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Bipolar Network News

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New Data Support the Efficacy of Lurasidone in Bipolar Depression

In two recent clinical trials that were presented at the annual meeting of the American Psychiatric Association in May 2012, **the atypical antipsychotic lurasidone (Latuda), which is currently used to treat schizophrenia, was associated with significant improvement in bipolar depression compared to placebo**. The studies, known as PREVAIL (or Program to Evaluate the Antidepressant Impact of Lurasidone), assessed lurasidone's efficacy as an adjunctive treatment and as a monotherapy.

PREVAIL 1 assessed lurasidone's efficacy and safety when the drug was added to treatment with lithium or valproate in bipolar patients who became depressed. In this 6-week study, scores on the Montgomery-Asberg Depression Rating Scale (MADRS) improved significantly more in patients taking lurasidone (20 – 120mg/day; N=183) in addition to their mood stabilizer compared to those who received placebo (N=165) in addition to their mood stabilizer.

In PREVAIL 2, patients received lurasidone at either 20-60mg/day (N=166) or 80-120mg/day (N=169) or placebo (N=170) as a monotherapy for bipolar depression. As measured by MADRS scores, lurasidone was significantly more effective in improving bipolar depression than placebo was by the end of the 6-week study period.

In both studies lurasidone showed significant effects on other measures and endpoints including: improvement in Clinical Global Impressions severity of depression (CGI-BP-S) scores, reductions in anxiety symptoms, and improvement in social or occupational functioning. Lurasidone also produced higher rates of response (50% improvement on the MADRS). The CGI-BP-S improved in patients on lurasidone significantly more than in those on placebo as early as week one.

Editor's Note: These two trials in bipolar depression suggest new possibilities for treating the depressed phase of bipolar disorder.

In studies of patients with schizophrenia, lurasidone has had an excellent safety and tolerability profile; it is relatively weight neutral and does not increase metabolic indices such cholesterol, triglycerides, or blood sugar.

Lurasidone also has an unusual mechanism of action, blocking serotonin 5HT 7 receptors, that may be related to its antidepressant effects. Antagonism of 5HT 7 receptors has been closely linked to antidepressant effects in studies of animal models of depression by two different investigators, Stephen Stahl and Herb Meltzer. It remains to be seen whether this or some other mechanism of lurasidone accounts for its antidepressant effects.

As we have noted before, since all antipsychotic drugs used in the treatment of schizophrenia (which block dopamine D2 receptors) also show efficacy in mania, it is likely that lurasidone will show the same effects. Studies of the drug in mania have not yet been presented. *Lurasidone is not yet FDA-approved for bipolar depression, but the PREVAIL studies may be sufficient for an application for FDA approval of lurasidone for this additional indication.*

Currently quetiapine (Seroquel) is the only monotherapy approved for bipolar depression. Studies of two other atypical antipsychotics, ziprasidone (Geodon) and aripiprazole (Abilify), failed to show efficacy in bipolar depression when compared with placebo. Ziprasidone's effects were similar to those of placebo, while aripiprazole showed evidence of significant improvement in the first weeks of treatment compared to placebo, but these failed to last, perhaps because of overly high doses that led to a high drop-out rate.

Antidepressants used for the treatment of unipolar depression are not FDA-approved for bipolar depression and did not appear to be beneficial compared to placebo in recent meta-analyses by Sidor and MacQueen. These antidepressants include the selective serotonin reuptake inhibitors (SSRIs), mixed serotonin and norepinephrine reuptake inhibitors (SNRIs), the dopamine active drug bupropion, and the older tricyclic antidepressants. Not only are these antidepressants not effective in bipolar depression, but some (especially the tricyclics and the SNRIs) appear to increase risk of switching into mania.

None of the mood stabilizers are FDA-approved for bipolar depression; these include lithium, valproate, carbamazepine, and lamotrigine. Thus, quetiapine has had the unique position of being FDA-approved

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Lurasidone

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to treat both phases of bipolar disorder – mania and depression – and for prevention of both mania and depression when used as an adjunct to lithium or valproate.

