

# Bipolar Network News

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Updates from the 2014 Meeting of the American Academy of Child and Adolescent Psychiatry

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## Bipolar Disorder Associated with High Verbal Ability and Sociability

A new study of twins (focused on sets in which one twin has bipolar disorder and the other doesn't) provides strong evidence that verbal fluency and positive social traits (such as social ease, confidence, and assertiveness) are more common in the non-ill twins of patients with bipolar disorder compared to non-ill twins of patients with schizophrenia or normal controls. This suggests that people with bipolar disorder are likely to have these positive traits, since the non-ill twin carries some of the same genetic predispositions as the ill twin, but without the detriments to cognitive skills and temperament that are common in bipolar illness.

**The traits of enhanced cognition and positive personality in the non-ill twin indicate that vulnerability to bipolar illness is associated with characteristics that convey a reproductive fitness advantage.**

Positive qualities like these may make people with bipolar disorder attractive mates, leading to the continued propagation of genes that promote bipolar disorder. This could help account for the persistence of bipolar disorder in the general population.

The researchers, led by Rachel G. Higier, used a Swedish registry of twins.

Many studies have found positive traits associated with bipolar disorder, particularly creativity. The 1990 book *Manic Depressive Illness* by Kay Redfield Jamison and Frederick K. Goodwin describes many of these findings. School performance has also been associated with bipolar disorder. In a 2010 article in the *British Journal of Psychiatry*, J.H. MacCabe et al. reported that boys with exceptional performance in school at age 16 were at higher risk for bipolar disorder in adulthood.

However, once patients become ill with bipolar disorder, many aspects

of the illness itself can cause decreases in cognitive functioning. Having more episodes of mania and depression is associated with greater degrees of cognitive impairment in multiple domains, and this is likely in part because brain-derived neurotrophic factor (BDNF), a protein that is important for learning and memory, decreases with every episode of mania or depression.

The critical clinical message is that long-term consistent treatment of bipolar disorder is necessary to prevent episode recurrence and the associated decreases in BDNF. Our motto remains: "Prevent Episodes, Protect the Brain." Perhaps we could add a further admonition, prevent episodes and preserve creativity and intellect!

## Atypical Antipsychotics in Bipolar Depression

A limited number of atypical antipsychotics are approved by the Federal Drug Administration for the treatment of depression in patients with bipolar disorder. This is important to note, because the widely used traditional antidepressants that are highly effective in unipolar depression are not effective in bipolar depression. **Here we review the status of the only three approved drug treatments for bipolar depression (olanzapine, quetiapine, and lurasidone) and highlight data on a promising new atypical antipsychotic, cariprazine.**

### Lurasidone (Latuda)

At the 2014 meeting of the International College of Psychopharmacology, researcher Joseph Calabrese reviewed the efficacy of the latest atypical antipsychotic to receive FDA approval for bipolar depression, lurasidone. In monotherapy, both low (20–60mg/day) and high doses (80–120mg/day) showed higher response rates (53% and 51%, respectively) than placebo (30%). When added to either lithium or valproate, lurasidone response

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# Atypical Antipsychotics For the Treatment of Bipolar Depression

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(57%) again exceeded that of placebo (42%). Calabrese also indicated that all of the other secondary outcome measures were also statistically significant, including scores on the Clinical Global Impressions scale for bipolar disorder, time to response, percentage of remitters, time to remit, scores on the Hamilton Anxiety scale, and a patient rated depression scale (QIDS).

Lurasidone is also approved for schizophrenia at higher doses (up to

160mg/day). At least twice as much of the drug is absorbed when food is in the stomach, so it is recommended that patients take it one to two hours after dinner or after a snack of 350 calories or more. The drug has an excellent side effects profile, as it is weight- and metabolically- neutral (i.e. it does not increase blood glucose, cholesterol, or triglycerides).

## Quetiapine (Seroquel)

The atypical antipsychotic quetiapine has been FDA-approved for bipolar depression for a number of years. It consistently performs better than placebo in bipolar depression, and unlike lurasidone, quetiapine is also FDA-approved for mania, as well as for long-term prevention of both manic and depressive episodes as an adjunct to either lithium or valproate. Quetiapine is also superior to placebo for prevention of both manic and depressive episodes as a monotherapy, but is not FDA-approved for this indication. A good target dose for bipolar depression is 300mg/day of the extended release preparation taken several hours prior to bed time. Higher doses of 400 to 800mg/night are used for mania and schizophrenia. Quetiapine is also FDA-approved as an adjunct to antidepressants in unipolar depression. The drug has sedative side effects, perhaps because of its potent antihistamine effects. It can also increase weight, glucose, and cholesterol slightly more than placebo.

## Olanzapine and Fluoxetine

Olanzapine (Zyprexa) and a combined preparation of olanzapine and fluoxetine (Symbyax) are also approved for bipolar depression, but many guidelines suggest that these be considered secondary treatments because they are associated with weight gain and adverse metabolic effects.

## Cariprazine Effective in Bipolar Depression and Mania

At the 2014 meeting of the International College of Neuropsychopharmacology, researcher Suresh Durgam presented a poster on the first study of the atypical antipsychotic cariprazine in bipolar depression. There have also been three positive placebo-controlled studies of the drug in mania. It is a dopamine D2 and D3 partial agonist, with greater potency at the D3 receptor than the atypical antipsychotic aripiprazole (Abilify). In the large placebo-controlled eight-week study, doses of 1.5mg/day were superior to placebo in bipolar depression, but higher (3mg) and lower doses (0.75mg) were not.

Another poster presented by the same research group also reported that augmentation of antidepressants with cariprazine in unipolar depression had results that were significantly better than placebo.

*Editor's Note: While all atypical antipsychotics that have been tested for mania have antimanic efficacy (lurasidone has not been studied in mania), their antidepressant profiles differ considerably. Only the three atypical antipsychotics noted above (olanzapine/fluoxetine, quetiapine, and lurasidone) are FDA-approved for bipolar depression, and in light of recent findings, cariprazine is likely to follow soon.*

*The atypical antipsychotics NOT approved for bipolar depression include: aripiprazole (Abilify), risperidone (Risperidol), and ziprasidone (Geodon), with the first atypical antipsychotic clozapine and the most recent ones not yet formally tested as far as this editor is aware, including asenapine (Saphris), iloperidone (Fanapt), and paliperidone (Invega).*

*Only the atypical antipsychotics aripiprazole and quetiapine are FDA-approved as adjunctive treatments to antidepressants in unipolar depression, and cariprazine may soon be added to this list.*

### Bipolar Network News

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

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## Lamotrigine Effective in the Prevention of Bipolar I Disorder in Adolescents

At the 2014 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Robert Findling reported on a double blind, placebo controlled 36-week study of lamotrigine for children and adolescents with bipolar I disorder. The doses designed for maintenance treatment averaged about 225 mg/day, achieved by very slow increases over time in order to reduce the risk of a serious rash.

