

Bipolar Network News

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N-Acetylcysteine: A Potential Therapy For BP And Substance Abuse

Overview

N-acetylcysteine (NAC), a readily available substance from health food stores, is able to reestablish glutamate homeostasis (regulation and balance) in the reward area of brain (the nucleus accumbens), reported Peter Kalivas of the University of South Carolina at the “Staging neuropsychiatric disorders: Implications for idiopathogenesis and treatment” meeting in Mojacar, Spain this past November. Kalivas reported that NAC appears to be effective across a spectrum of addictions, including cocaine, heroin, alcohol, cigarette smoking, and gambling.

Even more remarkably, NAC also appears to have positive effects in placebo-controlled studies in the treatment of patients with bipolar illness, report Mike Berk and colleagues, who are studying the same substance in Australia. Compared with placebo, patients taking adjunctive NAC showed improvement in all outcome measures, especially depression, after 3 and 6 months. In another article, also published in *Biological Psychiatry* in 2008, Berk’s research group demonstrated that NAC improved some negative symptoms of schizophrenia. NAC has also shown positive effects in trichotillomania and on nail-biting, suggesting that it has a variety of potential clinical uses in conditions associated with pathological compulsive behavioral patterns.

EDITOR’S NOTE: This next section is fairly technical and can be skipped over with the bottom line message that NAC dampens an overactive glutamate response

in the reward area of the brain. However, some of the details about how Kalivas made these therapeutic discoveries based on data in the laboratory may be interesting to some.

N-acetylcysteine reduces cocaine and heroin re-instatement in animals and craving in humans

How Kalivas made his conclusions is an interesting story in and of itself. Much previous work had established that the n. accumbens was essentially a reward area of the brain and was also involved in the modulation of mood, motor activity, and motivation. The medium spiny neurons in this area of the brain have GABA as their neurotransmitter and receive both dopamine input from the midbrain ventral/tegmental area (VTA) below, as well as glutamate-mediated input from pyramidal cells in the cerebral cortex above (see schematic figure).

Increased dopamine release in the n. accumbens is associated with the reward properties of a variety of substances of abuse, and substance abuse behaviors appear to be exacerbated by inadequate prefrontal inhibition. Kalivas and associates stimulated the prelimbic part of the prefrontal cortex, which has direct synapses on the core of the n. accumbens, with either brief bursts of high-frequency stimulation or 15 minutes of low-frequency stimulation. The brief bursts of high-frequency stimulation were associated with synaptic enhancement, i.e. long-term potentiation (LTP), and the 15 minute increments of low-frequency stimulation were associated with synaptic

decrements in the form of long-term depression (LTD). Kalivas studied the modulatory effects of dopamine and glutamate in this reward area of brain and found that they were highly dysregulated after chronic cocaine administration in that both LTP and LTD were weak to nonexistent.

Kalivas also found that in rats, following self-administration of i.v. cocaine by pressing a bar that delivered the cocaine reward, the animals could go through an extinction phase where they learned that pressing the bar would no longer result in a cocaine reward. However, as in the clinical situation in which cocaine addicts rapidly relapse on occasions when stress occurs, cocaine cues are present, or cocaine is readily available, the rats behaved similarly. When a cue indicated that cocaine was again available or when the animals were stressed, they would again press the lever up to 100 times per minute, even though it no longer delivered cocaine.

This cocaine reinstatement behavior was associated with huge increases in glutamate levels measured in the n. accumbens. Kalivas reasoned that

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(con't.): N-Acetylcysteine May Decrease a Variety of Compulsive Behaviors

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if these large increases in glutamate could be suppressed, maybe reinstatement behavior would be suppressed as well. He found a way to decrease the excessive glutamate secretion via the n-acetylcysteine pathway. N-acetylcysteine is a glutathione precursor that increases the drive of a cystine-glutamate exchanger that is located outside the range of usual glutamate synapses. This in turn increases extracellular levels of glutamate and results in the increased occupation and subsequent downregulation of a different type of glutamate receptor (mGluR2/3) that is associated with inhibition of presynaptic glutamate release. This normalizes the abnormally high amount of glutamate released by stressors, conditioned cues, or cocaine.