If the lurasidone data lead to FDA approval of this drug as a monotherapy, it will be only the second monotherapy (after quetiapine) approved for bipolar depression. (The combination of olanzapine and fluoxetine is also approved for this indication.) Since bipolar depression can take a serious toll on patients' health, cognition, and life expectancy, the prospect of having another effective drug for this phase of the illness is especially promising.

Bipolar Network News

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

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

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

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Memantine May Be Effective as an Adjunct to Lamotrigine for Bipolar Depression

Memantine (Namenda), which is approved by the Federal Drug Administration (FDA) for use in Alzheimer's Dementia, is increasingly being used for other conditions. Some doctors prescribe memantine for hyperactivity and attention problems in attention deficit hyperactivity disorder (ADHD), for obsessive compulsive disorder (OCD), and most recently as an adjunct to lamotrigine in bipolar depression.

In *BNN* Volume 14, Issue 5 from 2010, we wrote about the findings of Amit Anand et al. on the use of memantine and lamotrigine, which have now been published in *Bipolar Disorders*. **In the 8-week study of memantine for augmentation of treatment with lamotrigine for bipolar depression, memantine's effects were not statistically significant. However, during the first four weeks of the study, while memantine doses were slowly increased, memantine was associated with significant improvements on the Hamilton Depression Rating Scale (HDRS).**

Editor's Note: The potential mechanism of this effect makes sense. Lamotrigine decreases release of glutamate, and memantine blocks glutamate's actions at the NMDA receptor. Thus the two together would more efficiently decrease glutamate's effects.

It is possible that memantine could be effective without effecting the normal functions of glutamate. The drug blocks NMDA glutamate receptors that are situated away from the synapse, while allowing NMDA glutamate receptors at the synapse to fulfill their normal functions that support learning and memory. The blocking of only those receptors outside the synapse (extra-synaptic) could explain why memantine has relatively few side effects.

Reminder: BNN Reports Are Preliminary

In 2010 we reported on the data by Anand et al. that came to be published in *Bipolar Disorders* this year. The above revision of our earlier report highlights a message that we have given in the masthead of each *BNN*. We have emphasized that we report on preliminary data, often using an abstract or an initial oral presentation of data. Consequently, this prepublication information cannot be considered reliable for clinical decision-making unless the findings are independently verified by other sources.

Research manuscripts often go through considerable editing and major revisions following the peer review process that precedes publication in a reputable scientific journal. There are typically some changes in meaning or nuance, and in some instances major changes in the way that data is presented or interpreted are seen upon publication.

We would like to highlight this specific instance of our reporting on memantine's ability to augment lamotrigine's antidepressant effects in bipolar depression. We initially reported that these were robust, but when the study was published, the authors presented a more equivocal perspective, revealing that the positive findings did not persist for the full duration of the study. Therefore, it is important to reiterate our caution that **the preliminary results of studies summarized in the BNN require separate verification, validation, and interpretation by a patient's treating physician, who must take primary responsibility for decisions that could be based in part on preliminary reports in the BNN.**

Although findings presented in this newsletter and the opinions of the editor and others expressed in it must be taken as preliminary and in need

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Memories Erased From the Amygdala of Rats

A recent study found that in rodents, new negative memories can be deleted. Rats in the study were taught conditioned avoidance. For example, a light or a sound would signal that a mild shock would be delivered through the floor of the chamber in which the rat was housed. The rat could avoid the shock by running to the other side of the cage. Once the rat learned that the light or sound signal preceded a shock, the rat began switching sides when the light or sound cue appeared, even if no shock was given. This response to the conditioned signal is evidence that learning has taken place and is stored in memory.

The researchers found that when a rat formed a new conditioned avoidance memory, there were increases in cyclic AMP response element binding (CREB) protein in specific neurons in the rat's lateral amygdala (about 20% of the total number of neurons in the amygdala). Then, using extraordinarily sophisticated molecular biology, the investigators attached a diphtheria toxin onto the CREB protein, which caused the specific neurons involved in the conditioned avoidance learning to be killed while the other neurons in the amygdala (those not associated with the new memory) survived. As a result, the animals couldn't remember anything about the specific avoidance learning, but other memories could be formed and remained accessible.