Findling found that **lamotrigine was more effective than placebo in extending the time until a patient required an intervention for a new mood episode among the older children in the study (aged 13 to 17)**. Among the younger children in the study (aged 10 to 12), lamotrigine's effects were not statistically significant compared to placebo. Findling and colleagues concluded that lamotrigine appeared effective in delaying time to onset of a new episode in adolescents with bipolar I disorder.

Lamotrigine is approved by the Federal Drug Administration (FDA) only for the prevention of bipolar episodes in adults.

## Older Fathers More Likely to Have Offspring with Bipolar Disorder

In a huge study of Swedes, compared to offspring of young fathers (aged 20–24), **offspring of older fathers (over age 45) are 24.7 times more likely to develop bipolar disorder**. Older paternal age was also associated with other risks of mental disorders, such as autism, attention deficit hyperactivity disorder (ADHD), suicide attempts, substance abuse and psychosis, but the strongest finding was of a relationship with bipolar disorder.

Mutations that occur during the production of sperm may be responsible for the increased risk of illness in the offspring of older fathers.

The population-based cohort study published by Brian M. D'Onofrio et al. in the journal *JAMA Psychiatry* included all individuals born in Sweden between 1973 and 2001.

## Effect Sizes of Various Autism Treatments

At the 2014 meeting of the American Academy of Child and Adolescent Psychiatry, Fung et al. presented a meta-analysis of treatments for autism that ranked them in terms of statistical effect size, ranging from 0.9 (large), to 0.5 to 0.8 (medium), to <0.4 (small). **The only drug with a large effect size was risperidone, at 0.9. Most effect sizes were medium, including aripiprazole at 0.8 and N-acetylcysteine (NAC) at 0.7. Both clonidine and methylphenidate had effect sizes of 0.6, and tianeptine's was 0.5.**

Fung and colleagues noted that the first two on the list, the atypical antipsychotics risperidone and aripiprazole, often have problematic side effects (such as sedation, weight gain, and motor symptoms) that must be balanced against their effectiveness. In contrast, NAC is well tolerated with few side effects, and two placebo controlled studies showed that it was effective both alone and as an adjunctive treatment to the antipsychotic risperidone.

## Multivitamin and Mineral Preparations for Childhood Bipolar Disorder

Researcher Charles Popper gave a talk at the 2014 meeting of the American Academy of Child and Adolescent Psychiatry on the benefits of nutritional supplements designed to provide multiple vitamins and minerals to children with bipolar disorder and other dyscontrol syndromes, such as attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder. Popper reviewed the literature on the substantial incidence of vitamin and mineral deficiencies among these children.

Some recent data supports the effectiveness of supplements for children

with these disorders. One of these supplements is called EMPowerPlus and is sold online. It is moderately expensive and must be given under the supervision of a knowledgeable treating physician. While it is relatively safe in medication-free children, Popper says it can exacerbate withdrawal reactions from some psychotropic medications.

In addition, EMPowerPlus greatly increases lithium-related side effects. In patients taking lithium, the dose must be reduced to about one-tenth of a normal dose for those who are adding EMPowerPlus.

Popper and another researcher, Mary Fristad, have both seen excellent responses to this type of supplementation in children with bipolar disorder who have been unresponsive to more traditional drugs.

In another study by Rita Aouad et al., **72.3% of 980 children with a variety of psychiatric diagnoses had insufficient vitamin D levels (values <30 nanograms/ml) and 26.7% had vitamin D deficiency (values <20 nanograms/ml)**. These data support the rationale for vitamin D supplementation, especially in those who have low levels to start with.



## Offspring of Parents with Bipolar Disorder At Risk for Mood Disorders

In a symposium at the 2014 meeting of the International College of Neuropsychopharmacology, four researchers shared insights on children who are at higher risk for bipolar disorder because they have a parent with the disorder.

Researcher John Nurnberger has been studying 350 children of parents with bipolar disorder in the US and 141 control children of parents with no major psychiatric disorder, following the participants into adolescence. He found **a major affective disorder in 23.4% of the children with parents who have bipolar disorder and 4.4% of the controls**. Of the at-risk children, 8.5% had a bipolar diagnosis versus 0% of the controls.

Nurnberger found that disruptive behavior disorders preceded the onset of mood disorders, as did anxiety disorders. These diagnoses predicted the later onset of bipolar disorder in the at-risk children, but not in the controls. A mood disorder in early adolescence predicted a substance abuse disorder later in adolescence among those at risk.

In genome-wide association studies, the genes CACNA1C and ODZ4 are consistently associated with risk of bipolar disorder, but with a very small effect size. Therefore, Nurnberger used 33 different gene variants to generate a total risk score and found that this measure was modestly effective in identifying relative risk of developing bipolar disorder. He hopes that using this improved risk calculation along with family history and clinical variables will allow better prediction of the risk of bipolar onset in the near future.

Researcher Ann Duffy reported on her Canadian studies of children who have a parent with bipolar disorder and thus are at high risk for developing the disorder. In contrast to the studies of Nurnberger et al. and many others in American patients, she found almost no childhood onset of bipolar disorder

before late adolescence or early adulthood. She found that anxiety disorders emerge first, followed by depression, and then only much later bipolar disorder.

Bipolar disorder occurred with comorbid substance abuse disorders in only about 10-20% of cases in 1975, but substance abuse increased to 50% of bipolar cases in 2005. The incidence of comorbid substance disorder and the year at observation correlated strongly, indicating a trend toward increased substance

abuse over the 30-year period. Duffy found that **having parents who were ill as opposed to recovered was associated with a more rapid onset of mood disorder in the offspring, usually in early adulthood**. Duffy emphasized the need to intervene earlier in children of parents with bipolar disorder, but this is rarely done in clinical practice.

Duffy also reported that even in individuals doing well on lithium (without major mood fluctuations), there were still fluctuations in cortisol and its ability to be suppressed by dexamethasone. She found that those with remitted bipolar disorder had the highest cortisol levels, at-risk offspring (who had not yet become ill) were intermediate, and controls the lowest.

Duffy quoted the 2013 data of researchers Baethage and Cassidy that among 10- to 24-year-olds, suicide was the second highest cause of death

(accidents was first). **Ninety percent of the suicides were related to mood disorders**, with a high percentage being bipolar mixed, early onset, and

associated with substance abuse.