This modulation of glutamate release onto the medium spiny

neurons of the n. accumbens was in fact found to inhibit cocaine reinstatement in the animal studies. **Kalivas and co-workers quickly took these preclinical observations into the clinic and found that n-acetylcysteine decreased cocaine craving in humans as well.**

This substance found at health food stores appears to have positive effects both on mood and addictions.

In further animal studies, the same large increase in glutamate release in the reward area of brain was found to occur following heroin self-administration and extinction training; heroin re-instatement behavior too was suppressed by n-acetylcysteine. Likewise, clinical placebo-controlled studies suggest that NAC decreases heroin craving in people.

Part of the reason that such high glutamate levels occurred in the n. accumbens was that prior substance abuse had downregulated glutamate transporters on glial cells (astrocytes), which normally help to remove glutamate from the synapse. NAC helped reestablish the appropriate number of glutamate transporters, which in turn helped clear synaptic glutamate.

Kalivas also found that a unique type of antibiotic (with a beta lactam structure), which currently can only be administered intravenously in humans, is associated with stimulation of the DNA promoter for the formation of more glutamate transporters in astrocytes, and thusly the antibiotic increases the rate at which excess glutamate is removed from the synapse. His research group determined that the administration of this antibiotic also blocked cocaine-

induced reinstatement behavior in rats. Currently, attempts are in progress to find a more clinically feasible beta lactam antibiotic that can be given orally, in order to see whether it, as well as NAC, would help patients with a variety of addictions. **N-acetylcysteine may be useful as an adjunctive treatment for bipolar disorder**

Unbeknownst to each other, while Kalivas studied NAC in the U.S., Mike Berk and colleagues in Australia completed parallel studies. Berk's group reasoned that NAC was a glutathione precursor and thus might have antioxidant and neuroprotective effects in bipolar disorder, since increasing data have indicated an excess of inflammatory cytokines and oxidative stress in the illness, as noted on page 7. Berk and colleagues administered NAC in 500mg capsules twice per day for one week and then two capsules twice a day thereafter to patients who maintained their prior drug regimens. Berk's group found that compared to the addition of placebo, with the addition of NAC, residual symptoms of bipolar illness that had been inadequately treated by the prior drug regimens had improved remarkably after a period of three months and continued to improve through the six-month study period.

In another double-blind study, Berk's research group found that some of the negative symptoms in schizophrenic patients were also improved with the administration of NAC.

In 2009, another team of researchers, Grant and colleagues, published an article in the *American Journal of Psychiatry* reporting that NAC given to patients with trichotillomania (chronic, persistent, obsessive pulling out of one's hair) was associated with marked improvement in this behavior after two months, compared

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

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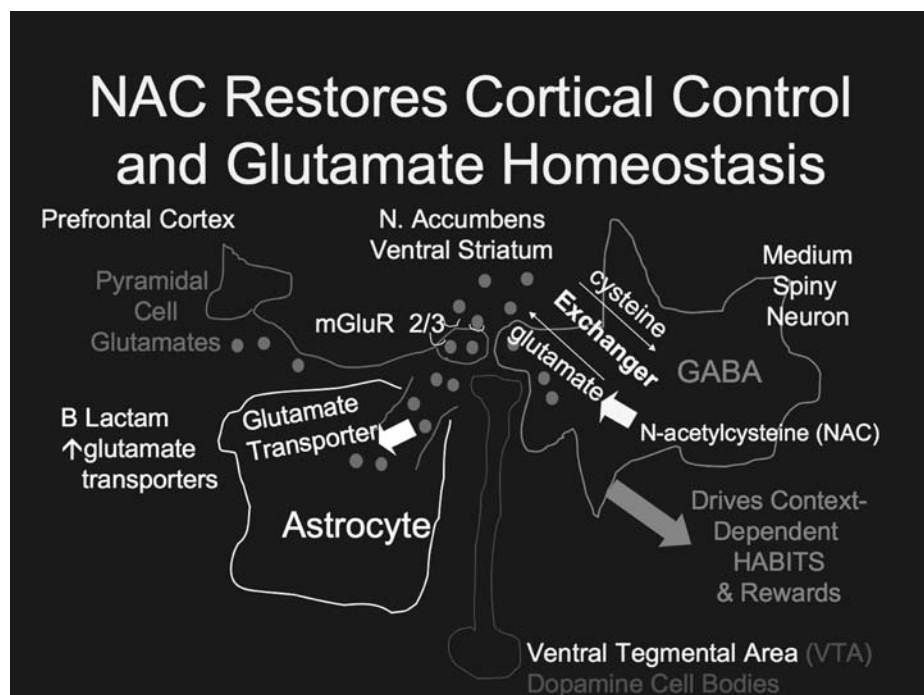
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with only a very small percentage of patients improving on placebo. What was remarkable about this trial was that the side effects were non-significantly different on NAC and placebo, and actually were present in a few patients on placebo and not on NAC, indicating that it was a readily tolerable drug at these doses.

