

Bipolar Network News

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Good Weight Loss With the Combination of Bupropion Plus Naltrexone

A 2013 article by Smith et al. in the journal *Diabetes, Obesity, and Metabolism* reports that **obese patients treated with the combination of bupropion (Wellbutrin) and naltrexone (Revia) had excellent weight loss and reduction in body fat compared to those treated with either drug alone or with placebo**. The combination resulted in about a 14% reduction in body fat, while placebo, bupropion alone, and naltrexone alone each brought about only a 3-4% reduction.

Editor's Note: Researcher Roger McIntyre is an expert on the metabolic syndrome in patients with bipolar illness and has been using this combination with success in patients with mood disorders. He finds the combination of

bupropion and naltrexone more helpful than the anticonvulsants topiramate (Topomax) or zonisamide (Zonegran) or the anti-diabetes drug metformin.

Since obesity and the metabolic syndrome occur in approximately 40 to 50% of bipolar patients and significantly increases cardiovascular risks such as heart attack and stroke, and since bupropion is widely used in the treatment of bipolar depression, this combination appears worthy of consideration for those with obesity. Its use should be accompanied by a good diet and an exercise regimen. Decreasing cardiovascular risk is a very important component of the treatment of bipolar disorder, and the combination of bupropion and naltrexone could have substantial benefits.

Vitamin D3 has Positive Effects in Depressed Patients on Prozac

A recent study of patients taking fluoxetine (Prozac) for major depression found that adding 1500 IU of vitamin D3 to their treatment regimen improved their response significantly. The article was published in the *Australian and New Zealand Journal of Psychiatry*.

According to the Mayo Clinic, "The term 'vitamin D' refers to several different forms of this vitamin. Two forms are important in humans: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D2 is synthesized by plants. Vitamin D3 is synthesized by humans in the skin when it is exposed to ultraviolet B

(UVB) rays from sunlight. Foods may be fortified with vitamin D2 or D3."

Editors Note: Here is another augmenting agent that could be considered for the treatment of those with residual depression. While vitamin D has not been studied directly in bipolar depression, we could ask, "Why not try it?" Other nutritional supplements in this category might be folate and N-acetylcysteine.

Vitamin D supplements are definitely indicated for the large percentage of those in the US who are vitamin D deficient. Given the data from this randomized trial, vitamin D3 could be considered in those with normal levels of vitamin D as well.

Also in this issue:

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Vitamin D Low in Youth with Mania

Vitamin D3 is low in children and adolescents with mania, but taking a supplement could help. Vitamin D3, which we absorb via food and sunlight, is converted by the liver to a form called 25-OH-D. In a small study, Elif Sikoglu et al. found that children and teens with mania had lower levels of 25-OH-D in their blood compared to typically developing youth of similar ages. This deficit was associated with lower brain GABA levels measured with magnetic resonance spectroscopy. GABA dysfunction has been implicated in the manic phase of bipolar disorder. **An 8-week trial of Vitamin D3 supplements significantly reduced manic symptoms and tended to increase GABA levels.**

Editor's Note: Other data have suggested that children with psychosis have low Vitamin D3, and in a recent clinical trial in adults, Vitamin D3 supplementation improved antidepressant response more than placebo. Many children in the US are Vitamin D deficient. Test them and, if necessary, treat them, especially if they have bipolar disorder.

Despite FDA Warning: Antidepressants Do Not Increase Suicidality

In 2007, the FDA began labeling antidepressants with a warning that patients aged 18-24 were at risk for increased suicidality during the first weeks of treatment. **New evidence shows antidepressants actually have beneficial effects on suicide risk in adults and youth.** A study of all published and unpublished data on the SSRI fluoxetine (Prozac) and the SNRI venlafaxine (Effexor) published in 2012 by Gibbons et al. in the *Archives of General Psychiatry* showed that these antidepressants substantially reduced suicidal thoughts and

behavior in adults and produced no increase in suicidal thoughts or behavior in children and adolescents.

The protective effect on suicidality in adults was mediated by mood, i.e. the patients' mood improved and they became less suicidal. Children's mood also improved on the antidepressants, but their risk of suicidal ideation did not change.

Editor's Note: These are important findings. When the FDA box warning on antidepressants and suicidal ideation appeared, antidepressant treatment of youth decreased without an accompanying increase in psychotherapy, and the actual suicide rate in youth increased.

We now know that childhood-onset depression carries a bigger risk for a poor outcome in adulthood than adult-onset illness. In parallel, greater numbers of depressions are associated with more impairment, disability, cognitive dysfunction, medical comorbidities, treatment resistances, and neurobiological abnormalities.

It is important to treat illness in youth in order to prevent these difficulties, and the suicide warning should not deter the use of antidepressants. Clinicians should be careful about suicidal ideation in the first several months after a patient starts an antidepressant, as other data suggest that this is a time of slightly increased risk of suicidal thoughts in children and adolescents.

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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Antiepileptic Drugs for Bipolar Disorder Do Not Increase Risk of Suicidal Behavior

A 30-year observational study published by Andrew Leon and colleagues in the *American Journal of Psychiatry* has found that **anticonvulsants used in epilepsy and for bipolar depression (carbamazepine, lamotrigine, and valproate) do not increase suicidal behavior in bipolar patients.**

Editor's Note: The FDA gave a warning in 2009 that these anticonvulsants were associated with suicidal ideation. This was based on studies of a mixed group of psychiatric and neurological patients in acute placebo-controlled studies, where suicidal ideation is typically a reason for exclusion from the study. Leon et al. used more powerful longitudinal methods to compare the risk of suicidal ideation in individuals

taking and not taking anticonvulsants and found no such increase in suicidal behavior.

