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Bipolar Network News

Published since 1995 "The latest news on bipolar disorder research from around the world" www.bipolarnews.org

Vol. 12, Issue 4, 2008

Meeting Update

New Data about Treatments for the Most Severe Depression: Different Approaches to Brain Stimulation

At the 26th Collegium Internationale Neuropsychopharmacologicum (CINP) Congress held in Munich, Germany in July 2008, a Symposium on Brain Stimulation was held. A number of new and clinically important findings were presented, some of which are briefly summarized below.

1. Electro-Convulsive Therapy

ECT Should Be Given With Right Unilateral, Ultra-Brief Pulse Stimulation

Harold Sackeim of Columbia University presented new findings on electroconvulsive therapy (ECT). New ultra-brief stimulation parameters for ECT combine both excellent efficacy and minimal-to-no cognitive side effects. Instead of the stimulation being delivered in the form of biphasic sine wave, which lasts about ten milliseconds, a brief pulse can now be delivered that lasts 1.5 milliseconds, and even an ultra-brief pulse lasting 0.3 milliseconds, which is now recommended.

When this new ultra-brief waveform is delivered unilaterally to the right frontal cortex, the efficacy is equal to that of bilateral stimulation with the usual parameters, but it does not lead to ECT-induced retrograde amnesia, as bilateral ECT can. Retrograde amnesia causes substantial impairment to autobiographical memory. Previous work from this research group had indicated that the degree of retrograde amnesia seen in patients was directly proportional to the number of bilateral ECT treatments they had received.

Sackeim also compared ultra-brief unilateral with ultra-brief bilateral ECT. Surprisingly, ultra-brief pulse bilateral ECT only led to a 35% response rate, while ultra-brief pulse unilateral ECT resulted in a 75% response rate. Thus, right unilateral ultra-brief pulse ECT is recommended over any form of bilateral ECT.

Editor's note: If a patient decides to have a course of ECT, this author now follows the recommendation of Sackeim and colleagues and most other investigators in the field, that ultra-brief pulse right unilateral ECT should definitely be utilized. If bilateral ECT is offered, the patient and/or a family member should discuss the unilateral ultra-brief option with the treating physician and cite the new data published by Sackeim and colleagues in Brain Stimulation*, 2008.*

It is this editor's view that if the treating physician still insists on use of bilateral ECT, the patient should consider seeking an alternative opinion. Based on the new data published and presented at the meeting, there appears to be little rationale for using the old bilateral parameters.

2. Deep Brain Stimulation

Deep brain stimulation (DBS) was reviewed by Ben Greenberg of Brown Medical School. Several groups have reported response rates of 50% or more with DBS aimed at either the anterior cingulate gyrus (area 25, Helen Mayberg) or the nucleus accumbens (Schlaepfer et al.). In Greenberg's own study, the electrode site was aimed at the ventral portion of the internal capsule with the electrode extending down near the nucleus accumbens site stimulated by Schlaepfer and colleagues. They observed 50% response rates and 30% remission rates in highly treatment-refractory depressed patients who had failed at least three antidepressant trials, two augmentation trials, psychotherapy, and a course of electroconvulsive therapy (ECT). In their OCD patients, many subjects became better able to engage in cognitive behavioral therapy following DBS at this site.

Editor's Note: DBS remains highly experimental, and is suitable for only the most treatment-refractory patients with depression and obsessive-compulsive disorder. Further examination of the best parameters and best locations for stimulation producing antidepressant effects is needed.

3. Transcranial Direct Current Stimulation

Transcranial direct current brain stimulation (tDCS) represents a unique form of brain alteration because it is not brain stimulation per se, but neural modulation, in that it exerts a low-level constant electrode field across the brain. Felipe Fregni of Harvard Medical School reviewed results suggesting that longer periods of stimulation with 1 milliamp of current produced successively longer after-effects, with a 30-minute stimulation session showing

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Transcranial Direct Current Stimulation (continued)

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after-effects lasting 90 minutes, and a 60-minute stimulation producing after-effects lasting 150 minutes.

Opposite effects on neuropsychological function and perhaps mood are observed, depending on whether anodal or cathodal tDCS current is delivered to the dorsolateral prefrontal cortical region, with the other electrode more towards the orbital frontal cortex, with cathodal current yielding improvements. They found in two pilot projects that five sessions of 20 minute duration with one milliamp cathodal current over the left dorsolateral prefrontal cortex yielded about 40% response rate (measured in terms of improvement on the Beck Depression Inventory), while occipital cathodal tDCS produced much lower percentage response rates and sham treatment only about 10% improvement.