Duffy also added to the growing literature on the high levels of the inflammatory marker IL-6 present in early stages of illness prior to the onset of bipolar disorder, with a decrement in IL-6 in later stages of full-blown bipolar disorder. Similar increases in the neurotrophic factor BDNF were seen in early stages, and decreases in later stages. There were also differ-

ences in these indices as a function of the common and better functioning val-66-val allele of proBDNF (which has been associated with early onset bipolar disorder) versus the met-66-met allele, which functions less well and has been associated with mild cognitive deficits in various populations. More details of this study were published in the *International Journal of Bipolar Disorders* in 2014.

Researcher Jan Scott discussed the 2011 study by Gore et al. that showed that bipolar disorder produced the fourth highest global burden of disease (with unipolar depression first, traffic accidents next, and schizophrenia third).

Scott also mentioned a study by Bruce Birmaher that showed that children with diagnoses of bipolar disorder not otherwise specified (NOS), when followed for several years, converted to full-blown BP I or BP II

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## Children and Teens at High Risk for Mood Disorders

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disorder 58.5% of the time when there was a family history of bipolar illness and 35.5% of the time when there was no family history of the illness.

Scott cited six studies of children at high risk who were treated with psychotherapy – two with family focused therapy (FFT), two with cognitive behavioral therapy (CBT), and two with interpersonal therapy (IPT). The results were promising across the board, and each therapy was endorsed along with psychoeducation (PE) and mindfulness training. These data support the utility of preventive psychotherapeutic intervention in children at high risk because of a family history of mood disorders.

*Editor's Note: In studies this editor (Robert M. Post) worked on in the US, we found a high incidence of illness not only in the parents of patients with bipolar disorder, but also in the grandparents. Greater total illness across the two generations was associated with more complex illness in the patients. They not only had bipolar disorder, but also a higher incidence of early onset illness, anxiety and substance abuse comorbidity, more episodes, and rapid cycling. These data along with Scott's review offer strong reasons to provide psychotherapy to those at very high risk due to having two generations of relatives with multiple illnesses.*

Scott discussed the link between sleep disturbance and rumination in mood disorders. Sixty-two percent of patients with bipolar disorder have delayed onset sleep, versus 30% with unipolar depression, and 14% in controls. A ruminating coping style (as opposed to distraction, active coping, or risk-taking) was associated with poor sleep, high cortisol, low mood, and substance abuse.

Phillip Mitchell gave the final talk at the high-risk symposium. He explained that compared to control populations, at risk offspring of bipolar parents had increased odds ratios (between 1.3 to 3.9) of having an affective, anxiety, disruptive behavioral, or substance abuse disorder, or any two of these diagnoses. In patients who had already been diagnosed with bipolar disorder, the risk of having comorbidities was even higher. The odds ratios for the above comorbidities compared to the controls ranged from 6.2 to 9.7, and the odds ratio for having two or more diagnoses was 28-fold higher.

The at-risk offspring had other characteristics that more closely resembled the participants with bipolar disorder than the control participants without a family history of bipolar disorder, including: increased sleep in 66.7%, early onset of a mood or anxiety disorder before age 18 in 47.6%, and 33.3% with four or more atypical features to their depression, which included hypersomnia, hyperphagia, leaden paralysis, psychomotor retardation, psychosis, and mood fluctuations.

## Lithium Effective In Adolescent Mania And Increases White Matter Volume

At the 2014 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Adelaine Robb reported that **in 81 children with mania (aged 7-17), lithium was superior to placebo in reducing the severity of mania** measured on the Young Mania Rating Scale. There had been some debate about the efficacy of lithium in young children with mania, but this study clearly indicates lithium's effectiveness. The drug is approved by the Federal Drug Administration (FDA) for use in patients with bipolar disorder aged 12 and up.

Another researcher, Vivian Kafrantaris, found that in children who averaged 14.5 years of age, **lithium increased the volume of the corpus callosum, a bundle of neural fibers that connects the brain's right and left hemispheres. Lithium also normalized white matter integrity in other neural fiber tracts** – the cingulum bundle and the superior longitudinal fasciculus. The authors concluded that lithium may “facilitate microstructural remodeling of white matter tracts involved in emotional regulation.”

*Editor's Note: There is much research showing that in adults, lithium has positive effects on the brain, including increases in hippocampal and cortical grey matter volume. Now it appears that lithium can improve white matter integrity in the developing brain as well.*

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## Differentiating ADHD and Bipolar Disorder in Adolescents and Children

Three articles in the September 2014 issue of the journal *Psychiatric Annals* (Volume 44 Issue 9) discussed differentiating pediatric bipolar disorder from attention deficit hyperactivity disorder (ADHD). The first article, by Regina Sala et al., listed reasons to suspect bipolar disorder in a child with ADHD, shown at right.

The second article, by this editor Robert Post, Robert Findling, and David Luckenbaugh, emphasized the **greater severity and number of symptoms in childhood onset bipolar disorder versus ADHD**. Children who would later develop bipolar disorder had brief and extended periods of mood elevation and decreased sleep in the early years of their lives. These, along with pressured speech, racing thoughts, bizarre behavior, and grandiose or delusional symptoms emerged differentially from age three onward. In contrast, the typical symptoms of ADHD such as hyperactivity, impulsivity, and decreased attention were equal in both diagnoses.

In the third article, Mai Uchida et al. emphasized the utility of a family history of bipolar disorder as a risk factor. Moreover, a child with depression plus ADHD is at increased risk for a switch into mania on antidepressants if there is a family history of mood disorders, emotional and behavioral dysregulation, subthreshold mania symptoms, or psychosis.

*Editor's Note: The differential diagnosis of ADHD versus bipolar disorder (with or without comorbid*

### Signs of Possible Bipolar Disorder in a Child with ADHD

Regina Sala, *Psychiatric Annals*, 2014

- The ADHD symptoms appear for the first time after age 12.
- The ADHD symptoms appear abruptly in an otherwise healthy child.
- The ADHD symptoms initially responded to stimulants and then did not.
- The ADHD symptoms come and go and occur with mood changes.
- A child with ADHD begins to have periods of exaggerated elation, grandiosity, depression, decreased need for sleep, or inappropriate sexual behaviors.
- A child with ADHD has recurring severe mood swings, temper outbursts, or rages.
- A child with ADHD has hallucinations or delusions.
- A child with ADHD has a strong family history of bipolar disorder in his or her family, particularly if the child does not respond to appropriate ADHD treatments.

ADHD) is critical, as drug treatment of these disorders is completely different.

*Bipolar disorder is treated with atypical antipsychotics; anticonvulsant mood stabilizers, such as valproate, carbamazepine, or lamotrigine; and lithium. Only once mood is stabilized should small doses of stimulants be added to treat residual ADHD symptoms.*

ADHD, conversely, is treated with short- or long-acting stimulants such as amphetamine or methylphenidate from the

onset, and these may be augmented by the noradrenergic alpha-2 agonists guanfacine or clonidine. The selective noradrenergic re-uptake inhibitor atomoxetine is also approved by the Federal Drug Administration (FDA) for the treatment of ADHD, and the dopamine-active drug bupropion has mild anti-ADHD effects, as do the anti-narcolepsy drugs modafinil and armodafinil.