This is like the FDA warning for antidepressants and suicide, which was based on data from placebo-controlled clinical trials in acute depression (where suicidal patients are excluded). When investigators used the same longitudinal methods as Leon et al. in the anticonvulsant study, they found that antidepressants actually reduced suicidal behavior by 30%.

The bottom line is that the use of anticonvulsants for bipolar disorder should not be discouraged based on the FDA warning about suicidal ideation in mixed neurological and psychiatric patients. In bipolar patients, anticonvulsants do not increase the risk of suicidal behaviors, i.e. suicidal acts or completed suicides.

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Chromium Picolinate May Be Worth Another Look In Atypical Depression

Atypical depression is characterized by overeating and oversleeping compared to the loss of appetite and early morning awakening associated with melancholic depression. A recent placebo-controlled study of chromium picolinate (600µg of elemental chromium) for atypical depression was not initially successful, but researcher Maurizio Fava and colleagues re-analyzed the data using a "population-enrichment strategy" to control for excessively high or low placebo response rates. Their analysis looked more positive than the initial analysis, but remained non-significant, possibly due to the small size of the study. However, **the positive trend they saw made the researchers think that chromium picolinate is worthy of future study.**

Editor's Note: Chromium picolinate had previously been shown (in one study by John Docherty et al.) to have positive effects in reducing carbohydrate craving when compared to placebo. If it only did that, it would still be useful for those struggling with overeating, even if it failed to improve other aspects of atypical depression.

Lisdexamfetamine Is Effective For Binge Eating

Susan McElroy and colleagues are investigating whether lisdexamfetamine dimesylate (LDX) can treat binge eating. The research group carried out an 11-week blind randomized placebo-controlled trial of the drug at three different doses (30mg/day, 50mg/day, and 70mg/day). Patients taking the 50mg and 70mg doses of the drug did significantly better than those taking placebo on most end points, including global improvement and reducing number of days bingeing. **More of the patients taking those doses of lisdexamfetamine were able to achieve a 4-week cessation of bingeing.** The researchers concluded that larger trials are warranted to confirm the drug's efficacy and safety profile among binge eaters.

Editors Note: The anticonvulsants topiramate and zonisamide have also shown efficacy in reducing the number and severity of binges in other placebo-controlled studies by McElroy et al.

Botox May Improve Depression

Relaxing facial frown muscles with Botox may produce antidepressant effects. The muscles on the forehead between the eyebrows tend to tense and constrict during episodes of depression, anxiety, and grief. A placebo-controlled clinical trial by Eric Finzi and Norm Rosenthal has shown that **paralyzing these frown muscles can produce antidepressant results.**

Study participants with treatment-resistant depression received either paralyzing injections of botulinum toxin, better known by its trade name Botox, or placebo injections. The antidepressant response rate was 51% among patients who received Botox and 14% among those who received placebo. The remission rate was 27.3% with Botox versus 7.3% with placebo injections. These data are particularly striking because these patients had, on average, been ill for more

than two years, during which time they had been through multiple unsuccessful antidepressant trials.

In 1872, Charles Darwin emphasized the importance of facial muscles in social communication and affect, and in 1890 William James suggested that sensory feedback from musculature changed people's affect, rather than the opposite and conventional view that affective and emotional states cause muscles to tense and contract. The new data from Finzi and Rosenthal's study are consistent with James' view.

The investigators concluded that the data from this study suggest frowning itself may cause depression. More controlled trials using other injection sites would be helpful to further document the efficacy and selectivity of these Botox injections for the treatment of depression.

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Epigenetics Update: How We Pass On More Than Our Genes

In the *BNN* we have previously written about the role of epigenetics in the onset and course of bipolar disorder. Epigenetics refers to the idea that events and substances in the environment can affect the structure of DNA by adding chemicals (often methyl or acetyl groups) onto DNA and histones (structures around which DNA is wound) in such a way that the DNA is more or less likely to be transcribed and activated to produce new proteins. Thus our DNA is shaped not only by the genetic inheritance we receive from our parents, but also by events in the environment (which do not alter the sequence of DNA but can influence how easily the DNA gets turned on to produce proteins in our bodies.)

Researcher David Sweatt published a review article on epigenetics and memory in the journal *Neuropsychopharmacology* in 2012. In it he examined research on rodents who show epigenetic changes after repeatedly being exposed to stimuli such as a fear-inducing environment or cocaine and learning to respond in a certain way.

Sweatt made two main points about the potential therapeutic implications of mechanisms by which this learning influences gene expression. The first is that histone deacetylase (HDAC) inhibitors like sodium butyrate and valproate can enhance the extinction of contextual fear conditioning (when a rodent experiences danger in a particular place and begins to associate fear with that particular physical environment).

Similarly, in rodents who have been given cocaine and whose interest in

cocaine is associated with the physical environment they were in while receiving the cocaine, researcher Marcelle Wood reports that extinction of this context-dependent cocaine-induced place preference could also be enhanced with an HDAC inhibitor.

Sweatt's second point was that DNA methylation is necessary for long-term memory, and traumatic learning like that of the rodent avoiding the

place it encountered danger can actually be erased using zebularine, an inhibitor of DNA methylation.