Editor's Note: These investigators found that stimulation at 2 milliamps for two weeks (five sessions/week of 20 min duration each, for a total of 10) produced minor skin lesions, and the issue of tissue heating and electrolysis at the electrode site are side effects that require monitoring. It does appear that the cathode electrode over the left dorsolateral prefrontal cortex is more effective than anodal stimulation in this and other studies.

Issues including ease of use/administration of tDCS and expense of equipment leave tDCS as a promising treatment option in need of further clinical testing before it is routinely brought to the clinic. This is especially true because one abstract presented at the meeting by another research group did not show significant differential effects of tDCS compared with sham treatment. That group was going to explore longer durations of treatment application.

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.

Publication of the BNN is made possible by an unrestricted grant from the Dalio Foundation.

As per recent journal disclosure requirements, Dr. Post has consulted to and spoken for Abbott, Astra Zeneca, Bristol-Myers Squibb, and Glaxo-SmithKline.

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4. Repeated Transcranial Magnetic Stimulation

An Update On Technique

Two papers were presented on advances in the application of repeated transcranial magnetic stimulation (rTMS). In the first, Levkovitz presented data regarding the new H1, H2, and H1L coils. They deliver stimulation deeper into the brain than standard rTMS, approximately 5-6 centimeters in the case of the H1 coil, compared with the usual 1 centimeter delivered by the traditional figure-eight coil. Using this new H1 coil, 45% remission rate was achieved when stimulation was delivered at 120% of motor threshold (MT). However, no remissions were achieved at 110% MT, indicating that higher intensity of stimulation was important.

Also, delivering stimulation bilaterally with the new H2 coil resulted only in 15% remission rates suggesting that, like ECT above, in this case left unilateral rTMS is better than bilateral stimulation, and higher intensities are better than lower.

In the second paper, Frank Padberg reviewed ways of increasing effectiveness of rTMS by altering its parameters. He found, giving 2 to 10 second trains of 5 Hz (theta bursts) or 10 Hz, that the frequency of 10 Hz was equally effective to amphetamine in inhibiting dopamine receptor binding in the human striatum, indicating that acute rTMS increased dopamine release. He then compared continuous vs. intermittent theta stimulation and found that the intermittent stimulation decreased working memory and activated the left prefrontal cortex and insula. The two types of stimulation had different effects on current density as well.

Padberg also found that the direction of changes in neural activity on brain imaging scans was dependent on the initial activity of the brain state. Animal studies report similar state-dependent effects of rTMS. When administered during periods of low spontaneous firing rates, rTMS increased firing rates, but when neural activity was at baseline high rates, the same rTMS produced decreases in firing. Similar observations were also made by Siebner, that pretreatment stimulation with transcranial direct current stimulation (tDCS) with anodal versus cathodal current yielded opposite effects when followed by the same rTMS parameters.

These findings are likely to be clinically important for the ultimate identification of optimal parameters of rTMS in the treatment of depressed patients. The data suggest the possibility that patients with more left prefrontal activity at baseline may benefit from lower stimulus frequencies (1 Hz rTMS) in order to normalize the fast firing, while those with baseline hypoactivity on their PET scans may benefit from higher stimulation frequencies (10 to 20 Hz) in order to increase activity in this area of brain, as previously postulated.

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Treatment Update

Thyroid Hormone Helps Antidepressant Response in Unipolar Depression

At the Collegium Internationale Neuro-psychopharmacologicum (CINP) meeting in July 2008, Bernie Lerer presented new data on the use of thyroid hormone to treat unipolar depression, and added mechanistic data to further support its rationale. Some studies have indicated that thyroid potentiation of antidepressant response by adding the thyroid hormone T_3 (triiodothyronine or Cytomel), as opposed to T_4 (levothyroxine or Synthroid), to one of the older tricyclic antidepressants at the onset of treatment can accelerate the rate of response to the antidepressant. In those who have had an incomplete response to the first generation antidepressants, T_3 augmentation is more effective than placebo in decreasing the severity of depression, as shown in a recent meta-analysis.

T_3 augmentation has not been explored as extensively with newer antidepressant agents, but a recent article by Kazaz in *Archives of General Psychiatry* (2007) reported that T_3 enhanced the antidepressant effects of the serotonin-selective antidepressant sertraline (Zoloft).