Editor's Note: Obviously, this type of approach is not yet pertinent to clinical therapeutics in humans, but this research does teach us that in rodents, a conditioned avoidance memory activates a subset of the neurons in the lateral amygdala, and the elimination of these neurons eliminates specific learned memories, but not other types of learning.

Ultimately this kind of preclinical data may lead to novel clinical approaches to specific traumatic memories that are associated with post-traumatic stress disorder (PTSD).

Reminder: Data Reported Here Are Preliminary

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of verification by other sources, we attempt to present a wealth of early, preliminary, and often unpublished data with the hope that this will aid physicians and their patients in considering new information that may ultimately be published in peer-reviewed journals.

The precision of the reported findings and the initial interpretations of them in the *BNN* must be considered highly exploratory and only approximations of what may be ultimately published in peer-reviewed journals. Similarly, the editors' preliminary statements of opinion and summaries of the literature should be viewed as personal and potentially idiosyncratic views, and ones that are often based on slight or indirect evidence, which needs to be updated and revised as new data become available.

Finally the same very strong caveat needs to be repeated about the potential safety and risk:benefit ratio of any potential treatment approach discussed in the *BNN*. While we occasionally attempt to review new safety concerns that emerge in the literature, these and the short reports on various topics regarding potential effectiveness cannot be taken as comprehensive or even token reviews of the range of safety concerns that occur with almost any new or old treatment approach. The BNN is indeed a newsletter, and other sources should be consulted in order to obtain a more accurate, complete, and balanced perspective on new treatment research.

Memory Consolidation and Reconsolidation: Cortisone After Trauma Could Prevent PTSD

Memories are created in a series of phases in which different neurobiological mechanisms are required. In order for short-term memories to be placed in long-term storage, new protein synthesis is required. If protein synthesis is inhibited during a window about 2-4 hours after the short-term memory was encoded, consolidation into long-term memory does not occur.

In addition to the initial phase of memory consolidation, a second phase of memory reconsolidation is now recognized. During this phase, memory is again alterable.

The alterability of memories has implications for some types of post-traumatic stress disorder (PTSD), in which emotional memories repeatedly intrude into consciousness. **Pharmacological intervention during the time period of intial memory consolidation during reconsolidation may be able to reduce the impact of traumatic memories.**

One example of an attempt to alter memory consolidation after trauma has been reported by researcher Ariel Shalev and colleagues. These researchers found that administration of a high dose of intravenous cortisone (100 to 240mg) immediately following an extreme trauma was able to decrease the incidence of PTSD. One month after a traumatic event, the incidence of PTSD was 60% in those who received placebo, compared to only 16% in those who received the intravenous cortisone.

Procedures with Rapid-Onset Antidepressant Effects

At a recent scientific meeting, Carlos Zarate of the National Institute of Mental Health (NIMH) discussed a variety of rapid-onset antidepressant manipulations. The talk focused on intravenous (IV) administration of the NMDA receptor antagonist ketamine and the anticholinergic drug scopolamine.

IV Ketamine

Intravenous ketamine has been administered to approximately 1000 patients at research centers at Mount Sinai Hospital in New York, Yale University, and at the NIMH in Bethesda. The results have been consistent; more than half of the patients experienced a rapid onset of antidepressant effect, usually within the first 2 hours. However, the effects of intravenous ketamine tend to disappear after 3 to 5 days.

In both unipolar and bipolar depressed patients whose illness has been highly resistant to multiple treatments, ketamine also brings about a rapid-onset decrease in suicidal ideation and intent. In some cases these positive effects have lasted a week or more. Thus intravenous ketamine could potentially be used at hospitals to treat suicidal emergencies.

Scopolamine

New data indicate that intravenous scopolamine brings about onset of antidepressant effects in up to one day and sometimes in a matter of hours. As with ketamine, these effects occur in both unipolar and bipolar depressed patients.

Mechanisms of Action of Ketamine and Scopolamine

Editor's Note: New data from animal studies may be able to explain some of the mechanisms behind the rapid onset of antidepressant effects that occurs with ketamine and scopolamine. Both drugs cause increases in brain-derived neurotrophic factor (BDNF), which is important for the development and health of neurons. In rodents, new synaptic proteins are created following intravenous administration of both ketamine and scopolamine.