Editor's Note: Zebularine can also reverse other lifelong responses to neonatal trauma such as decreases in brain-derived neurotrophic factor (BDNF), a neuroprotective factor necessary for long-term memory, in the prefrontal cortex. Zebularine can also

block the long-lasting increases in motor activity in response to repeated cocaine use, i.e. cocaine sensitization. Thus, it looks like much of what one learns or responds to in the environment is coded at the level of epigenetics when DNA or histones are methylated and/or acetylated (among other chemical modifications).

Amazingly, some of these epigenetic marks on our DNA and histones can even be transmitted to the next generation!

At a recent conference, researcher Johannes Bohacek reported that in an experiment in which rat pups were repeatedly separated from their mothers for 3 hours at a time and the mothers were exposed to unpredictable stressors, not only were the pups more stressed as adults, but when

the males were mated with females who had not been exposed to stress as pups, the father's stress alone produced epigenetic effects in the next 3 generations. Surprisingly, with each generation, the sex of the offspring affected alternated. Males in the first generation showed more floating in a swim stress paradigm (indicating they gave up trying to swim, an indirect measure of depression) while females in the second generation were affected, and then males were again affected in the third generation. Social interaction deficits also crossed generations.

Also at the conference, Eric Nestler showed that the depression- and anxiety-like behavioral effects of defeat stress (which occurs when a small rodent is repeatedly exposed to the threat of a larger rodent defending its territory) could be transmitted (presumably via sperm) to a second and third generation.

Researcher Jasmine Hurd, likewise, reported that some of the behavioral effects of tetrahydrocannabinol (marijuana) could be transmitted to the next generation.

Moral of the story: Not only do we get our unalterable genetic inheritance from our mother and father, but some of what our parents learned or experienced could be passed on to us and perhaps to subsequent generations by epigenetic mechanisms, i.e. ones that do not change the genes or DNA sequences, but can change how easily our inherited genes get turned on or off and thus affect our behavior. The wistful admonition to "choose your parents well" may be more meaningful than we ever realized, since catastrophic stressors they experienced may in some instances affect us. Note of caution—it is clear that the genes we inherit do not deterministically dictate our traits or life course, and epigenetic influences are likely to have even more subtle effects on our behavior and to be further modified by other environmental influences.

Twins Shed Light on Epigenetic Mechanisms Implicated In Bipolar Disorder

At the 5th Biennial Conference of the International Society for Bipolar Disorders, H. Sugawara and colleagues reported on a particular example of epigenetics, an emerging field that studies ways that events and substances in the environment affect the structure of DNA. Often methyl or acetyl groups attach to DNA, making it easier or more difficult to transcribe. Sugawara's group discussed hypermethylation of the serotonin transporter gene in bipolar disorder in an analysis of monozygotic twins discordant for bipolar disorder.

Monozygotic (identical) twins are highly concordant for bipolar disorder, meaning if one has the illness the other is likely to, but this does not occur 100% of the time. Thus, environmental or epigenetic mechanisms could account for the lack of genetic transmission of

the illness in the odd cases in which one twin does not develop the illness.

Sugawara's research group found that **DNA hypermethylation of the allele encoding the serotonin transporter occurred in the twins with bipolar illness but not in those without**. Once the expression of this particular gene had been identified as a difference between twins with and without bipolar disorder, the researchers examined the gene in non-twin patients with bipolar disorder compared to healthy controls and confirmed that **people with bipolar disorder were more likely to have the hypermethylated allele**.

The researchers believed that carrying a short form of the serotonin transporter was associated with DNA hypermethylation, and they went on to study the expression of mRNA for the

transporter in bipolar patients carrying the short form of the allele. They found that DNA methylation was also higher at the serotonin transporter site in postmortem brains of bipolar patients.

Editor's Note: This study provides one of the first insights into possible environmental mechanisms that explain why some people at risk for bipolar disorder develop the illness and others do not. Another possible mechanism for differential expression of the illness has been suggested by E.F. Torrey and colleagues, who believe that a viral infection may enter an individual's genome and directly alter DNA sequences. The current data from Sugawara's research group suggest the importance of further study of the serotonin transporter site in bipolar disorder and the mechanistic reasons for the DNA hypermethylation that occurs there.

Depression Associated with Increased DNA Methylation on Genes

Epigenetics is an emerging field in which researchers are studying the ways environmental events and biochemical changes can affect the structure of DNA. Chemicals such as methyl groups can accumulate on DNA (a process called methylation), which usually results in suppression of genes in that area. DNA is tightly wound around proteins called histones, which can also be methylated or acetylated (when acetyl groups accumulate) based on events in the environment, including stressors and drug use. The environmental events do not change the genetic inheritance people receive from their parents, but instead change the ease with which genes are transcribed (or switched on).

At the 2012 meeting of the Society of Biological Psychiatry, Dr. Yurong Xin et al. presented an abstract that indicates that **depressed patients may have much more DNA methylation at CpG sites on genes**. CpG sites occur

in many genes and refer to a place where a cytosine and a guanine (two of the four building blocks of DNA) sit next to each other on the same strand of DNA (the 'p' refers to the chemical bond between the two). CpG sites can become methylated. Xin and colleagues measured 27,578 CpG sites across 14,000 genes in the human genome. They found an eightfold increase in DNA methylation at these CpG sites in depressed patients compared to controls.

