped establish the prevailing view that maintenance treatment with the full-dose regimen required to achieve a good initial acute response is also the optimal approach to long-term continuation and prophylactic treatment.

Angst found good results even at low doses, but his data may not be in conflict with Frank and Kupfer's, as a person who responds well acutely to low doses may also be able to maintain good enough response to them to prevent recurrences in the long term.

Incidence of Bipolar Disorder in Adolescents Similar to Incidence in Adults

Angst also presented data from the Adolescent Supplement to the National Comorbidity Study (NCS-A), which analyzed interviews with approximately 10,000 adolescents (aged 13-17) in the US. He found a 7.6% incidence of major depression, a 2.5% incidence of bipolar I or II disorder, and a 1.7% incidence of mania. There was an even higher incidence of sub-threshold bipolar disorder, when there are not enough symptoms or a long enough duration of symptomatology to meet diagnostic criteria for bipolar I or II disorder. These data published by Merikangas et al. in 2009 provide clear epidemiological data that there is a substantial incidence of bipolar disorder in adolescents in the US, roughly similar to that seen in adults.

Kennedy Says Parity in the Treatment of Mental Illnesses Is Needed

At the 10th International Conference on Bipolar Disorders in 2013, Congressman Patrick J. Kennedy addressed the combined audience of the Depression Bipolar Support Alliance (DBSA) and members of the International Society of Bipolar Disorders. He gave an inspiring speech about de-stigmatizing advocacy, and the need to have a unified message that promotes parity in the care of mental illnesses and physical illnesses. He suggested that mental disorders should be compared to heart attacks, with the mantra, "We want no more, and we should demand no less."

Kennedy revealed his own dual diagnosis of bipolar disorder and alcohol abuse and the need to come out of the shadows, such as the basements of churches where people seeking treatment from Alcoholics Anonymous all too often remain unknown and anonymous.

Kennedy framed the issue of parity in the care of mental illnesses as a

new civil rights battle. People with mental illness have been grossly discriminated against, stigmatized with derogatory epithets, and treated with indignity in the past. He stressed the need for all to advocate not so much for themselves, but for others, and to join in community to solve our current problem of isolation and alienation.

Kennedy indicated optimism for the parity mission and suggested that a good way to achieve it would be to join forces with another isolated group of people – veterans returning from Iraq and Afghanistan. While many veterans return with brain injuries and post-traumatic stress syndrome (PTSD), seventy-two percent of veterans never go to the Veteran's Affairs hospitals, many are ignored, and too many are locked up in prisons. Kennedy called them "prisoners of their war injuries" and "walking prisoners of war." Twenty-two die each day by suicide.

Kennedy said we in the mental health community must stand with

them and their hidden brain injuries. They are wounded, but they never receive a purple heart. He quoted a speech his uncle Robert F. Kennedy gave in Cape Town, South Africa in 1966 before anyone thought that apartheid would end. "It is from numberless diverse acts of courage and belief that human history is shaped. Each time a [person] stands up for an ideal, or acts to improve the lot of others, or strikes out against injustice, [that person] sends forth a tiny ripple of hope, and crossing each other from a million different centers of energy and daring, those ripples build a current that can sweep down the mightiest walls of oppression and resistance."

In the mental health community we need each other and can't afford different messages or fragmentation. Mental health advocates joining with veterans and their search for good care will be our salvation, as will our connectedness, togetherness, mutual respect, and these will yield solutions for both groups.

NIMH Director and APA Clash Over Diagnostic Manual of Mental Disorders

The psychiatric community has been preparing for the 2013 release of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by the American Psychiatric Association for years. Each new edition of the manual reflects changing conceptions of illnesses and their diagnosis and treatment.

Tom Insel, the director of the National Institute of Mental Health (NIMH), the largest research organization in the world devoted to the understanding and treatment of mental disorders, caused a stir this past spring when he wrote in a blog post that the DSM-5 lacks validity and that patients deserve better.

The DSM-5 guidelines for diagnosis of mental disorders rely on descriptions of clusters of symptoms, and Insel suggested that new methods of diagnosis that rely on laboratory measure should be developed. The NIMH is launching a project called Research Domain

Criteria (RDoC) to incorporate genetics, imaging, and other data in a new classification system for illnesses, and is re-orienting their funding toward projects that "look across current categories," for example by including all patients in a mood disorder clinic rather than only those who meet DSM-5 criteria for major depressive disorder.