What is noteworthy about most T_3 augmentation studies is that **thyroid potentiation with T_3 is effective regardless of whether baseline thyroid function is normal**. However, in the sertraline study, it was found that those who remitted on treatment had lower T_3 levels at baseline, suggesting that T_3 could be augmenting thyroid effects in someone with relatively lower T_3 but within normal limits. In addition, Lerer reported that in laboratory animals, T_3 increased frontal cortical levels of serotonin and helped in the downregulation of $5HT_{1A}$ and $5HT_{1B}$ receptors. Thus, it is possible that the **T_3 effects** are independent of any thyroid effect and **may be active through mechanisms that affect serotonin.**

A further rationale for the use of T_3 is that Ambrogini (*Neuroendocrinology,* 2005) indicated that T_3 was necessary for the production of new neurons in the central nervous system (neurogenesis). Eitan et al. (2008) reported that in animals, T_3 by itself had marginal **effects on neurogenesis**, while fluoxetine had positive effects, but **when T_3 and fluoxetine were used in combination, the effects were additive**.

Thyroid hormone is originally released from the thyroid gland as T_4 (thyroid hormone with four iodines attached), but then is converted to T_3 in the blood by an enzyme that removes one of the iodines. Some individuals have deficient de-iodinase, resulting in lower T_3 levels at baseline. Targeting those with a common variant, or a single nucleotide polymorphism (SNP), that results in deficient de-iodinase might make it possible to select those who would respond best to thyroid augmentation.

Clinically, most studies of thyroid augmentation have used 25-50 µg/ml of T_3 (Cytomel) for augmenting antidepressant effects, and have found this range of doses to be well tolerated. Even minimal degrees of tachycardia (rapid heartbeat), anxiety, or sweating are rare with these lower doses of T_3.

Editor's note: T_3 has promising effects in patients with bipolar as well as unipolar depression, in unpublished observations of Frye and associates. Thus, it would appear worthwhile to augment initially with T_3 (Cytomel), which has a short half-life and rapidly disappears from blood on discontinuation of the drug, should there be side effects. (This is in notable contrast to the administration of T_4, which has a much longer half-life of 10 to 12 days' duration. If one took T_4 and experienced unwanted side effects, stopping the treatment immediately would only halve blood levels of T_4 after 10-12 days. For this reason, T_4 dosing should be titrated upward very gradually.)

T_4 rather than T_3 has been used in high (or supraphysiologic) doses for augmentation of other incompletely effective treatment approaches for those with rapid cycling bipolar disorder and refractory unipolar depression. Mark Bauer (now in Providence, RI) and Peter Whybrow (Chairman of the Department of Psychiatry at UCLA) performed studies with high dose T_4, following the work of others (Gjessing) who saw that use of thyroid extract was helpful in the treatment of periodic catatonia. Mike Bauer(of UCLA Medical School and Charité-University Medicine Berlin) has performed a placebo-controlled study comparing 200 µg of T_4 to placebo and has reported positive effects with substantial clinical responses in some of the patients studied, but the blind has not yet been broken.

Given the ambiguities of the current high-dose T_4 data and some concerns about medical side effects when the free thyroxine index is pushed to 150% of normal with this approach, it would appear prudent to initially explore T_3 augmentation and other antidepressant approaches in unipolar and bipolar depression relatively early in the treatment algorithm and save the supraphysiological dosing with T_4 for much later in the treatment sequence if needed for those who continue to exhibit refractory affective symptomatology.

These recommendations also converge with those of Andy Nierenberg and colleagues in the STAR-D trial, in which they compared T_3 and lithium augmentation for initial inadequate responders to the serotonin-selective antidepressant citalopram (Celexa) in unipolar depression. T_3 was associated with remission in 24.7% of the instances, while lithium augmentation (another commonly used approach) was associated with remission in 15.9% of patients, a substantial difference, but one that was not statistically significant, potentially because of the small number of subjects entered into the trial. In that study, lithium doses were given at up to 900 mg/day and T_3 doses were given at up to 50 µg/day. T_3 was also associated with fewer adverse side effects.