Editor's Note: Previous research has found that early life experiences like psychosocial stress can lead to epigenetic changes. The new findings by Dr. Xin indicate that DNA methylation may occur and accumulate across the lifespan and suggests that DNA methylation may be associated with the emergence and progression of depression. Future treatments for depression could target this DNA hypermethylation, but determining how to do that selectively without affecting normal functioning may be a challenge.

Rats Exposed to Jet Fuel Pass Epigenetic Changes On to 3rd Generation

A recent study of rats showed that **exposure to hydrocarbons (jet fuel JP-8) can bring about disease not just in the rats who were exposed, but also in subsequent generations**. Epigenetics is the study of how environmental events or biochemical changes can affect the structure of DNA, e.g. by attaching extra methyl groups. (These kinds of "epimutations" are separate from the inherited genetic makeup we receive from our parents, but new evidence suggests that some can be passed on to future generations.)

When first generation female rats were exposed to jet fuel, third generation rats showed 33 different examples of DNA methylation as well as obesity.

Previous research has shown similar signs of transgenerational transmission of disease resulting from first generation exposure to chemicals such as bisphenol A, phthalates, dioxins, and pesticide mixtures.

Reminder: Multiple Risks for Fetus in Mothers Treated with Valproate

In pregnant women, exposure of the fetus to the anticonvulsant valproate (VPA or Depakote) is associated with a variety of serious problems that include congenital malformations, developmental delay, and autism.

The major congenital malformations that can result from valproate exposure include spina bifida, which results in lifelong paralysis of the child's lower limbs.

Developmental delay resulting from valproate exposure can cause an average loss of 9 IQ points compared to children exposed to other anticonvulsant drugs in utero. The effects appear to be in part dose-related and dependent on the intensity of combination treatment with other agents. These deficits were originally seen in children at 3 years of age and were shown to persist in six-year-olds according to an article by Meador et al. this year in *Lancet Neurology*.

Now in addition, fetal exposure to valproate has been linked to autism and related disorders in an 11-year longitudinal study published this year in the *Journal of Neurology, Neurosurgery and Psychiatry*. A diagnosis of a developmental disorder occurred in 17% of children whose mothers were on valproate as opposed to 2% whose mothers were on carbamazepine and 7% whose mothers were on lamotrigine.

Neurologists are increasingly recommending that all women of childbearing age who are on a treatment regimen including valproate be treated with folic acid and vitamins B6 and B12, in the hopes that these might mitigate valproate's effects on the fetus in the case of an unplanned pregnancy. The effectiveness of these vitamins has not been directly demonstrated. However, the study by Meador et al. did show that children of mothers who

took prenatal folic acid supplements had IQs on average 7 point higher than children whose mothers did not. The benefit was seen only when mothers were already taking folic acid when they became pregnant and was not observed in children of mothers who began taking it after the first trimester.

Women of childbearing age should avoid valproate and if this is not possible, they should carefully protect themselves against an unwanted pregnancy. Women with bipolar disorder are 3.9 times more likely to have unplanned pregnancies than women of similar age in the general population. These data suggest the importance of careful education about birth control in patients with bipolar illness so that pregnancies can be planned for periods of good health and so that appropriate pharmacological measures can be taken.

Preterm Birth Is Risk Factor for Bipolar Disorder

A study published in the *Archives of General Psychiatry* in 2012 sampled over one million births in Sweden and suggested that **preterm birth (from 32 to 36 weeks) doubled the risk that a child would develop bipolar disorder later in life**. Those born even earlier had a sevenfold increased risk for bipolar disorder.

Editor's Note: A robust research literature indicates that schizophrenia is related to obstetrical and other pre- and perinatal medical problems. Now it seems bipolar disorder may be as well, with some caveats. Low Apgar score (which indicates difficulties at birth) and delayed growth were not found to relate to bipolar risk. Thus something about the shortened preterm development seems to convey the risk. The authors suggest that there may be different types of factors that predispose a person to develop bipolar disorder,

and that in some people the illness may have development origins.

These data also fit with observations that only about 50% of patients with bipolar disorder have a positive family history of the illness. Thus, while bipolar disorder does run in families and has a strong genetic basis in many instances, there are many people who develop the illness without having this genetic/familial risk. Very preterm birth appears to be one other contributing risk factor, presumably among many others.

Understanding the neurobiological mechanisms occurring before birth that mediate this risk may lead to direct preventive measures to lessen the risk. In the meantime, traditional measures supporting good maternal and fetal health are a good place to start. These include regular prenatal checkups, good nutrition, and prenatal vitamins that include high doses of folic acid.

Intermittent SSRI Treatment Helps Premenstrual Syndrome

Research has shown that serotonin-selective reuptake inhibitor (SSRI) antidepressants can be useful for severe premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). According to a 2006 article by Steiner et al. in the *Journal of Women's Health*, there are various ways that SSRIs can be used to treat PMS symptoms such as irritability, depressed mood, dysphoria, bloating, breast tenderness, appetite changes, and psychosocial function, including continuous and intermittent dosing. Usually doses for PMS are lower than those used to treat depression.

For those women with mood symptoms only during PMS, intermittent dosing from around the time of ovulation to a few days after the period begins seems to be helpful and minimizes side effects of the SSRIs.