**Join the Child Network! See page 10.**



## New Data on Vortioxetine for Cognition in Unipolar Depression

A 5mg dose of the antidepressant vortioxetine (Brintellix) was previously reported to have positive cognitive effects in elderly depressed patients. In a 2014 article in the *International Journal of Neuropsychopharmacology*, researcher Roger S. McIntyre et al. presented data from FOCUS, a study of cognition in depressed patients. The eight-week double-blind study included 18- to 65-year-olds (who were not selected for having cognitive problems per se).

McIntyre and colleagues used two tests of cognition, the Digit Symbol Substitution Test (DSST), which measures attention, psychomotor speed, and executive function, and the Rey Auditory Verbal Learning Test

(RAVLT), which measures memory and acute and delayed recall. The researchers found that both the 195 patients taking 10mg/day of vortioxetine and the 207 **patients taking 20mg/day of vortioxetine had better performance on both tests than the 196 patients who received placebo.**

Response rates (meaning a patient achieved a 50% improvement on a scale of depression) were 47.7% on 10mg of vortioxetine, and 58.8% on 20mg of vortioxetine, compared to 29.4% on placebo. Remission rates were 29.5% on 10mg of vortioxetine and 38.2% on 20mg of vortioxetine versus 17% on placebo. McIntyre suggested that the drug worked both directly and indirect-

ly, improving depression in some, but also improving cognition even in those whose depression did not improve.

The mechanism that could account for vortioxetine's cognitive effects has not yet been identified. Like other selective serotonin reuptake inhibitor (SSRI) antidepressants, vortioxetine is a potent blocker of serotonin (5HT) reuptake, which it does by inhibiting the serotonin transporter (5HT-T). **Unlike other SSRIs, vortioxetine is also a blocker of 5HT3 and 5HT7 receptors, an agonist at 5HT1A and 5HT1B and a partial agonist at 5HT1D receptors.** It could be considered a polymodal 5HT active drug in contrast to the more selectively active 5HT-T-inhibiting SSRIs.

## Saffron May Treat Mild Depression

Saffron, the expensive yellow spice derived from the plant *Crocus sativus*, was the subject of a recent meta-analysis in the journal *Human Psychopharmacology*. The meta-analysis included six studies of a total of 230 adult outpatients with major depressive disorder. In two of these studies, **30mg/day of saffron extract was as effective a treatment for mild to moderate depression as 20mg/day of the antidepressant fluoxetine and 100mg/day of imipramine had been in other studies.**

Saffron is suggested to have anticancer, anti-inflammatory, antioxidant, and antiplatelet effects, and current clinical trials are exploring whether it could prevent and treat Alzheimer's disease.

The current study was an effort to systematically analyze clinical trials on saffron to establish treatment parameters such as dosage in addition to safety information.

## Study Finds No Substantial Risk of Infant Cardiac Problems from Antidepressant Use During Pregnancy

In the past there has been some concern that selective serotonin reuptake inhibitor (SSRI) antidepressants taken during pregnancy could increase an infant's risk of cardiac problems. There was particular concern that the SSRI paroxetine could lead to right ventricular outflow tract obstruction, and sertraline could lead to ventricular septal defects. A 2014 study by KF Huybrechts et al. in the *New England Journal of Medicine* analyzed data from 949,504 women in a Medicaid system from three months before pregnancy until one month after delivery during the years 2000-2007.

Infants born to mothers who had taken antidepressants during their first trimester were compared to infants whose mothers had not taken antidepressants. In total, 6.8% or 64,389 women had used antidepressants in their first trimester.

**While the rate of cardiac defects in newborns was greater among those mothers who had taken antidepressants (90.1 infants per 10,000 infants who had been exposed to antidepressants versus 72.3 infants per 10,000 infants who had not been exposed to antidepressants), this relationship diminished as confounding variables were removed.** The relative risk of any cardiac defect after taking SSRIs was 1.25, but this decreased to 1.12 when restricted to only those mothers who were diagnosed with depression, and to 1.06 when the researchers controlled for things like depression severity. (All relative risk numbers were calculated with a 95% confidence interval.)

The researchers concluded that there is no substantial risk of increased cardiac defects in children born to mothers who took antidepressants during their first trimester.

# Treatments with Rapid-Acting Antidepressant Effects

At the International College of Neuropsychopharmacology (CINP) World Congress of Neuropsychopharmacology in 2014, several presentations and posters discussed treatments that bring about rapid-onset antidepressant effects, including ketamine, isoflurane, sleep deprivation, and scopolamine.

## Ketamine's Effects

Multiple studies, now including more than 23 according to researcher William "Biff" Bunney, continue to show the rapid-onset antidepressant efficacy of intravenous ketamine, usually at doses of 0.5 mg/kg over 40 minutes. Response rates are usually in the range of 50–70%, and effects are seen within two hours and last several days to one week. **Even more remarkable are the six studies (two double-blind) reporting rapid onset of anti-suicidal effects, often within 40 minutes and lasting a week or more.** These have used the same doses or lower doses of 0.1 to 0.2mg/kg over a shorter time period.

Attempts to sustain the initial antidepressant effects include repeated ketamine infusions every other day up to a total of six infusions, a regimen in which typically there is no loss of effectiveness. Researcher Ronald Duman is running a trial of co-treatment with ketamine and lithium, since both drugs block the effects of GSK-3, a kinase enzyme that regulates an array

of cellular functions, and in animals the two drugs show additive antidepressant effects. In addition, lithium has been shown to extend the acute antidepressant effects of one night of sleep deprivation, which are otherwise reversed by a night of recovery sleep.

Ketamine's effects are related to the neurotransmitter glutamate, for which there are several types of receptors, including NMDA and AMPA. Ketamine causes a large burst of glutamate presumably because it blocks NMDA glutamate receptors on inhibitory interneurons that use the neurotransmitter GABA, causing glutamatergic cells to lose their inhibitory input and fire faster. While ketamine blocks the effects of this glutamate release at NMDA receptors, actions at AMPA receptors are not blocked, and AMPA activity actually increases. This increases brain-derived neurotrophic factor (BDNF), which is also required for the antidepressant effects of ketamine. Ketamine also increases the effects of mTOR, a kinase enzyme that regulates cell growth and survival, and if these are blocked with the antibiotic rapamycin, antidepressant effects do not occur.

Several treatments can bring about antidepressant effects in as little as 24 hours. These include intravenous ketamine, one night of sleep deprivation, intravenous scopolamine, and possibly inhaled isoflurane.