NAC had also been used previously in a preparation called Mucomyst and was given to those with Tylenol overdoses because of its ability to protect against liver damage and its antioxidant properties. **NAC may work in bipolar illness and substance craving by re-regulating an overactive habit memory system**

How does NAC have such a remarkably broad spectrum of therapeutic effects across so many addictions as well as in schizophrenia, bipolar illness, and trichotillomania? Consider the **two kinds of memory**. One is **conscious or representational memory**, which is dependent on circuits in the medial temporal lobe (i.e. the amygdala and hippocampus). This kind of memory allows you to remember things that happened in the past. Another form of memory, **habit memory**, is developed through **multiple repetitions** of the basic learning or conditioning paradigm, and is dependent on a basal ganglion structure called the striatum. This is the kind of memory that allows you to learn to ride a bicycle—it comes naturally without thinking, and you never forget how to do it. While habit memory is most closely linked to alterations in the dorsal part of the striatum, habit memory may also involve the motivation, reward, and motor activity-related processes mediated by the ventral striatum, also known as the n. accumbens.

Learned, context-dependent, and automatic habits may depend on this n. accumbens substrate,



and this relationship may be the basis for the common therapeutic effects of NAC in widely diverse compulsive behaviors. All of these behaviors appear to represent habits that are extremely hard to suppress and are based on compulsive impulses that have some reward value, whether they involve substance abuse, nicotine, alcohol craving, gambling addiction, or hair-pulling.

It is not clear which actions of NAC improved symptoms in bipolar illness, but this editor has for many years suggested that repeated episodes of mania and depression occur increasingly autonomously, that is, they do not require precipitation by psychosocial stresses in order to emerge. One hundred years ago, Emil Kraepelin observed that initial episodes of the illness were typically associated with psychosocial stresses, but with sufficient numbers of repetitions, these occurred more independently as well. We have reasoned that this repeated occurrence of affective episodes may shift some of the neural substrates of stress and affective episodes from the conscious representational

memory system in the amygdala and hippocampus into the unconscious habit system in the striatum. This would theoretically be the reason that after many repetitions, affective episodes can appear to come "out of the blue," and why conscious efforts coded in the representational memory circuit are often unable to ward off an impending episode (even if one understands the dynamics of one's mood). Should this analysis prove correct, NAC might be able to rebalance the circuitry of the n. accumbens to target the automaticity of affective illness recurrence, just as it is helpful in blocking the automatic habits associated with substance use or hair-pulling.

Even if this analysis proves to be incorrect, and NAC's mechanisms of action in affective illness and schizophrenia are dissociated from those in addictions and habits such as trichotillomania, the findings are nonetheless of very considerable clinical interest from several perspectives. 1) NAC may rebalance glutamate homeostasis in the

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A Large Replication Study Indicates that rTMS Is Effective in Major Depression

Mark George from the Medical University of South Carolina presented a sham-controlled, multi-site, randomized trial of repeated transcranial magnetic stimulation (rTMS) in 199 antidepressant-free patients with unipolar non-psychotic major depression. The rTMS was delivered to the left prefrontal cortex for 37.5 minutes at 120% of motor threshold (MT), with a 10 Hz, four-second train duration and 26-second inter-train interval, yielding 3000 pulses/session, with a figure-eight solid core coil. Compared with the sham treatment (which plays the same role a placebo would in a drug trial), active rTMS had a significant effect ($p = .015$), with 14% of patients remitting on the treatment compared with 5% on the sham procedure. Thus, the odds of attaining remission (the primary outcome measure) were several times greater with active rTMS than sham.