Editor's Note: While SSRIs sometimes take weeks to reach maximum benefit for those with depression, intermittent dosing for women with severe PMS seems to be helpful. This may be because SSRIs acutely increase the neurosteroid allopregnanolone, which enhances GABA-A receptor activity, associated with improvement in mood and anxiety.

Women with Bipolar Disorder at Higher Risk for Postpartum Depression

The risk of having a depressive episode during pregnancy compared to afterward have not often been studied. A 2011 review article by Viguera et al. in the *American Journal of Psychiatry* compared rates of affective episodes among women with bipolar I and II disorders and recurrent major depressive disorder, both during pregnancy and the postpartum period. Risks were higher for women with bipolar disorder.

Among women with bipolar disorder, 23% experienced mood episodes during the pregnancy, while 52% had an episode in the months after giving birth. Among women with unipolar depression, 4.6% had a mood episode during pregnancy, while 30% did during the postpartum period, which is about double the risk seen in the general population. Depression was the most common type of morbidity the women experienced before and after giving birth.

Risk factors associated with mood episodes during pregnancy included (in descending order): younger age at illness onset, previous postpartum episodes, fewer years of illness, bipolar disorder, fewer children, and not being married. Risk factors associated with postpartum episodes included: younger age at illness onset, illness during pregnancy, bipolar disorder, fewer children, and more education.

Editor's Note: The risk of postpartum depression increases from 15% in the general population, to 30% among women with unipolar disorder, to 50% in women with bipolar disorder. Special precautions should be taken to monitor and treat depression during and after pregnancy, in all women but particularly in those with a prior history of unipolar or bipolar disorder.

Choline Treatment For Pregnant Mothers And Newborns Improves Babies' Cognition and Normalizes a Risk Factor for Schizophrenia

Deficiencies in GABA inhibition have been linked to the risk of schizophrenia (and perhaps bipolar disorder). GABA receptors are initially excitatory but switch to being inhibitory early in life. Choline derived from phosphatidylcholine or from eggs and meat in the diet is important in increasing GABA receptor development and maturity.

Ross et al. reported this year in the *American Journal of Psychiatry* that in a placebo-controlled study in which mothers took phosphatidylcholine in the last 2 trimesters of pregnancy (at doses of 3,600mg in the morning plus 2,700mg in the evening) and infants took 100mg/day for 12 weeks, **the infants who received choline showed better neuronal inhibition than infants who did not receive choline** on a P50 test of auditory evoked potential, in which the brain's response to a series of beeps is recorded. An overactive P50 response is a sign of deficiencies in GABA inhibition.

In infants with a common gene variant in the alpha 7 nicotinic receptor that makes it function less well (which also may be a risk factor for the development of schizophrenia), the choline regimen normalized the P50 test, while

placebo had no effect. However, in a recent study by Cabranes et al. published in *Psychiatry Research*, there was no association of the alpha 7 gene variant and schizophrenia or bipolar disorder, although patients with bipolar disorder and patients with schizophrenia did perform differently on the P50 evoked potential test than controls did.

Editor's Note: In an editorial by Judy Rapoport that accompanied the Ross et al. study, the difficulty of using the findings in clinical practice are discussed. Meck et al. showed in 1999 that choline supplementation enhanced spatial memory, and in several cases nutritional supplements can have beneficial effects on the brain. Rapoport notes the success of perinatal folate in preventing neural tube defects and the likelihood that Vitamin D supplementation can prevent some cases of schizophrenia.

However, extrapolating the choline findings of Ross et al. to clinical practice, especially given the lack of association of the alpha 7 gene variation to psychiatric illness in the study by Cabranes et al., might be premature. Instead, Rapoport recommends a good diet and prevention of infection as first steps for treatment. Choline supplementation would be roughly equivalent to three eggs a day.

No Relationship Between SSRIs in Pregnancy and Stillbirths or Neonatal Mortality

Much has been written about the use of selective serotonin reuptake inhibitor (SSRI) antidepressants during pregnancy. In a review of 920,620 births in Denmark (1995 to 2008) that Jimenez-Solem published this year in the *American Journal of Psychiatry*, **no link was found between any of the SSRIs used in any trimester and risk of stillbirth or neonatal mortality.** The only exception was a possible association of three-trimester exposure to citalopram and neonatal mortality.

Editor's Note: These new data may be of importance to women considering antidepressant continuation during pregnancy when there is a high risk for a depressive relapse. A maternal depressive episode (like other stressors such as anxiety or experiencing an earthquake) during pregnancy does convey adverse effects to the fetus, so appropriate evaluation of the risk/benefit ratio or staying on an antidepressant through a pregnancy is important.

Folic Acid During Pregnancy May Lower Autism Risk

A study of 85,000 children in Norway that was recently published in the *Journal of the American Medical Association* showed that **women who took folic acid during pregnancy were 40% less likely to have a child who developed autism.**

A summary of the research by National Public Radio explained, "Folic acid is the synthetic version of a B vitamin called folate. It's found naturally in foods such as spinach, black-eyed peas and rice. Public health officials recommend that women who may become pregnant take at least 400 micrograms of folic acid every day to reduce the chance of having a child with spina bifida."

The folic acid's effect reduced the most severe cases of autism but did not seem to have an effect on the incidence of more mild forms, such as Asperger syndrome. The benefits were seen in those women who had been taking folic acid for 4 weeks before conception and continued to take the supplement during the first 8 weeks of pregnancy.