**In animal studies, ketamine increases dendritic spine growth and rapidly reverses the effects of chronic mild unpredictable stressors on the spines** (restoring their mature mushroom shape and increasing their numbers), effects that

occur within two hours in association with its rapid effects on behaviors that resemble human depression.

About 50–70% of treatment-resistant depressed patients respond to ketamine. However, about one-third of the population has a common genetic variation of BDNF in which one or both valine amino acids that make up the typical val-66-val allele are replaced with methionine (producing val-66-met proBDNF or met-66-met proBDNF). The methionine variations result in the BDNF being transported less easily within the cell. Patients with these poorly functioning alleles of BDNF are less likely to get good antidepressant effects from treatment with ketamine.

## Ketamine in Animal Studies

Researcher Pierre Blier reviewed the effects of ketamine on the neurotransmitters serotonin, norepinephrine, and dopamine. In rodents, a swim stress test is used to measure depression-like behavior. Researchers record how quickly the rodents give up trying to get out of water and begin to float instead. Blier found that ketamine's effects on swim stress were dependent on all three neurotransmitters. For dopamine, ketamine's effects were dependent on increases in the number of dopamine cells firing, not on the firing rate, and for norepinephrine, ketamine's effects were dependent on increases in burst firing patterns. Each of these effects was dependent on glutamate activity at AMPA receptors. Given these effects, Blier believes that using ketamine as an adjunct to conventional antidepressants that tend to increase these neurotransmitters may add to its clinical effectiveness.

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# Rapid-Onset Antidepressant Treatments

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## Important Anecdotal Clinical Notes

Blier reported having given about 300 ketamine infusions to 25 patients, finding that two-thirds of these patients responded, including one-third who recovered completely, while one-third did not respond to the treatment. **Patients received an average of 12 infusions, not on a set schedule, but according to when they began to lose response to the last ketamine infusion. If a patient had only a partial response, Blier gave the next ketamine treatment at a faster rate of infusion and was able to achieve a better response.** These clinical observations are among the first to show that more than six ketamine infusions may be effective and well tolerated.

In a personal communication, researcher Robert Kowatch indicated that he is also using intravenous ketamine at doses of 0.5mg/kg over a 20-minute period in adolescents (age 13 to 17) with treatment-resistant depression, with some success.

## Ketamine's Effects on Human Brain Activity

Austrian researcher Rupert Lanzenberger used imaging techniques to study the effects of ketamine on different parts of the brain. He observed increases in serotonin and dopamine. Glucose metabolism increased in the thalamus and the frontal and parietal cortices, and decreased in the right habenula and insula. Increases in metabolism in the subgenual cingulate cortex were related to the degree of clinical antidepressant response to ketamine. Measuring blood flow, Lanzenberger saw increases in activity in the anterior cingulate cortex and

the medial and inferior frontal cortices, but decreases in the cerebellum.

*Editor's Note: Ketamine reverses (or normalizes) typical regional neurophysiological signs of depression, including frontal lobe underactivity and overactivity in the habenula and cerebellum.*

## Isoflurane: Rapid Onset Antidepressant Effects

The anesthetic isoflurane may also produce rapid onset antidepressant effects (some but not all studies have been positive), and does not appear to work by increasing BDNF or inducing synaptic spine effects as ketamine does. Isoflurane rather appears to cause shrinkage and loss of dendritic spines in the hippocampus. It is conceivable that isoflurane could work in ketamine non-responders, as its mechanism of action is different and it does not require BDNF increases or spine alterations, which ketamine does. However, a recent study indicated that isoflurane's effects were mediated by TrkB, the receptor for BDNF, so BDNF activity at its receptor may still be important.

## Sleep Deprivation: Overnight Antidepressant Effects

At the Congress, Bunney reviewed the extensive and consistent literature on the acute antidepressant effects of one night of sleep deprivation. **These antidepressant effects can be extended beyond one day by co-treating the patient with lithium or with the use of bright light (10,000 Lux) in the morning along with a phase advance** (going to sleep from 6pm to 2am the following night, 7pm to 3am the next, and 8pm to 4am the next, and so on until a normal sleep schedule occurs). This alters circadian rhythms and the expression of CLOCK

genes, which control these rhythms. Bunney believes that this alteration in CLOCK gene expression could be responsible for the antidepressant effects.

Researcher Francesco Benedetti reported that a series of three nights of sleep deprivation (every other night) while patients took lithium and received light therapy resulted in positive and extended antidepressant effects. Most intriguingly, he reported that even non-responders to sleep deprivation showed improvement in suicidal ideation with this regimen. There are normal variations in CLOCK genes in the general population, and Benedetti linked the presence of the CC allele (as opposed to the TT allele) of the gene to both insomnia and suicidal ideation.

## Rapid Onset Antidepressant Effects with Scopolamine

Scopolamine is another drug that can be used intravenously to bring about rapid onset of antidepressant effects at doses of 4 micrograms/kg. Scopolamine blocks acetylcholine muscarinic receptors. Researcher Ronald Duman suggests that scopolamine blocks these receptors on inhibitory GABA interneurons synapsing on glutamatergic cell bodies, thus causing a rapid increase in glutamate similar to that brought about by ketamine. Scopolamine also increases BDNF and mTOR, and rapidly increases synaptic spines in the prefrontal cortex, as ketamine does.

*Editor's Note: Since chronic oral scopolamine also augments the effects of antidepressant drugs over a period of several weeks, the acute short-lived antidepressant effects of intravenous scopolamine could theoretically be extended with oral scopolamine, but this possibility has not yet been studied.*

## The Good and Bad News About Deep Brain Stimulation for Treatment-Resistant Depression

Deep brain stimulation is a treatment in which electrodes are implanted in the brain to treat movement or affective disorders. At the 2014 meeting of the International College of Neuropsychopharmacology, Thomas Schlaepfer reviewed the current status of studies of deep brain stimulation for depression. The bad news is that two double-blind randomized controlled studies are no longer recruiting patients because interim analysis failed to show a benefit to the deep brain stimulation over a sham stimulation. The studies targeted two of the most promising parts of the brain for deep brain stimulation—the subgenual anterior cingulate (important for motivation) and the anterior limb of the internal capsule (which contains nerve fibers going to and from the cerebral cortex), so their failure is a big disappointment.

**The better news is that Schlaepfer repositioned the electrodes to target a site in the medial forebrain bundle nearer to the ventral tegmental area. After this shift he observed rapid onset of antidepressant response (within two days) in seven of the first eight patients studied, and these responses persisted over many months of follow up.** This response was achieved at 2.8 microamps, a lower stimulation current than was used in other studies of deep brain stimulation.