A major concern about this change at the NIMH, which funds much of the research that leads to Federal Drug Administration-approved treatments, is that it will diminish funding for treatment studies in specific diagnostic categories where research is already sparse, such as childhood onset bipolar illness. This may leave many children and adults without a sound evidence base upon which their doctors can base treatment decisions.

Under the NIMH's new rubric, clinical treatment studies to collect comparative data and evidence-based

treatment research would likely lose out to studies focused on the broad collection and identification of biomarkers and the pursuit of new treatment targets. Answering an important clinical question such as whether symptoms of childhood onset bipolar disorder respond to the same medications as oppositional defiant disorder (ODD) or disruptive mood dysregulation disorder (DMDD) might not be a high priority for study.

David Kupfer, chair of the APA's DSM-5 Task Force, responded to Insel's statement saying that while it would be great to identify biomarkers and genetic indicators for mental illnesses, "this promise, which we have anticipated since the 1970s, remains disappointingly distant." Insel acknowledged in his statement that this is only the beginning of development of research domain criteria, and that "for the present" the DSM will continue to be used.

Bipolar Illness is Worse in the US than in Germany and the Netherlands

At a symposium celebrating the retirement of Willem Nolen, a researcher who spent 40 years studying unipolar and bipolar disorder, from his position at Groningen Hospital in the Netherlands, this editor (Robert Post) discussed progress in the treatment of bipolar disorder over the past 40 years. Despite the availability of lithium; many new mood stabilizers (carbamazepine, valproate, lamotrigine); and many atypical antipsychotics, all of which are anti-manic and some of which are antidepressant (quetiapine and lurasidone), there is still a very high rate of continued illness and treatment resistance, especially in the US.

In fact, research from the Bipolar Collaborative Network, a treatment research network including sites around the US (one run by this editor) and in Germany and the Netherlands, shows that almost everything about bipolar disorder is worse in the US. **Americans have more genetic vulnerability because more of their parents have bipolar disorder, and**

they are more likely to have environmental vulnerability as a result of childhood adversity. Patients in the US also reported having had more stressors at the onset of their illness and more stressors prior to the last episode they had before entering the network at an average age of 40.

Age at illness onset is much lower in the US than in the Netherlands and Germany. About two-thirds of American patients had onset in childhood or adolescence (under 19 years), while only about one-third of the European patients in this study showed these early onsets.

The course of illness is also more difficult in the US. There is more anxiety, substance abuse, and medical comorbidity, and there are more episodes and more rapid cycling. All this resulted in more US patients than European ones who did not respond to naturalistic treatment in our treatment network despite being prescribed multiple medications.

The implication of these data is that we need a new and more concerted approach to bipolar disorder in the US, beginning with early diagnosis and treatment during childhood and adolescence, instead of the 10- to 15-year average delay that was typical about twenty years ago. The duration of the delay to first treatment with a drug to treat mania or depression was an independent predictor of a worse outcome in adulthood. Early intervention should also include therapy and education.

Family-Focused Treatment (FFT), a method pioneered by researchers David Miklowitz and Kiki Chang, has been shown to be much more effective than treatment as usual in children who are at high risk for developing bipolar disorder because they have a family history of the illness and symptoms of an anxiety or depressive disorder or bipolar not otherwise specified (BP-NOS). In this way it may even be possible to head off the full-blown illness before it starts in those children at highest risk.

Some Astonishing Facts About Your DNA and Its Epigenetic Modifications

- The DNA in just one of your body's cells would be 2 meters long if stretched out.
- All of that DNA is stuffed into each cell's nucleus, which measures only 6 microns in diameter.
- If DNA were folded, it would take 10,000 to 300,000 layers to fit into the nucleus.
This is miraculous given that a very thin piece of paper can only be folded over on itself about seven times. (Try it!)
- When DNA is tightly packed and wound around histones, transcription is inhibited. Stressors and chemicals in the environment can change the packaging of DNA (not its inherited sequence) by adding extra chemical groups (e.g. methyl and acetyl groups) on DNA and histones.
- When histones are acetylated, DNA is wound more loosely and can be more easily transcribed.
- Histone deacetylases (HDACs) remove the epigenetically mediated acetyl groups and keep the DNA tightly wound. Histone deacetylase inhibitors keep the acetyl groups in place and facilitate transcription (sometimes facilitating new learning and memory).

BNN
PO Box 18
Beltsville, MD 20704-0018

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