Folic Acid Not Linked To Cancer

Folic acid is often recommended for patients with difficult-to-treat depression and for pregnant women. A recent study suggested that when taken before and in the first weeks of pregnancy, the vitamin supplement can reduce the risk of autism in the child. However, some concern was raised after a 2007 study that suggested a possible link between folic acid and cancer risk. **New research indicates that cancer is not a risk of folic acid supplementation.**

In a meta-analysis that analyzed data from 13 different trials of folic acid that included a total of over 49,000 patients,

no increased risk of cancer was found in patients taking folic acid. The meta-analysis was published this year in the *Lancet*.

Editor's Note: In addition to folic acid's beneficial effects during pregnancy, it can also enhance the effects of antidepressants and mood stabilizers. The dose typically recommended for depression is 1mg for women and 2mg for men. Fifteen percent of the population has an inefficient form of the enzyme methylenetetrahydrofolate reductase (MTHFR), which converts folate to methylfolate. For treatment of depression in these individuals, l-methylfolate should be used instead of regular folic acid.

Arbaclofen May Improve Social Behavior in Fragile X Syndrome and Irritability in Autism

Fragile X syndrome is a genetic condition that is the most common single-gene cause of autism and inherited cause of intellectual disability. In addition to mental disabilities it is also characterized by certain physical characteristics (elongated face, protruding ears, and large testes in boys), stereotypic movements such as hand-flapping, and social anxiety.

When autism is associated with Fragile X, a mutation in the Fragile X gene is responsible for the autism. (It is also possible to have autism without Fragile X, or to have Fragile X without autism.) Fragile X is a genetic disorder like Down's Syndrome, while autism is a complex behavioral disorder, likely involving multiple genetic and environmental vulnerabilities.

A new drug called arbaclofen seems to improve social avoidance and problem behaviors in adults and children with Fragile X. Researchers hypothesize that normal social stimuli overwhelm a Fragile X patient because of a defect in inhibition, and arbaclofen acting on presynaptic GABA-B

receptors reduces glutamate release, thereby reducing the overactive signaling associated with this defect.

In a 6-week placebo-controlled study of arbaclofen among 63 patients with Fragile X ranging in age from 6 to 39, patients 11 years old and younger received 10mg twice a day and patients 12 and up received 10mg three times a day. The drug was well-tolerated, with only a few reports of sedation or headache. While problem social behaviors and neurobehavioral function improved, irritability did not. The study considered irritability because that is the aspect of autism most often improved by other Federal Drug Administration-approved drugs for autism, such as risperidone and aripiprazole. In another study of arbaclofen in autism spectrum disorders, it did improve irritability and agitation.

Editor's Note: The GABA-B agonist arbaclofen has previously shown positive effects in motor spasticity. The positive effects noted here in the social domain of autism spectrum disorders and Fragile X are very promising.

Physical Punishment Linked to Mood Disorders

Physical punishment of children has long been a controversial subject. A 2012 article by Afifi et al. in the journal *Pediatrics* suggests that **having experienced harsh physical punishment during childhood is associated with mood disorders, anxiety disorders, substance abuse and dependence, and personality disorders in adulthood.**

In this study harsh physical punishment included pushing, grabbing, shoving, slapping, or hitting. Participants who had experienced more severe maltreatment in childhood (including physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect, and exposure to violence between intimate partners) were excluded from the study, and the results were adjusted for sociodemographic variables and family history of dysfunction, suggesting that physical punishment was the mediator of these effects.

Drug for Fluid Retention May Be Useful in Autism

Bumetanide has been used for decades to treat fluid retention in those with heart failure or liver or kidney disease. In the brain, it allows chloride ions to leave cells more easily. Scientists researching pediatric seizures think that reducing the chloride inside brain cells helps GABA neurons' inhibitory functions work better. This led to speculation that bumetanide could be useful in neonatal epilepsy and autism.

In a 2012 study by French researchers including Eric Lemonnier that was published in the journal *Translational Psychiatry*, 60 patients aged 3 to 11 who had been diagnosed with autism or Asperger's syndrome were given either placebo or 1mg of bumetanide daily for 3 months. By the end of the study, the children who received bumetanide showed an average reduction of 5.6 points on the Childhood Autism Rating Scale (CARS), which is assessed from observing behavior during videotaped sessions of children playing with their

caregiver and questioning the child's parents. Children taking placebo showed a reduction of 1.8 points (a statistically significant difference).

Clinicians in the study rated almost twice as many children who took bumetanide as having made a significant or a small improvement. Stereotyped behavior and restricted interest were the areas of behavior that seemed to improve most after treatment with bumetanide. Patients with milder autism when the study began tended to improve more than those who started out with more severe symptoms. Symptoms returned to previous levels within a month the study's end.

Bumetanide's side effects are well known. It can sometimes cause decreases in potassium in the blood (hypokalemia), so the children's potassium levels were monitored closely. One child was withdrawn from the study for hypokalemia, which can predispose one to cardiac arrhythmias.

Adolescent Brain Particularly Susceptible to Decline in IQ from Marijuana Use

A decades-long study in New Zealand suggests that **people who use marijuana persistently during adolescence lose 8 IQ points by adulthood compared to their peers who never use marijuana.** Quitting or reducing cannabis use after adolescence did not restore the intellectual abilities in those who used it persistently in their youth. This is the first study of its kind that controlled for differences in functioning that existed before adolescence.