*Editor's Note: Since patients started to feel better when they were still on the operating table, this may offer an opportunity to more rapidly assess effectiveness, do a double-blind study, and see if the findings can be replicated as another mode of achieving rapid-acting and long-lasting antidepressant effects in treatment-resistant patients. Intravenous ketamine has rapid-onset antidepressant effects, but its effects are short-lived.*

## Antidepressants and Ketamine Promote Resilience in Animal Studies

To study depression in humans, researchers look to rodents to learn more about behavior. Rodents who are repeatedly defeated by more aggressive animals often begin to exhibit behavior that resembles depression. At the 2014 meeting of the International College of Neuropsychopharmacology (CINP), researcher Andre Der-Avakian reported that in a recent study, repeated experiences of social defeat led to depressive behavior in a subgroup of animals (which he calls susceptible), but not in others (which he calls resilient). **Among many biological differences, the resilient animals showed increases in neurogenesis in the dentate gyrus of the hippocampus.**

Chronic treatment of the susceptible animals with the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine or the tricyclic antidepressant desipramine,

which both increase neurogenesis, also reversed the depressive behavior in about half of the animals. A single injection of the anesthetic ketamine (which has rapid-acting antidepressant effects in humans) reversed social avoidance behavior in about 25% of the animals. One depression-like symptom was anhedonia (loss of pleasure from previously enjoyed activities), which researchers measured by observing to what extent the animals engaged in intracranial self-stimulation, pressing a bar to stimulate the brain pleasurable. The effectiveness of the drugs in inducing resilient behavior was related to the degree of anhedonia seen in the animals. The drugs worked less well in the more anhedonic animals (those who gave up the intracranial stimulation more easily, indicating that they experienced less reward from it.)

## The Child Network is Coming!

Parents, if your child aged 2–12 has mood, anxiety or behavioral difficulties, we would like to enlist your participation in the Child Network, a research network that will provide information about how children with these problems are being treated in the community and how well the treatment is working.

Parents would complete ratings of their child's symptoms and medications (if any) once a week using a secure and confidential web-based system approved by the Johns Hopkins University Institutional Review Board.

We would also like parents with a diagnosis of bipolar disorder whose children are not currently symptomatic to participate, since they may wish to monitor their children's mood and behavior more systematically.

If you are interested in participating in this network, sign up to learn more by going to our website, [www.bipolarnews.org](http://www.bipolarnews.org), and clicking on the Child Network tab. In several weeks, the network will be up and running, and the website will provide more detailed information and a statement about informed consent.

## Antidepressants and Ketamine Reverse Animal Models of Depression

Researcher Tony Pitts presented a study at the 2014 meeting of the International College of Neuropsychopharmacology (CINP) that described the neurobiology of an animal model of depression in rodents. In animal models, researchers provoke depression-like symptoms in animals with the hopes of finding neurobiological clues to human depression. Pitts' studies explored the effects of acute stressors as well as more chronic long-term stressors such as learned helplessness.

In the rodents, acute stressors caused increased cell firing in the hippocampus, which caused increases in burst firing and an increase in the number of cells firing in the ventral tegmental area, which then led to increased activity in the nucleus accumbens (the brain's reward center). However, after the stressor was over, there was an opponent process that resulted in a much more prolonged period of inhibition in the nucleus accumbens, with associated decreases in psychomotor activity and reward seeking. The rodents lost their preference for sucrose and engaged in less intracranial self-stimulation, pressing a bar to stimulate the brain pleurably. These and other effects suggest an analogy to anhedonia (loss of pleasure in activities that were previously enjoyed), which is a key component of human depression.

In related studies, after experiencing periods of inescapable shocks, rodents developed learned helplessness, failing to avoid the area

where shocks were delivered even when an exit was readily available. **Rodents who had learned helplessness showed inhibited firing of cells in the ventral tegmental area, less activity in the nucleus accumbens, and apparent anhedonia.** This inhibition was mediated via messages from the infralimbic prefrontal cortex (the equivalent to the subgenual cingulate cortex in humans, important for motivation) to the amygdala and then the GABAergic ventral pallidum, which decreased the number of dopaminergic cells firing in the ventral tegmental area. Blocking the amygdala input to this inhibitory pathway reversed the low dopamine firing and the anhedonia-like behaviors.

**The anesthetic ketamine (which has rapid-acting antidepressant effects in humans) produced an immediate reversal of the learned helpless behavior in the rodents and increased the number of dopamine cells firing in the ventral tegmental area.** Ketamine administered directly into the nucleus accumbens induces long-term potentiation (enhanced synaptic responsivity) and reverses helpless behavior and the long-term depression of neural firing that is associated with it.

Thus, when an acute stressor is over and the opponent process emerges, or following long-term chronic stressors such as learned helplessness, the excitatory path to the ventral tegmental area is absent, while the inhibitory path

to the ventral tegmental area (via the infralimbic prefrontal cortex, amygdala, and ventral pallidum) predominates. Ketamine is able to re-activate the activating pathway and increase activity in the ventral tegmental area and the nucleus accumbens, changes that are associated with the reversal of learned helplessness and anhedonia.

*Editor's Note: In the previous BNN, we reported researcher Scott Russo's findings that input from the intralaminar nucleus of the thalamus was critical to the depression-like behaviors seen in a different animal model of depression, social defeat stress, where repeated exposure to defeat by a larger, more aggressive animal produces behaviors that resemble human depression. Here in Pitts' research, learned helplessness is induced by inescapable shocks. Both models share the finding that firing decreases in the reward area of the brain (the nucleus accumbens). However, the key part of the brain driving the low levels of activity in the nucleus accumbens and the associated depression-like behavior appear to be different in these two different models. **The intralaminar nucleus of the thalamus plays a key role in the social defeat stress model, while the infralimbic cortex and the amygdala play key roles in the learned helplessness model.** These data together suggest that part of the reason depression differs from person to person may be because the illness can be driven by different brain areas as a result of different kinds of stressors.*



# CLARITY Technology Lights Up Neural Networks in Mice

A new technology is making it possible to view the mammalian brain's structure and connectivity for the first time. Karl Deisseroth discussed the technology, called CLARITY, at a plenary lecture at the 2014 meeting of the International College of Neuropsychopharmacology.

The way CLARITY works is by replacing lipids in the brain with a hydrogel substance. This preserves the structure of the brain's neural networks, leaves proteins and nucleic acids intact, but allows for observation by rendering the brain transparent. This can be done in a system as large as the entire adult mouse brain. Early attempts took a whole day, but Deisseroth eventually found a way to render a mouse's brain transparent in a matter of minutes.

The pictures are truly amazing, allowing for the visualization of previously microscopic neurons, dendrites, axons and connections in life-sized images. Pictures and details are available at [www.clarityresourcecenter.org](http://www.clarityresourcecenter.org).