If animals are subjected to chronic unpredictable stress, dendritic spines (on which synapses are formed) appear to shrink. However, when ketamine is administered intravenously to these animals, not only is their behavior rapidly ameliorated, but the thin dendritic spines shift back to their more mature, mushroomed-shaped form within a few hours. (A slightly slower, less dramatic change in spines occurs with scopolamine.) A loss of dendritic volume has also been demonstrated in depressed people.

Several approaches can alleviate depression rapidly (in less than a day), but these effects are transient. Ways to extend them are currently being explored.

The data in animals are not only valuable for their potential application in clinical treatment and emergency situations involving suicidal ideation, but they also demonstrate a mechanism by which a single administration of intravenous ketamine or scopolamine is capable not only of reversing depressive behaviors in animals, but changing dendritic spine morphology. Given this development, it may be possible to identify other treatments that induce rapid-onset antidepressant effects using other parts of the same neurological pathways.

Other Rapid-Onset Approaches: TRH, Sleep Deprivation, and BDNF

Intravenous thyrotropin releasing hormone (TRH) also has rapid-onset antidepressant effects within 24 hours in depressed patients, but tolerance develops after repeated use.

Surprisingly, one night of complete sleep deprivation can also bring about dramatic onset of antidepressant effects the following day in approximately 50% of severely depressed patients.

In animal studies by Ron Duman and colleagues at Yale University, administration of brain-derived neurotrophic factor (BDNF) either into a rodent's blood or its brain has induced rapid-onset antidepressant-like effects.

Taken together, these data indicate that there are ways to bring about rapid improvement in depression, even if conventional antidepressants usually require 2 to 4 weeks to exert their maximum antidepressant effects.

Extending the Rapid-Onset Antidepressant Effects

The question now is how to sustain these antidepressant effects in the longer term. In a study at Mt. Sinai Hospital in New York, ketamine was administered in five intermittent doses over 10 days to two weeks, and the antidepressant effects were sustained during that period. The repeated doses of ketamine were well tolerated in the study. However, the safety of repeated ketamine administrations has not been systematically assessed.

Researchers are currently investigating whether other treatments that are currently available could be successful in sustaining the initial positive effects achieved on ketamine.

Effectiveness of Antidepressants

The dramatic rapid-onset antidepressant effects achieved with ketamine and scopolamine as well as other drugs currently in development provide a new perspective on

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Antidepressants Useful for Long-Term Prevention of Unipolar Depression

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the debate in some media circles about the effectiveness of antidepressants.

Because depression sometimes spontaneously improves, placebo effects in studies of antidepressants for acute depression treatment can be large. This has led to some controversy over the magnitude of effect of antidepressants over placebo, especially in those with milder forms of depression.

The new data reported here refute the argument that antidepressants are not much more effective than placebo for acute treatment of depression. Moreover, they show that both biochemical and structural changes in the brain and behavioral improvement can be achieved in just a few hours.

Critics of antidepressants also typically fail to mention the most important data about antidepressants for patients with recurrent depression: the drugs' preventative effects. All treatment guidelines of which this author is aware recommend that patients with two or three prior episodes of depression continue long-term prophylactic treatment after a good antidepressant effect is achieved. Continuation of an active antidepressant (compared to changing to placebo) brings about an approximate 70% reduction in depressive recurrences.

In March 2012, the CBS news program 60 Minutes was the latest to gloss over the benefits of antidepressants, discussing the placebo effects in the acute antidepressant studies while leaving out the drugs' unequivocal efficacy in long term prevention. It is hard to imagine a media campaign against useful drugs to treat other forms of illness, such as cancer or heart disease. Oversights like these are all the more egregious in light of World Health Organization data that depression is one of the top causes of disability worldwide and causes or exacerbates many other medical illnesses.

More Reasons to Use Antidepressants for Long Term Prevention of Recurrent Unipolar Depression

As we wrote in "5 Myths About Antidepressants" in BNN Volume 14, Issue 3 from 2010, it is crucial that patients learn about the overwhelming efficacy of antidepressants in long-term prevention, particularly because recurrent depression carries many adverse outcomes beyond the considerable pain and suffering with which it is associated.