The number needed to treat (NNT), a measure of the number of patients who would need to be treated with active rTMS in order to get one more responder compared to the number of responders seen on sham rTMS (the smaller the number, the more effective the treatment) was 12. However, as in other previous studies, most of the remitters had prior low antidepressant-rated degrees of treatment resistance. When the blind study was complete and patients were openly given rTMS treatments (a practice known as open label extension), approximately 30%

of the patients from each condition were able to achieve remission.

EDITOR'S NOTE: This large study, sponsored by NIMH rather than the pharmaceutical industry, confirms previous industry-related findings that active rTMS is more effective than sham in the treatment of major depressive disorder. These data also conform to recent meta-analyses of many smaller studies indicating that high intensity rTMS treatment is clinically effective for major depression. In prior rTMS studies, those with bipolar depression appeared to respond at about the same rate as those with unipolar illness, suggesting the possibility that these findings might also generalize to those with bipolar disorder, although this remains to be studied more systematically.

This study showed that patients with greater degrees of initial treatment resistance had less optimal outcomes to active rTMS. Some studies also show that electroconvulsive therapy (ECT) decreases in effectiveness in those with greater degrees of treatment-resistance. Response rates to ECT are approximately 40-50% in those with high degrees of treatment-resistance compared with 60-80% in those without. The rTMS data suggest that the treatment as studied may be a useful alternative to antidepressants for some patients with major depression, but it may not be an optimal approach for those with the highest degrees of treatment resistance. Further studies are warranted in patients with high treatment resistance in order to define optimal stimulation parameters that may be more successful for them.

(cont.) NAC May Eventually be Used to Treat BP and Substance Craving

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reward area of brain; 2) a compound readily found in nature can achieve this effect; and, 3) it can apparently do so with remarkable safety. NAC takes two months to work in trichitillomania and three months in bipolar illness, but may work more rapidly in the substance abuse addictions.

Potential implications for clinical treatment

It is clear that the NAC story is evolving rapidly, and currently looks almost too good to be true. We must wait for further research and clarification. In the meantime, it may be worthwhile for some patients to talk with their physicians about the

Aripiprazole (Abilify) Now FDA-Approved to Decrease Irritability in Children with Autistic Disorder

In a recent study, children 6-12 years old with autism were treated with aripiprazole and showed improvement in irritability. The study lasted 52 weeks and had an open-label flexible-dose design (ranging from 2-15 mg/day) with an average dose of 9.6 mg/day. Few discontinuations occurred due to adverse effects, suggesting that aripiprazole is generally safe for use in this patient cohort. Increase in weight gain was the reason seven subjects (2%) discontinued the drug, although weight gain appeared to plateau with continued treatment.

Aripiprazole is already FDA-approved for the treatment and prevention of mania in adults and children (10-17 years). It is also approved as an adjunct (add-on) to poorly effective antidepressants in adults with unipolar (non-psychotic) major depression.

EDITOR'S NOTE: The general safety and tolerability of aripiprazole for the treatment of irritability in children with autistic disorder in this study means the drug can be added to the list of potential treatments for patients with autism. Previously, only risperidone had shown strong placebo-controlled data for efficacy in autism. A study by Hollander published in Neuropsychopharmacology this year indicated that valproate was also significantly better than placebo in treating irritability in children with autism spectrum disorders.

potential utility of a clinical trial in their illness. Unipolar depression, bipolar disorder, and schizophrenia are too often compounded by substance abuse problems. It is hoped that NAC could ultimately provide a two-for-one benefit, i.e. helping in both the spheres of bipolar and

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High Incidence of Medical Comorbidities in Those with Bipolar Illness Compared with the General Population

In a poster at the 8th International Conference on Bipolar Disorder, Goldstein et al. presented data from the National Epidemiological Survey in 2001-2002 that included 41,682 representative adults in the U.S. population compared with 1,411 in the community sample who had a diagnosis of bipolar disorder.

Those with bipolar disorder had a 3.86 times higher odds of having coronary heart disease compared with those in the general population. They were also 2.15 times more likely to have hypertension. Most disturbingly, the mean age of those with coronary heart disease in the general population was 62.1 years of age, but in those with bipolar illness, it was 50.4 years of age. **This indicates that the markedly increased risk and incidence of coronary artery disease occurred approximately 11 years earlier in those with bipolar illness compared with those without. Most interestingly, the number of prior depressive episodes correlated**

(cont.) NAC

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schizophrenic affective dysregulation and substance addiction.