Participants took part in neuropsychological testing at the age of 13, prior to any cannabis use, and then

were periodically interviewed about their use of the drug (at the ages of 18, 21, 26, 32, and 38). At age 38 they underwent IQ testing again.

Although persistent cannabis users tended to have fewer years of education, the lack of education was not responsible for the difference in adult IQ.

Those participants who only began using cannabis persistently in adulthood did not see a decline in IQ, suggesting that the adolescent brain is particularly susceptible to damage from cannabis use.

Synthetic Marijuana Has Many Risks, Especially in Pregnancy

Synthetic marijuana, otherwise known as spice, skank, or K2, is not only vastly more potent than the tetrahydrocannabinol (THC) in marijuana plants, but it also lacks cannabidiol (CBD), the calming, antipsychotic substance also present in the plants. This makes spice much more likely to induce major psychiatric effects.

New evidence links use of synthetic marijuana during pregnancy to a tragic birth defect, anencephaly, or absence of the cerebral cortex. It can also lead to the later development of attention-deficit hyperactivity disorder, learning disabilities, memory impairment, depression, and aggression.

Effects of THC on gestation may occur as early as two weeks after conception, meaning by the time a woman realizes she is pregnant, the fetus may have been harmed by exposure to the drug.

Other new finding associate use of spice with acute coronary syndrome and the kind of acute kidney injury that can lead to the organ shutting down.

Editor's Note: It has now been found that synthetic marijuana, or spice, can lead to psychosis, delirium, acute coronary syndrome (heart attack) in young people, and now kidney dysfunction, in addition to causing birth defects if used by pregnant women. Not only is spice made up of more potent THC without the calming effects of CBD, but it is often laced with unknown contaminants, which are likely the cause of the heart and kidney damage.

Smoking regular marijuana is bad enough – it doubles the risk of psychosis and may precipitate the onset of schizophrenia. It may also cause long-lasting effects on cognitive function. Since many states are legalizing marijuana, it is important to know the risks. In any case the risks are much more serious with the synthetic product, and synthetic marijuana should be avoided at all costs.

Access to nimodipine?

Several patients have had trouble finding the drug nimodipine. If any of our readers are aware of a US pharmacy that carries nimodipine, or another source of the drug, please let us know.
Email mccauleybcn@gmail.com.

Adding an Exercise Regimen Helps Improve Residual Depression

Many patients with depression require two or more treatments in order to achieve remission. In a 2011 study by Trivedi et al. published in the *Journal of Clinical Psychiatry*, **patients with major depressive disorder who had not responded adequately to selective serotonin reuptake inhibitor (SSRI) antidepressants improved when an exercise regimen was added to their regular treatment.**

The patients, aged 18-70 years old, were all sedentary at the start of the trial. They were randomized to one of two exercise regimens: a high dose regimen (16 kcal/kg per week, equivalent to walking at about 4 mph for 210 minutes per week) or the low dose (4 kcal/kg per week, equivalent to walking at 3 mph for about 75 minutes per week). Both groups improved significantly by the end of

the study. Remission rates (adjusted for differences between groups) were 28.3% for the high dose group and 15.5% for the low dose group.

The rates of improvement with exercise were similar or better to those commonly seen with other augmenting agents such as lithium, T3, buspirone, and atypical antipsychotics, but without side effects and other inconveniences such as blood monitoring.

Other studies have indicated that exercise by itself and in combination with other treatments has efficacy in depression. Exercise can change serotonin and norepinephrine function and can increase brain-derived neurotrophic factor (BDNF) and neurogenesis in the hippocampus.

The researchers looked for moderating variables that may have affected the outcomes of various participants. Men,

regardless of family history of mental illness, had better remission rates in the high dose group. Women without a family history of mental illness also improved more in the high dose group, while women with a family history of mental illness improved more in the low dose group, though this finding was statistically nonsignificant.

While the researchers observed that those in the high-dose group did exercise more than those in the low-dose group, participants in the high-dose group had more difficulty sticking to their exercise regimen. It may be that even though high doses of exercise offer slightly higher rates of remission, lower doses may be more effective clinically if patients can stick to the low-dose regimen better.

Lifetime Heart Disease Risk Increases Dramatically When One or More Risk Factors Are Present in Middle Age

A meta-analysis of 18 studies that was published by Donald Lloyd-Jones in the *New England Journal of Medicine* in 2012 shows that increasing cardiovascular risk factors during middle age can dramatically increase a person's risk of experiencing fatal cardiovascular disease, fatal coronary heart disease, nonfatal heart attack, or stroke later in life.

Data were analyzed from 257,384 patients, who included black and white men and women spanning a 50-year range of birth cohorts. The studies examined cardiovascular risk factors such as smoking, cholesterol levels, diabetes, and blood pressure at ages 45, 55, 65, and 75.

Having even one risk factor at age 55 dramatically increased the lifetime risk of cardiovascular disease compared to having no risk factors, and having more risk factors during middle age increased risk even further. Among

people with no risk factors at age 55 (meaning cholesterol under 180mg/dL, blood pressure under 120 mm Hg systolic and 80 mm HG diastolic, nonsmoking and nondiabetic), men had 4.7% risk of death from cardiovascular disease by age 80 (compared to 29.6% for those with 2 or more risk factors). Women had a 6.4% risk of death from cardiovascular disease by age 80 (compared to 20.5% among those with 2 or more risk factors).

Lifetime risk of death from cardiovascular disease and coronary heart disease and risk of nonfatal heart attack were about twice as high in men, while risk of stroke was similar for men and women.