While some controversy remains about the magnitude of antidepressants' acute effects compared to placebo, patients should know the magnitude of their effects in preventing subsequent depressions are large, statistically reliable, and significant.

Some risks are cognitive. Data suggest that cognitive dysfunction increases with the number of previous depressive episodes, and a diagnosis of dementia in old age is twice as likely to occur if one has experienced four or more episodes of unipolar or bipolar depression.

In addition, depression is a risk factor for many medical illnesses and comorbidities. For example, a depressed person is twice as likely to have a heart attack than a person who is not depressed, and is twice as likely to die of a heart attack compared to someone who is not depressed who has a heart attack.

Most medical illnesses are vastly more difficult to treat in depressed people as well.

Life expectancy is lowered dramatically in patients with major psychiatric illness (including bipolar disorder, unipolar depression, schizophrenia, and ADHD).

Prophylactic Treatment of Mood Disorders May Protect the Brain

There is good news. All antidepressants appear to increase neuroprotective factors (such as BDNF) and, in rats, neurogenesis (the creation of new neurons). Being on antidepressants more of the time has been shown to prevent decreases in volume of the hippocampus with aging in patients with unipolar depression.

As we noted briefly in our page 1 article on lurasidone, antidepressants are not indicated for bipolar depression or its prevention, only for unipolar depression.

For those with bipolar disorder, most mood stabilizers also increase BDNF. Lithium increases hippocampal and cortical gray matter volume in humans. New data suggest that lithium may have neuroprotective effects even at low doses, and data from a large study in Denmark suggest that chronic lithium treatment may decrease the incidence of a diagnosis of dementia.

Thus a new mantra from this editor about treatment of both unipolar depression with antidepressants and bipolar disorder with mood stabilizers is: "prevent episodes, protect the brain."

Sleep Apnea Common Among Rapid Cyclers

Kellen and colleagues presented a poster at the 9th International Conference on Bipolar Disorder (ICBD) held in Pittsburgh in 2011, in which they reported that **21% of patients with rapid cycling bipolar disorder have confirmed sleep apnea**. Since many patients who screened positive for sleep apnea on the study's sleep questionnaire did not undergo follow-up sleep studies to confirm the diagnosis, it is estimated that up to 40% of rapid cycling patients may, in fact, have sleep apnea.

Editor's note: Given such a high incidence of sleep apnea among rapid cycling bipolar patients, it would be prudent for patients and clinicians to be alert to the possibility of sleep apnea and follow up with appropriate sleep studies. Sleep apnea can cause daytime fatigue, cognitive dysfunction, and treatment resistance, so its identification and treatment with continuous positive airway pressure (CPAP) may be enormously beneficial to a substantial number of rapid cycling bipolar patients. A just-published article by Sukys-Claudino in Sleep Medicine presents findings that compared to placebo, the anti-Alzheimer's drug donepezil (Aricept) started at 5mg/day for 2 weeks and then increased to 10 mg given twice a day (20 mg/day total) helped all measures of sleep apnea including daytime sleepiness.

Clinical hints that a patient may be suffering from sleep apnea include loud snoring, long pauses between breaths, and non-restorative sleep. The likelihood of sleep apnea increases with age and with overweight or obesity.

Quetiapine Monotherapy Efficacious

An article published by Weisler et al. in the *Journal of Clinical Psychiatry* in 2011 suggests that quetiapine may be effective as a monotherapy maintenance treatment for bipolar I disorder. It has previously been shown to work in combination with lithium or divalproex and is approved by the Federal Drug Administration for this combination treatment.

Adult patients diagnosed with bipolar I disorder who were currently or recently in a mood episode received open-label quetiapine in doses of 300-800mg per day for up to 24 weeks. Patients who became stable either remained on quetiapine or were switched to lithium (at doses of 0.6-1.2 mEq/L) or placebo. This double-blind phase of the study continued for up to 104 weeks.

The study began with 2,438 patients, 1,172 of whom made it to the second phase of the trial. On the main outcome measure of time to recurrence of any mood event, both quetiapine and lithium were significantly better than placebo.