WARNING: Even though N-acetylcysteine (NAC) is available in health food stores, one should not begin taking the substance without first carefully discussing it with one's treating physician. While it looks safe now, large-scale trials have not yet been reported, interactions with other drugs remain to be studied, and the possibility of idiosyncratic negative reactions on NAC or during its withdrawal are possible. If you are a patient you can assist your doctor and improve your own evaluation of any therapeutic maneuver you are trying by systematically charting your prior and future course of illness to identify whether a given treatment is really working.

with the presence of either coronary heart disease or hypertension.

These data are also compatible with those reported by Ice et al. in poster 97, which showed a high incidence of metabolic abnormalities in patients with bipolar disorder: 64% of this same group were overweight or obese, 31% had elevated triglycerides, 14% had increased glucose levels, 28% had hypertension, and 42% had abnormally low levels of high-density lipoproteins (i.e. good cholesterol). They found that adjunctive ziprasidone treatment was associated with positive effects on weight and metabolic profiles during long-term maintenance treatment. Another poster by Jerrell et al. (p100) indicated that many of these adverse medical changes begin in those with bipolar disorder in adolescence.

There appear to be multiple interacting factors elevating the risk of cardiovascular disorders in patients with bipolar illness, including all of the elements of the **metabolic syndrome**,

which is characterized by **any three of the five following factors: increased waist circumference, glucose elevation or insulin intolerance, elevated triglycerides, increased cholesterol, and elevated blood pressure.**

Some 60-80% of patients with bipolar illness are current or former smokers, and this is a far higher percentage than the rest of the general population. Therefore, all the increased cardiovascular risk that comes with smoking may be additive to a panoply of other factors noted above.

In addition, there appear to be many other mechanisms of increased risk including that derived from depression-related increases in inflammatory cytokines, increases in glucocorticoids, and decreases in neuroprotective factors such as interleukin 10 and BDNF. Increased stiffness of the inner wall (intima) of arteries has also been reported in association with the affective disorders, as well as increased stickiness of platelets.

Clinical Implications of the High Incidence of Medical Comorbidities in Bipolar Disorder

Taken together, the above data suggest that there must be increased vigilance to the presence of the metabolic syndrome and other risk factors for cardiovascular disease in patients with bipolar illness; active treatment and prevention of these conditions should be routine. Moreover, **in those at high risk, very active and aggressive treatment of these medical risk factors should be pursued, including attempts at encouraging smoking cessation.** One of the more disturbing factors is a lack of adequate health care access in many patients with bipolar disorder and, in these instances, it would appear appropriate and necessary for the treating psychiatrist to provide some of the medical evaluation and treatment including lipid and blood pressure-lowering drugs where indicated.

Another major clinical implication of these data is the need for careful choice of

medications in patients who are already at increased risk for medical comorbidities in order not to further increase these factors as a result of pharmacological treatment wherever possible. Thus, long-term tolerability and lack of effects on metabolic indices needs to be factored into efficacy considerations in arriving at the most appropriate risk/benefit evaluation for each individual patient.

There appears to be a substantial gradation in difference among the atypical antipsychotics in their potential for increasing metabolic and cardiovascular risks. Disappointingly, one of the most effective treatment agents, clozapine (Clozaril), is a major offender for weight gain, and the same is the case for olanzapine (Zyprexa), which can cause substantial increases in weight as well as increases in cholesterol and triglycerides.

A Positive Placebo-Controlled Trial of Valproate (Depakote) for the Treatment of Children and Adolescents with Autistic Spectrum Disorder

A recent issue of the *Journal of Neuropsychopharmacology* reported that a placebo-controlled trial of valproate (Depakote) showed the drug is effective in treating irritability in those with autism. Approximately 50% of the participants were less irritable on valproate compared with only about 15% on placebo. Valproate was also generally well-tolerated.

EDITOR'S NOTE: This is a particularly important finding, both for clinical treatment and for its potential theoretical implications. Valproate, in addition to its properties as a mood-stabilizing anticonvulsant that increases brain GABA levels and exerts a variety of other neurobiological effects, is also a histone deacetylase inhibitor.