What You Read In The Newspapers May Be Bad For Your Health:
The Myth of Antidepressant Ineffectiveness in Unipolar Depression

Recent articles in newspapers and the lay press have suggested that the **acute** antidepressant effects of the older tricyclic antidepressants and the new second generation antidepressants, such as the serotonin-selective antidepressants, the serotonin-noradrenergic antidepressants including venlafaxine (Effexor) and duloxetine (Cymbalta), and the dopamine-active compound bupropion (Wellbutrin), are not as robust as originally surmised.

A new analysis ("Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy," Turner et al., New England Journal of Medicine, Jan 17, 2008) of all the published and unpublished data suggested that many of the antidepressants failed to beat a placebo in some studies that were not published.

However, this lack of publication of negative studies was largely due to the fact that the Federal Drug Administration (FDA) required only two positive antidepressant trials showing a drug superior to placebo (and did not care if there were one or many negative trials). Given that depression is a highly intermittent illness with spontaneous improvement and placebo responses occurring in a substantial percentage of patients, it would be expected that even highly effective agents like fluoxetine (Prozac) might, in some instances, fail to differentiate from placebo.

What these recent articles fail to address is the overwhelming data supporting the long-term efficacy of virtually all of the antidepressants compared with placebo. That is, after a patient has an acute antidepressant response to a drug and continues to be well on it for a considerable period of time (indicating that the depressive episode has remitted and the patient has recovered), if he or she is then randomized to continuation of that antidepressant or switched over to placebo, **the results dramatically support the efficacy of long-term drug continuation and prophylaxis** (preventative therapy).

In 1992, John Davis completed a meta-analysis of the randomized placebo-controlled studies and found that the antidepressant drug effect was robust, with an effect size similar to that of penicillin. The likelihood of this drug effect resulting from chance was miniscule. It was very clear that drug continuation was more effective than placebo. Usually, a clinical trial is considered effective if the chances are better than 95% that the drug is more effective than placebo (i.e. $p < .05$). **In Davis' meta-analysis, the likelihood that the drug effect was a chance finding was $p < 10^{-34}$.**

All types of antidepressants increase neuroprotective factors and the production of new neurons in the brain.

There have been dozens more positive antidepressant prophylaxis studies since 1992, particularly since European regulatory approval processes require antidepressants to be studied in the long term. The likelihood that all the positive studies are due to chance is infinitesimally small. In addition, many studies have indicated that with longer term treatment, the drug/placebo difference can increase over time, as illustrated in a recent study of the randomized continuation of venlafaxine vs. placebo, where the drug/placebo differences are highly significant in the first year of the randomized study, but even more impressive in the second year.

Almost all the academic bodies and clinical research societies who have examined the data suggest that it is important to consider long-term prevention with antidepressants after the occurrence of two or three prior depressive episodes. **In someone who has had several prior depressive episodes, the chance of having a relapse when his or her antidepressant is replaced with a placebo is about 50% in the first year,** increasing to 75% in the second year off the drug, and increasing to about 85% by the third year off the drug. With most of the drugs studied, this rate of relapse is reduced by more than half. The odds of staying well with antidepressant continuation thus greatly exceed those of discontinuing a drug, even if one uses a slow taper.

These well-described clinical findings and study data are now supplemented by a variety of new perspectives about the potentially toxic effects of recurrent depressive episodes themselves, whether unipolar or bipolar. As reviewed in other *BNN*s, new data suggest that every episode of depression is associated with increases in oxidative stress and decreases in brain-derived neurotrophic factor (BDNF), a chemical needed to help keep cells healthy and maintain long-term memory. Stress also decreases BDNF in the brains of laboratory animals that experience early severe traumatic events. These data have been partially replicated in patients who have experienced severe abuse in childhood and have been found to have low BDNF in their blood as adults. Virtually all antidepressant modalities increase BDNF and prevent stress from decreasing BDNF.

The antidepressants, as well as the mood stabilizers for bipolar illness, lithium and valproate, not only increase BDNF, but they also increase

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Antidepressants Effective in Preventing Unipolar Recurrences

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neurogenesis, or the formation during adult life of new neurons, which migrate into the hippocampus and become functional. Data now indicate that that the longer people are depressed, the greater their decrease in hippocampal volume as measured on the MRI. **However, if patients with depression are treated with antidepressants more of the time, they do not show the loss in hippocampal volume** that those treated with antidepressants less of the time do.