Deisseroth and colleagues have used CLARITY imaging to determine where neurons fire during different social activities. By placing photosensitive fibers in selected neurons using a virally based gene insertion technique, Deisseroth and colleagues were able to selectively fire dopamine neurons in the ventral tegmental area, part of the brain's reward system, and thus increase or decrease the social interaction of mice by increasing or decreasing firing. The effects were selective to social interaction; the firing did not affect locomotor activity or exploration of an inanimate object.

The ventral tegmental area contains neurons that project to several locations in the brain, and Deisseroth and colleagues hoped to observe which were important to social interaction.

**Stimulating the ventral tegmental area to drive the medial prefrontal cortex caused anxiety in the mice and made them averse to social interaction. However, when the ventral tegmental area was used to selec-**

**tively drive the nucleus accumbens, another part of the brain's reward system, social interaction increased.**

Deisseroth wanted to know if the nucleus accumbens was also involved in normal spontaneous social interactions. The researchers used a virus to insert an opsin-sensitive calcium gene that could give an ongoing readout of neural activity. (Opsin is a light-sensitive receptor found in cells in the retina.)

The team found that the nucleus accumbens was implicated in social interaction with another mouse, but not in exploration of a novel object. Based on CLARITY imaging of the structure of ion channels (which are so small they cannot even be seen with an electron microscope), Deisseroth was able to selectively alter ion fluxes and turn neuronal firing on or off at will.

In the last 50 years, the brain and its billions of neurons and hundreds of trillions of synapses have gone from complete inaccessibility toward increasing clarity.

## Halting Marijuana Use Might Improve Memory in Adolescents

Researcher Amanda Roten reported at the 2014 meeting of the American Academy of Child and Adolescent Psychiatry that adolescents who stopped heavy marijuana use showed improvements in multiple areas of learning and memory. These data support previous findings that pot can cause impairments in cognitive functioning, but that abstaining from the drug can bring about improvement relative quickly.

These data contrast with others that suggest side effects may linger. A 2009 study by J. Jacobus et al. in the journal *Pharmacology Biochemistry and Behavior* suggested that some changes in brain structure resulting from marijuana use, such as decreases in cortical volume, can persist for one to three months following abstinence.

Madeline Meier, another researcher at the meeting, reported that **1,037 participants who used marijuana persistently from about age 13 to age 38 lost an average of 8 IQ points.** Controlling for years of education and other potential confounds such as alcohol and drug use did not affect these findings. Moreover, Meier found that **"cessation of cannabis use did not fully restore IQ among adolescent-onset cannabis users."**

*Editor's Note: The popular view that marijuana is a benign substance overlooks some key facts. The main pharmacological effect of pot is amotivational syndrome, causing apathy and lack of drive to participate in work, study, and other activities. Heavy use of pot doubles the risk of psychosis, and this risk is further increased if a user has a common genetic variation in*

*the enzyme catechol-o-methyl transferase (COMT), which metabolizes dopamine. The more efficient allele of COMT (known as val-56-val, identifying two valine amino acids) lowers frontal cortex dopamine more, and increases the risk of delusions and hallucinations. Marijuana alters brain structure and impairs memory. It may now be legal in some states, and while reducing penalties for smoking marijuana may be a good idea, this does not mean the drug is a harmless substance.*

The moral of the story is that avoiding marijuana use in the first place, especially for people with bipolar disorder, should make it easier to get well and stay well. For current marijuana users, N-acetylcysteine (NAC, a nutritional supplement available without a prescription from health food stores) has been shown to help adolescents decrease marijuana use more than placebo.

# How the Chemicals in Marijuana Work in the Brain

Raphael Mechoulam, who first synthesized THC, the main ingredient in marijuana, gave the history of marijuana and its receptors in the central nervous system in a plenary talk at the 2014 meeting of the International College of Neuropsychopharmacology. In Syria hundreds of years ago the drug was named ganzigunnu, meaning “the drug that takes away the mind.” It has also been called azalla, meaning “hand of the ghost.” Among the 100 compounds in marijuana, the best-known ingredient is delta-9-tetrahydrocannabinol (delta-9 THC), which produces most of the actions of the drug. **There is another active ingredient, cannabidiol (CBD), which has calming and anti-anxiety effects, but is present in very low levels.**

The brain has cannabinoid receptors that respond to ingredients in marijuana in addition to other chemicals produced in the brain. They modulate calcium ions and decrease the release of many neurotransmitters.

THC acts at CB-1 receptors, producing the high. The CB-1 receptor is synthesized on demand, post-synaptically, and is transferred to the pre-synaptic terminal where it decreases calcium and transmitter release. Consistent with marijuana's

appetite-stimulating properties (“the munchies”), if the CB-1 receptor is blocked in animals, they lose their appetite and die of hunger.

There are also low levels of CB-2 receptors in the brain, whose activation does not cause a high, and whose levels may increase dramatically in pathological situations. Activation of the CB-2 receptor is anti-inflammatory and, in the same way that the immune system acts against foreign proteins, CB-2 acts as a protector against non-proteins.

CBD does not bind to any cannabinoid receptors, but its actions are blocked by cannabinoid antagonists.

**There are two chemicals in the brain (endogenous ligands) that act at cannabinoid receptors – anandamide and 2-arachidonoylglycerol (2-AG).** They are soluble only in lipids (not in water), and have never been given to people. In animals, 2-AG has neuroprotective effects, decreases the size of a stroke by 60%, and increases recovery from stroke.

Marijuana and CBD in particular have also had beneficial effects in people. Marijuana decreases the nausea and vomiting associated with chemotherapy in children, has anti-inflammatory effects in rheumatoid arthritis (decreasing inflammatory

marker TNF alpha), and has anti-diabetes and anti-convulsant effects.

In 2012, researcher F. Markus Leweke and colleagues showed that CBD was about as effective as the atypical antipsychotic amisulpiride in alleviating the psychotic symptoms of schizophrenia. CBD's other effects include reducing anxiety and improving psoriasis by increasing DNA methylation (Pucci et al. 2013).

It seems possible that some of these myriad effects of marijuana and endogenous ligands at CB receptors could be exploited for clinical therapeutics, as Mechoulam endorses, but when and how that will take place remains an unanswered question.