Histone deacetylase inhibitors may counteract problems with excitatory transmission. There is increasing evidence that in several animal models of autism and in patients with genetic disorder fragile X, there is increased binding of protein MeCP2 to DNA, which inhibits excitatory transmission. The main excitatory neurotransmitter in the CNS is glutamate, which is intimately involved in neuronal development, synaptic plasticity, and learning and memory. Thus a lower amount of excitatory neurotransmission could have profound effects on development in the short and long terms. In one animal model, the inhibitory effect of MeCP2 was reversed by treating the animals with two deacetylase-inhibiting drugs in combination that together blocked both histone-deacetylase type 3 and type 4. The deacetylase inhibitors keep acetyl groups on histones and render DNA more likely to be transcribed (or turned on).

Valproate exerts clinically significant histone-deacetylase activity on both type 3 and type 4 enzymes, which may explain its efficacy in autistic spectrum disorders. To clarify whether this is the mechanism by which valproate works, future studies could compare valproate with other drugs such as valnoctamide, which is an equally effective antimanic drug, but does not

inhibit histone-deacetylase. Should valproate alone prove effective in the treatment of autism, it would be likely that valproate's therapeutic effects depend on its histone-deacetylase mechanism.

As previously discussed in BNN Vol. 13(1), 2009, environmental factors can affect how easily DNA is transcribed by altering both DNA methylation and histone acetylation or methylation. Environmental events dictate the amount of methylation and acetylation, which is why the process is described as epigenetic. The inherited DNA code is not altered, only the degree to which additional molecules get attached to it during an animal's lifetime. DNA is tightly wrapped around histones, and when histones are acetylated, DNA is in a more open conformation, making it easier to transcribe.

Transcription basically consists of a read-out of the DNA and the construction of a chain of messenger RNA (mRNA), which then travels to the protein synthesis machinery of the cell (endoplasmic reticulum) in order to dictate the synthesis of new proteins based on the specific RNA sequences that code for individual amino acids. This production of new proteins by sequentially attaching strings of amino acids together based on the mRNA code is called translation.

In autism there appears to be a deficit in DNA transcription and subsequent mRNA translation of proteins in the brain that are important for ensuring adequate amounts of excitatory neurotransmission in the glutamate system. Thus, there is great potential for alleviating some symptoms of autism by preventing the removal of acetyl groups by de-acetylases in order to maintain higher levels of histone acetylation. With a histone-deacetylase inhibitor such as valproate, more histones remain acetylated and thus DNA is more readily transcribed. This could reverse the effects of MeCP2 in inhibiting excitatory neurotransmission in models of autism and in the fragile x syndrome.

If the valproate efficacy data are replicated and are ultimately attributed to inhibition of histone-deacetylation, this would open a whole new arena of potential therapeutic approaches to this most disabling disorder.

An environmentally-mediated epigenetic mechanism might also be consistent with the remarkable increased incidence of autism in more recent years. Autism was a relatively rare condition some two or three decades ago, but now is recognized in 1 per 100 to 125 live births. Currently only the atypical antipsychotics Aripiprazole (Abilify) and risperidone (Risperidol) are FDA-approved for the treatment of irritability in autism.

The Anticonvulsant Zonisamide (Zonegran) May Treat Alcohol Abuse

Albert Arias and collaborators from the University of Connecticut Health Center presented a study of zonisamide in which the drug provided significant benefits over placebo in patients with primary alcoholism (i.e., not with comorbid bipolar illness). Treatments began at 100 mg/day and increased to a maximum of 500 mg/day.

EDITOR'S NOTE: If replicated, this study would place zonisamide in a category with topiramate (Topamax), which has also been shown to decrease alcohol intake and craving. Both drugs also share the ability to cause minor weight loss as a potentially positive side effect, and both drugs have also proven effective in double-blind studies in the treatment of bulimia.

However, four double-blind, placebo-controlled studies found that topiramate did not have acute antimanic efficacy. Zonisamide has not been studied in a systematic fashion, but open studies suggest its potential utility in mania and, to a lesser degree, in depression.

Since zonisamide may have positive effects on mood in patients with bipolar disorder, and there is now placebo-controlled documentation of its

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efficacy in primary alcohol abuse disorders, its ultimate potential utility in patients with bipolar disorder and comorbid alcoholism deserves consideration.

A variety of approaches are now available to those with alcohol-related problems. These include several that are FDA-approved for those with primary alcoholism, including the opiate antagonist naltrexone, the glutamate-active agent acamprosate, and disulfiram (Antabuse) which makes patients sick if they revert to alcohol use. Zonisamide and topiramate are two drugs with anticonvulsant properties that now may also be of assistance in alcohol avoidance.