These data and many others strongly support the notion that the antidepressant effects on BDNF and neurogenesis measured in the brains of animals and in the blood of patients are likely relevant to the normal maintenance of brain structures such as the hippocampus. The new viewpoint is that depression is not only extraordinarily painful subjectively and somatically, but is also potentially toxic to normal cellular function and even cell survival.

Thus, for someone with recurrent depression, the importance of long-term preventive care cannot be overestimated from a clinical and empirical perspective, and now also from a neurobiological and theoretical perspective. Further supporting these observations of the exceedingly high benefit-to-risk ratio of long-term antidepressant prophylaxis for unipolar depression are the overwhelming data that **depression predisposes one to a variety of other medical illnesses, such as heart attacks and strokes, and makes the treatment of other illnesses such as diabetes more complicated and difficult**. Thus, depression is a potentially life-threatening illness based not only on the risk of suicide, which is estimated to be a 10-15% lifetime incidence in those with major depression, but also in terms of the very substantial loss of life expectancy based on increased mortality from other medical causes.

We could end this story at this juncture and hope we have sufficiently made our point clear. However, a bit of commentary may also be worthwhile in putting these findings into perspective.

Newspapers are in the business of selling papers, and creating sensational stories does so. However, when these kinds of stories are constructed purposefully and with ignorance of the larger picture, they can mislead the public and deserve being countered with a full set of facts. We emphasize this here because an overwhelming majority of patients in the US do not even complete a full course of acute antidepressant treatment, which is a suggested six to nine months after their first or second episode of depression has remitted. In someone who has had three episodes, staying

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FPO Venlafaxine slide

Long-term Antidepressant Treatment of Depression May Protect Brain

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on antidepressants for the long term provides strong support for one's psychiatric and medical health.

There must be a sea change in popular attitudes toward adequate acute and long-term antidepressant treatment. If you read articles in the newspaper critical of antidepressant use, know that you are not necessarily getting the entire truth and that this advice is not necessarily good for your long-term health or well being. Be informed, get the facts, talk to your doctor, and prevent recurrent depressions with long-term treatment. The data strongly suggest that it may help protect your brain.

If you have recurrent episodes of depression and are considering discontinuing the use of antidepressants even after a long period of wellness, you should discuss this carefully with your physician and reconsider. If a friend or family member is considering discontinuing antidepressants, show them this article and tell them that many recent newspaper articles have left out the essential facts, and stopping their antidepressants is not likely good for their long-term psychiatric or medical health.

Some newspaper articles have even suggested that the "overestimation" of the magnitude of acute antidepressant effects compared to placebo is a drug company conspiracy. The facts are that the acute effects of antidepressants are not always as good as we might hope, and additional treatments are often needed to achieve an acute remission.

Moreover, one of the reasons drugs work less well for an acute episode is that people often wait long periods of time and after the experience of a great many depressions to consider acute treatment of an episode. Substantial amounts of data support the disturbing view that the more depressions you have, the less likely you are to respond to an antidepressant. Thus, some of the recent articles in the press suggesting that the antidepressants might not work well compared to placebo might discourage people from seeking appropriate treatment for what is a very serious illness associated with among the highest rate of disability among all medical illnesses. *So much for the conflict of interest attributed to drug companies; the news media itself has plenty when it fails to give the full story about long-term prevention.*

Antidepressants are highly effective in preventing recurrence of unipolar depression; they should be used chronically like drugs for high cholesterol or blood pressure.

You might wonder about my own potential conflicts of interest. In the past two years, I have consulted or been on the speakers' bureau for drug companies including: Abbott Pharmaceuticals, Astra-Zeneca, Bristol-Myers-Squibb, Glaxo-Smith-Kline, and Jannsen. However, I do not receive any money when these or other drug companies' revenues increase or decrease, and I am not a holder of stock options, etc. On the other hand, I have spent my entire clinical research career, including 35+ years at the National Institute of Mental Health, trying to treat patients with the most severe forms of recurrent depression and bipolar illness. Almost every one of the many hundreds of patients I have treated wished they had started long-term preventive approaches to their illness much earlier, with the hope of warding off the more difficult, and in some cases, catastrophic consequences with which it is associated.

Finally, it must be re-emphasized that these are not my private or personal points of view, but ones shared by the vast majority of clinicians and investigators in academic medicine. **Long-term preventive treatment is recommended after three prior depressive episodes** by the American Psychiatric Association, the American College of Neuropsychopharmacology, the International Guidelines generated by the Collegium Internationale Neuropsychopharmacologicum, and every other academic or educational organization with which I am familiar. Just because depression is too often mistreated in the U.S. because of a lack of long-term follow through and prevention, does not mean that this should include you, your family members, or your friends.