Editor's Note: In the 50% of patients with a recent mood episode who were able to be stabilized on quetiapine monotherapy, those who remained on long-term quetiapine or those who switched to lithium were both much less likely to have subsequent relapses into either depression or mania than those who switched to placebo. Whether Astra-Zeneca, the company that produces quetiapine, will file to gain Federal Drug Administration approval of quetiapine monotherapy for long-term preventive treatment is not known.

New Research: Marijuana Users May Be At Risk for Psychosis

At a recent conference Robin Murray, a researcher based in London, gave a talk about the potential adverse effects of tetrahydrocanabinol (THC). **Considerable data indicate that chronic long-term smoking of marijuana is associated with a doubling in the risk of psychosis.** Moreover, if a marijuana user has a common genetic variant in the catechol-o-methyltransferase enzyme (COMT), they are at substantially increased risk for the development of psychosis.

New data also indicate that frequent use of marijuana can also be associated with an earlier onset of schizophrenic psychosis than would ordinarily occur without the substance use. Data also suggest that the psychosis associated with THC use is more difficult to treat than that without such use.

Murray also reported on a new risk that is associated with more potent new products. Older, natural forms of marijuana contained a compound called cannabidiol, which is associated with calming effects and possible antipsychotic effects. In a new synthetic preparation of THC called skank or spice, there is a higher amount of THC, but none of the positive diol compound. Thus there are some important caveats to the prevailing view that marijuana is relatively harmless.

Editor's Note: Marijuana use brings a clear-cut increased risk for psychosis, which appears to interact with a common gene polymorphism and which is increased with use of a new synthetic preparation called skank or spice. If a marijuana user has a concurrent mood disorder, the risks appear to be even greater. The one sure pharmacological effect of marijuana is an amotivational syndrome, and motivational deficits are one of the core components of depression.

Given the difficulty of treating the mood and schizophrenic disorders, a patient should not risk worsening their illness with marijuana. N-acetylcysteine is one treatment option that may bring about decreased craving for and avoidance of marijuana and a number of other abused substances, as well as being helpful in mood disorders and in negative symptoms in schizophrenia (withdrawal, autism, cognitive deficits, lack of insight, etc.).

The Link Between Inflammation and Mood Disorders

There is increasing evidence of a link between inflammation, brain function, and treatment resistance in the mood disorders. Obesity is also linked to inflammatory processes and thus may contribute to the development of treatment resistance in both unipolar and bipolar mood disorders.

Causes of Inflammation

Obesity is one factor that can lead to increases in inflammation. When people gain weight, the size of fat cells can increase to the point that the cells are deprived of oxygen and disintegrate. Then macrophages and other cells come in to sweep up the remaining particles of the fat cells. These scavenger cells then become activated and produce more regulatory chemicals called cytokines. The cytokines produced in the periphery (in the body outside the brain) can then enter the brain and affect brain function in a process that may ultimately be linked to fatigue, depression, and other adverse mood and behavior states that contribute to treatment resistance. There is a two-way street: the brain can influence the body and what goes on in the body can influence the brain.

Other factors that can lead to increases in inflammation and eventually to treatment resistance in the unipolar and bipolar mood disorders include early life stress, medical illness, and anxiety and personality disorders.

Anti-Inflammatory Treatments

Given the close links between inflammation and depression (discussed in BNN Volume 15, Issue 1 from 2011), Andrew H. Miller of Emory University decided to test a specific anti-inflammatory agent called infliximab (a TNF monoclonal antibody that inhibits TNF alpha actions) as an antidepressant. One sign of inflammation is a C-reactive protein (CRP) level of 2mg/L or greater. The effect of infliximab on the population of treatment refractory depressed patients who participated in Miller's study was not significant on the whole, but the drug did have significantly greater antidepressant effects than placebo in those patients with the highest levels of CRP. The investigators believe this demonstrates the principle that a drug that inhibits TNF alpha may be useful in patients with the greatest degree of inflammation.

Other approaches to anti-inflammatory mechanisms are also being pursued, including use of aspirin, COX-2 inhibitors, and the antibiotic minocycline. Minocycline has anti-inflammatory and neuroprotective effects and has been reported to have positive effects in cognition and negative symptoms of schizophrenia*(withdrawal, autism, cognitive deficits, lack of insight, etc.)*.

BNN
PO Box 18
Beltsville, MD 20704-0018

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