Researchers Litten and Falk have examined the time course of the emergence of anti-alcohol effects from naltrexone and topiramate seen in previous studies. They found that the drugs took one and two months, respectively, to achieve their maximum effects in decreasing the number of days of heavy drinking. The researchers suggest that this long delay be taken into consideration in the design of subsequent clinical trials, but the delayed onset of effect also has implications for clinical therapeutics. Those who are attempting to reduce days of heavy drinking with either agent should be persistent while waiting for positive effects to appear.

There are also other options for treating comorbid bipolar disorder and alcoholism. The anticonvulsant valproate, which, in contrast to topiramate and zonisamide, is effective and FDA-approved for the treatment of mania, has also been reported to have positive effects for alcohol avoidance in bipolar patients with comorbid problems with alcoholism. The anticonvulsant carbamazepine is widely used in Scandinavian countries instead of benzodiazepines for the acute management of alcohol withdrawal and for longer-term treatment of alcohol-related dysphoria and associated mood disturbances. Carbamazepine and valproate may have important roles to play in patients who have comorbid anxiety disorders, which are known to be highly associated with increased risk for alcohol abuse. These agents can be

Anti-inflammatory substances may augment mood stabilizers in bipolar patients

Bipolar patients treated with acetylsalicylic acid (aspirin) in conjunction with lithium prophylaxis needed fewer other adjunctive treatments, compared to patients treated with lithium alone, reports Stanley Rapoport of the National Institutes of Health. These retrospective epidemiological data are of considerable interest in relationship to evidence of an inflammatory component in the affective disorders, as reviewed in Vol. 13(2), 2009 of the BNN, but because the data is preliminary, more study is required.

EDITOR'S NOTE: Several measures of inflammation are higher in children and adults with bipolar disorder compared with controls. These include the ratio of inflammatory to anti-inflammatory cytokines, higher levels of TNF-alpha, and the inflammatory marker c-reactive protein. These peripheral markers measured in blood have been confirmed with direct measurements in postmortem brain autopsy specimens of people who had a history of bipolar disorder.

It is unclear how this information about inflammation in bipolar disorder may eventually inform treatment. In past BNNs, we have noted the positive effects of the anti-inflammatory antibiotic minocycline on schizophrenia, and stressed the need for studies of this compound in bipolar disorder. TNF-alpha inhibitors have also been associated with improvement in depression when used in the treatment of patients with rheumatoid arthritis and other autoimmune disorders.

This preliminary epidemiological analysis of those treated with lithium with and

without aspirin also must be replicated in order to document whether aspirin augmentation is indeed useful. Eventually, after further study, the data on inflammatory processes in the affective disorders may provide new treatment approaches.

In addition to providing hope of new treatments, new information about inflammation's role in bipolar disorder contributes to the understanding of how potential pathophysiological mechanisms could endanger neurons and glia, and thus may help explain how cognitive dysfunction emerges in the unipolar and bipolar disorders as a function of the number of affective episodes experienced. The new data emphasize the importance of long-term prophylactic treatment, not only to prevent episodes and their associated increases in inflammation, but also to prevent manic and depressive episode-related decreases in brain-derived neurotrophic factor (BDNF) and other neuroprotective factors.

A number of mood-stabilizing treatments either increase BDNF directly or prevent episode-related decrements in BDNF that can endanger neuronal and glial function. Without mood stabilization, the mechanisms of episode-related increases in inflammation and oxidative stress and decreases in neuroprotective factors may interact, making the brain especially vulnerable to functional deterioration. It is noteworthy that lithium, in addition to its ability to increase BDNF, also exerts some anti-inflammatory effects. How other approaches to inflammation in the affective disorders may ultimately improve therapeutic efficacy remains to be further studied.

utilized readily to treat anxiety syndromes and related alcohol withdrawal symptomatology without the risks of using benzodiazepines with their potential for abuse.

Because all of these potential approaches to alcohol-related problems in patients with bipolar disorder are considered off-label, and even those that are FDA-approved

for primary alcoholism have not been systematically studied in patients with bipolar illness, careful discussion and consultation between patient and physician is absolutely necessary before any of these types of approaches to alcohol abuse in the context of bipolar disorder are considered.

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