Across race, trends were similar, but this finding can be misleading. While African-Americans have more cardiovascular risk factors than whites, they are also more likely to die at younger ages from other

causes before developing serious cardiovascular illnesses. Large studies with Latino and Asian American participants were begun too recently to provide robust data about long-term risk, but this research is expected to become available soon.

Editor's Note: Watch out for the risk factors for heart disease (including high blood pressure, cholesterol, weight, and blood sugar), and reduce them. The more risk factors one has, the greater the increased risk of fatal cardiovascular illness.

Depression is also a risk factor for coronary artery disease, and should be treated just as aggressively and persistently as the other risk factors. Exercise is one element of a healthy lifestyle that can positively affect all of these risk factors. Implementing a healthy diet and exercise regimen by middle age will have long-term positive effects in reducing risks in older ages.

Cardiovascular Fitness At Age 18 Predicts Later Risk Of Depression In Men

Research has connected cardiovascular fitness with depression risk and treatment. A Swedish study published last year in the *British Journal of Psychiatry* examined records of men conscripted into the military at age 18 and compared their cardiovascular fitness at the time with hospital records from later decades. **Low cardiovascular fitness at the time of conscription was associated with increased risk for serious depression.**

Editor's Note: This study provides more evidence that exercise, which increases cardiovascular fitness and decreases many of the elements of the metabolic syndrome, is good for cardiovascular and neuropsychological health, including mood stability. It is noteworthy that exercise also increases both brain-derived neurotrophic factor or BDNF (important for neural development and long-term memory) and neurogenesis (in animals), effects shared by almost all treatments with antidepressant properties. Making exercise a routine part of a regimen aimed at medical and psychiatric health is a great idea.

Adolescent Obesity Connected to Brain Impairment

As childhood obesity has increased in recent decades, the metabolic syndrome has also become more prevalent among children and adolescents. The metabolic syndrome consists of five measures related to obesity: elevations in fasting glucose levels or insulin resistance, a high proportion of LDL ("bad" cholesterol) to HDL ("good" cholesterol), elevated triglycerides, hypertension, and abdominal obesity or high waist circumference. A patient with three of these abnormalities would be diagnosed with the metabolic syndrome.

In adults, the metabolic syndrome has been associated with neurocognitive impairments. Researchers decided to look at adolescents with the metabolic syndrome to determine whether these brain effects are a result of long-term metabolic

Depressive Symptoms Negate Effects of Heart-Healthy Behaviors (Exercise and Light Drinking)

Physical activity and light to moderate drinking (as is often associated with the Mediterranean diet) are recommended as ways to reduce risk for heart disease and type 2 diabetes. **New research shows that among healthy people, symptoms of depression can counteract the anti-inflammatory benefits of both exercise and light to moderate alcohol consumption.**

C-reactive protein (CRP) is a cardiometabolic risk marker. High measures of CRP are a sign of inflammation. Leisure-time physical activity and light to moderate alcohol intake (defined as about half a drink per day for women and one drink per day for men) are associated with lower levels of CRP. Depression is associated with higher levels.

A study by Edward C. Suarez et al. published recently in the journal *Brain, Behavior, and Immunity* examined 222 nonsmoking men and women aged 18-65 years. These participants were physically healthy and had no history or diagnosis of psychiatric conditions. Participants recorded the amount of alcohol they consumed and the amount of physical activity

in which they participated. CRP levels in their fasting blood samples were measured, and they also completed an inventory of depressive symptoms.

Those people who were physically active had lower levels of CRP, but the 4.5% of participants with depressive symptoms did not see any anti-inflammatory benefits from physical activity. Similarly, light to moderate drinking was associated with lower levels of CRP only in men who were not depressed.

Depression did not seem to affect other markers of physical health in this study, such as levels of triglycerides or cholesterol.

Editor's Note: This study suggests that treating depressive symptoms should be a part of any plan to reduce cardiovascular risk. It seems that depression has effects that go beyond psychological distress and may prevent patients from reaping the benefits of their healthy behaviors. The effect of depression in preventing heart healthy changes in CRP could be one of many factors mediating the high levels of cardiovascular risk in depression. People with depression are twice as likely to have a heart attack than those without depression.

impairment or whether they can take place after short-term periods of poor metabolism as well. In a study published by Yau et al. in the journal *Pediatrics* last year, 49 adolescents with the metabolic syndrome were compared to 62 adolescents without the syndrome who had been matched for similar age, socioeconomic status, school grade, gender, and ethnicity.

The adolescents with the metabolic syndrome had lower scores on tests of math, spelling, attention, and mental flexibility, as well as a trend for lower overall intelligence. In brain measures such as hippocampal volume, amount of brain cerebrospinal fluid, and microstructural integrity in white matter tracts, the seriousness of the metabolic

syndrome correlated with the level of abnormality on these measures.

Editor's Note: It seems as though even short-term problems with metabolism can lead to brain impairments like lower cognitive performance and decreased integrity of brain structures. These effects are even seen before vascular disease and type 2 diabetes develop.

It is doubly important, in terms of both cardiovascular and neurobiological risks, to maintain medical and psychiatric health. Reducing components of the metabolic syndrome should produce benefits for both the cardiovascular system and the central nervous system.

Almost 40% of patients with bipolar illness in the US have the metabolic syndrome, so considerable effort will be required to improve this public health crisis.

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