*Editor's Note: Despite all these potential positives of CBD, it should be noted that its levels are very low in marijuana, and that heavy smoking of marijuana has substantial adverse effects. These include low motivation, a doubling of the risk of psychosis, a hastening of the onset of bipolar disorder and schizophrenia, and cognitive impairment, as well as some changes in brain structure seen via magnetic resonance imaging (MRI). It may be becoming legal in many states, but is a bad idea for those at high risk for mood, anxiety, or bipolar disorders or for schizophrenia.*

## Methamphetamine Kills Dopamine Neurons in the Midbrain of Mice

Epidemiological studies have linked methamphetamine use to risk of Parkinson's disease, and animal studies of the illicit drug have shown that it harms dopamine neurons. A 2014 study by Sara Ares-Santos et al. in the journal *Neuropsychopharmacology* compared the effects of repeated low or medium doses to those of a single high dose on mice. **Loss of dopaminergic terminals, where dopamine is released, was greatest after three injections**

**of 10mg/kg given at three-hour intervals**, followed by three injections of 5 mg/kg at three-hour intervals, and a one-time dose of 30mg/kg. All of the dosages produced similar rates of degeneration of dopamine neurons via necrosis (cell destruction) and apoptosis (cell suicide) in the substantia nigra pars compacta (the part of the brain that degenerates in Parkinson's disease) and the striatum.

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## Statins May Prevent Cardiovascular Risk in Patients with Mental Disorders

People with major mental disorders such as schizophrenia and bipolar disorder are at increased risk for medical symptoms including overweight, obesity, high cholesterol or triglycerides, diabetes, and the metabolic syndrome, all of which increase risk of cardiovascular disease (heart attack), cerebrovascular disease (or strokes), and other medical difficulties. In a 2013 review article in the journal *Bipolar Disorders*, researcher Chittaranjan Andrade discussed the use of statins to prevent cardiovascular events in people with major mental disorders.

Statins decrease lipids, and have significant benefits in decreasing cardiac events, but their use is low among psychiatric populations. Psychiatric patients often receive less cardiac care. It may be up to their psychiatrists to push for aggressive prevention of cardiac illnesses.

The most significant side effect of statins is the possibility that they can increase risk of diabetes. In a meta-analysis by Preiss et al., **intensive dosing with statins increased the risk of diabetes but also lowered the risk of cardiovascular events.** In a year, 1,000 patients would get two extra cases of diabetes but 6.5 fewer cases of cardiovascular events. For patients at high risk for heart attack or stroke, a cardiovascular event is more dangerous than diabetes, so it makes sense to treat these patients with statins. In patients at lower risk, there is some evidence that diabetes risk was a problem mostly in patients with other risk factors for diabetes, including metabolic syndrome, impaired fasting glucose levels, a body mass index of 30 kg/m<sup>2</sup> or higher, or glycated haemoglobin A (1c) above 6%.

Most studies of statins are conducted on patients in middle age, but there is a rationale for treating even younger patients with statins.

Patients with bipolar disorder develop cardiovascular disease more than a decade earlier than controls. There is some evidence that cholesterol deposits in arteries begin even before age 20, and are cumulative. The risk-benefit ratio for statin use improves with years of use, so starting it earlier may lead to better prevention. Long-term use may reduce the risk of Alzheimer's disease and Parkinson's disease and some cancers in addition to reducing heart attacks and strokes.

Despite the risk of diabetes, it is important to consider statin use in psychiatric patients, especially those who receive antipsychotic medications. Even though these patients are also at higher risk for diabetes, the benefits of statins in reducing cardiac risks may outweigh these risks. Andrade suggests that a conservative rule of thumb would be that psychiatric patients above age 40 with clinically significant elevation of LDL ("bad")

cholesterol should be prescribed statins if three months of diet and exercise changes do not result in improvement, and patients above age 50 should be prescribed statins if they have diabetes or meet at least two of the criteria for the metabolic syndrome, keeping in mind that age and male gender are risk factors for cardiovascular disease, so many patients will already have several risk factors for heart disease. African, Hispanic, and South Asian patients are more vulnerable to cardiovascular disease, so statins may be more strongly indicated among these patients.

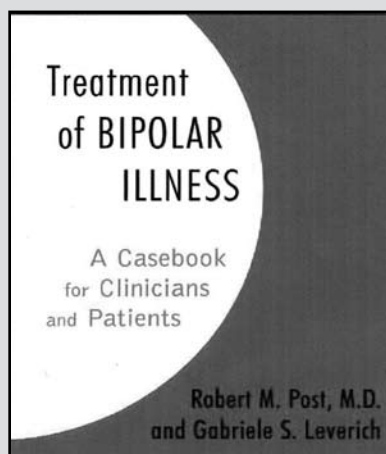
**Another rationale for the use of statins is the finding that they prevented future depressions in a general population**, as reported by Julie Pasco et al. in the journal *Psychotherapy and Psychosomatics* in 2010, and after a cardiac intervention, as reported by Leslie Stafford and Michael Berk in the journal *BMC Medicine* in 2013.

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## Inflammatory Marker NF-kB Elevated in Adolescent Bipolar Disorder

In a poster at the 2014 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Larissa Portnoff reported that **NF-kB, a marker of inflammation that can be measured in two types of white blood cells (lymphocytes and monocytes), was significantly elevated in adolescents who had bipolar disorder compared to healthy control participants.**

Several other inflammatory markers have been linked to bipolar disorder, including c-reactive protein (CRP) and TNF alpha. The new data about NF-kB suggests that another inflammatory pathway is overactive in the disorder. NF-kB levels did not correlate with the severity of manic or depressive symptoms, as do levels of some other inflammatory markers.

## Ratio of Cortisol to CRP: Different Effects in Women and Men

New research suggests that the ratio of cortisol to C-reactive protein (CRP), a marker of inflammation, may be a biomarker of depression that affects men and women differently. **In women, lower ratios of cortisol to CRP were associated with more severe depression symptoms, including poor quality sleep, sleep disturbances, and decreased extraversion. In men, higher ratios of cortisol to CRP were associated with more daytime disturbance and greater anxiety.** The study by E.C. Suarez et al. was published in the journal *Brain, Behavior, and Immunity*.

Further work must be done to confirm whether low cortisol and high inflammation predicts depression in women, while the opposite (high cortisol and low inflammation) predicts depression in men.

## Flavanols May Improve Age-Related Memory Loss

Flavanols, which are found in small amounts in raw cocoa, tea leaves, fruits, and vegetables, may be able to improve age-related memory loss. The normal process by which chocolate is made removes all flavanols from cocoa, but the Mars Inc. company recently developed a process to isolate flavanol in powder form.

In a 2014 study by Scott Small et al. in the journal *Nature Neuroscience*, of 37 participants between the ages of 50 and 69, **those who were randomized to a high-flavanol diet (900mg per day, from drinking the powder mixed with water or milk) over a three-month period showed more improvement on a memory test than those participants who were randomized to a low-flavanol diet (10mg per day).** The high-flavanol group both scored higher than the other group at the end of the study and showed more improvement relative to their own abilities at the start of the study. Small said that after three months of taking the flavanols, someone who began with a typical memory for a 60-year-old developed a memory more like a 30- or 40-year-old. The high-flavanol group also showed improvement in function in a part of the hippocampus called the dentate gyrus.

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