Depression hurts the brain and body as well as the mind and needs to be approached and treated with the same care and detailed attention as any other recurrent medical illness. Don't let the stigma that remains attached to the study and treatment of psychiatric illness be a critical variable in your choice of the most appropriate treatment.

Brain Stimulation: rTMS (continued)

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Padberg concluded that while rTMS has not definitively been shown to be effective in the treatment of depression, it is likely that as optimal parameters are achieved and individualized to patients' baseline states, rTMS will become a highly effective treatment for depression. In fact, one rTMS machine has been FDA-approved for stimulation at 10Hz and 120% of motor threshold (see below).

Editor's Note: We would echo this suggestion with the additional observations of Mark George of the Medical College of University of South Carolina (relayed in a personal communication) that using 10 Hz rTMS at 130% of motor threshold produced excellent response rates to rTMS treatment, even in a series of those who were highly treatment-refractory, as evidenced by their failure to respond to ECT.

Treatment Update

rTMS Now FDA Approved for Depression Treatment

One type of machine for administering repeated transcranial magnetic stimulation (rTMS) has been cleared by the U.S. Food and Drug Administration for the treatment of depression. The Neurostar apparatus is approved for the treatment of adult patients with major depressive disorder who have failed to achieve satisfactory improvement from one prior antidepressant medication at an adequate dose and duration in the current episode.

The machine is being leased to private doctors' offices for their use with individual patients. However, it may be some time before the procedure becomes widely available in the U.S.

Other types of rTMS devices were approved several years ago in Canada and some European countries for the treatment of resistant depression. The FDA approval of the new device was based on a large study showing that active rTMS over the left pre-frontal cortex at 10 Hz (cycles/second) at 120% of motor threshold was more effective than sham stimulation and was associated with few side effects (Riordan et al., *Biological Psychiatry* 2007). A few patients experienced pain as a result of their scalp muscles contracting with each stimulation, but there were no impairments in cognitive functioning. In contrast to ECT, rTMS does not involve anesthesia or the induction of a seizure; the patient remains awake during the entire procedure and is able to converse with their treating clinician.

Treatment Update

Omega-3 Fatty Acids Effective for Depression in Pregnant Women

At the Collegium Internationale Neuro-psychopharmacologicum (CINP) meeting in Munich in July 2008, K.-P. Su et al. of China Medical University Hospital reported that for women experiencing depression during pregnancy, a treatment of 3.4 grams of omega-3 fatty acids/day was significantly more effective than placebo. Sixty-two percent of the patients treated with omega-3 fatty acids improved versus only 27% on placebo ($p=0.03$). Omega-3 fatty acids also resulted in a higher rate of remission, but this finding did not reach statistical significance (38% vs. 18%). The omega-3 fatty acids were tolerated well, with no adverse effects on the women or the newborns.

Editor's note: This study offers a potential new way of treating unipolar depression during pregnancy. The use of more traditional antidepressant modalities has, in some cases, had controversial effects on the fetus. While most antidepressants have not been problematic, the omega-3 fatty acids may offer a route for those wanting to completely avoid such risks. Omega-3 fatty acids have the advantage that they are also potentially helpful for normal development in the newborn, as indirectly suggested by many studies observing the impact of diets rich in fish and other sources of omega-3 fatty acids during pregnancy.

Neurobiology Update

Amygdala Enlargement Found in Bipolar Patients

Glahn et al. (*Biological Psychiatry* 63, no. 7s, April 1, 2008 supplement) found amygdala enlargement in bipolar disorder. The amygdala is a region of the brain that plays a role in emotion and memory. The researchers used a novel computational method to test for changes in both shape and volume of the region based on MRI measurements. They found amygdala volumes on both the left and right were significantly larger in bipolar patients compared with healthy controls, as has been reported in other studies of adults. In addition, it appeared that the basolateral region was the area of particularly increased enlargement.

Editor's note: These data replicate findings of amygdala enlargement in bipolar adults, in contrast to findings in childhood-onset bipolar disorder, in which the amygdala is smaller than in normal controls. These sets of findings suggest that the trajectory of amygdala development may vary as a function of age and/or course of illness and that the mechanisms for the increasing size of the amygdala in adults should be studied further.

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