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A New Paradigm-Busting View of Genetics: Environmental Influences on Gene Structure May Be Transmitted to Offspring

It has been thought that one fundamental principle of genetics is that the impact of environment factors cannot be passed from one generation to the next via the genetic code. New data suggest this may not be true.

In an emerging field called epigenetics, researchers are finding the impact of environment and life experiences is not registered in DNA sequences, but can influence the structure of DNA or tightness of its packaging. **Early life experiences, particularly psychosocial stress, can lead to the accumulation of methyl groups on DNA (a process called methylation), which generally constricts DNA's ability to start transcription (turning on) of genes and the synthesis of the proteins the genes encode.** DNA is tightly wound around proteins called histones, which can also be methylated or acetylated based on events in the environment. When histones are acetylated, meaning that acetyl groups are attached to them, DNA is wound around them more loosely, facilitating gene transcription (i.e. the reading out of the DNA code into messenger RNA, which then arranges amino acids in order to construct proteins). Conversely, histone methylation usually tightens the winding of DNA and represses transcription.

Adverse early life experiences can lead to lifelong downregulation of the production of brain-derived neurotrophic factor (BDNF), which is necessary for long-term learning and memory as well as neural and glial health and survival, and of neurogenesis (the production of new neurons

for the hippocampus, a process that persists throughout adulthood).

A similar process occurs in adult animals. For example, repeated defeat stress, when a rodent is repeatedly defeated by a larger, more dominant rodent, can lead to the appearance of depressive-like behaviors and a reduction in hippocampal BDNF. The changes in BDNF and behavior are mediated by histone dimethylation, which persistently suppresses hippocampal BDNF. If antidepressants are given to the rodents during defeat stress experiences or if BDNF decrements in the hippocampus are prevented by selective molecular genetic manipulations, the animal does not exhibit the depressive-like behaviors. However, the epigenetic mark of dimethylation of a specific histone is not reversed, presumptively representing a neurobiological scar conveying ongoing vulnerability to defeat-stress-like behaviors in the animal.

Epigenetic alterations can be manipulated pharmacologically

DNA methylation and histone acetylation and de-acetylation had been thought to leave an enduring mark on DNA, but it is now known that DNA de-methylases, histone de-acetylases and histone de-acetylase inhibitors can be used to make DNA harder or easier to transcribe. The anticonvulsant valproate is a potent histone de-acetylase inhibitor, enabling acetyl groups to remain on histones and thus rendering the DNA in those areas more readily transcribed. In

animal studies, valproate is given during the extinction of a conditioned response, such as the avoidance of an environment associated with a shock stress, and facilitates extinction learning and increases in the amounts of BDNF transcribed and synthesized. Thus valproate enhances extinction learning via epigenetic mechanisms.

Epigenetics is a new paradigm for understanding how apparently genetic effects are really mediated by the environment. A good example is found in the instance of rat pups reared by an inexperienced and inadequate mother who repeatedly drops, drags, or even tramples them. This early adverse experience leads to an increase in DNA methylation and a lifelong reduction of BDNF levels in the forebrain, as seen in adolescent and adult animals. When female rodents who were reared by inadequate mothers produce a third generation, these offspring also exhibit a reduction in BDNF in their forebrain associated with increased methylation. It would be expected that this reduction in BDNF would be based on the repetition of the behavioral

Continued on Page 2

In this issue:

Epigenetics Update	p. 1-3
Inflammation	p. 3
Stress: Chronic v. Intermittent	p. 4
Brain Stimulation for Depression	p. 5
Atypical Antipsychotics	p. 6-8
Combination Therapy	p. 10

Epigenetics Research May Explain Environmental Influences on Genes

Continued from Page 1

repertoire of the inexperienced mother, and the methylation marks would be re-induced by adversities occurring in the first weeks of the rat pup's life. However, a publication by Roth et al. (2009) in *Biological Psychiatry* found that even when the third-generation rat pups are cross-fostered and reared by a highly competent mother, the methylation of the DNA promoter of BDNF remains. Since originally the DNA methylation was not thought to be transferred across generations, one interpretation of these data was that *in utero* anxiety experiences were sufficient to re-induce the methylation. However, it now appears that the alternate explanation is possible, and that DNA methylation marks are somehow transcribed directly to the offspring.

Researcher Eric Nestler has also raised this possibility after

finding similar evidence of trans-generational transmission of DNA methylation and other epigenetic markers.

Similarly, in a plenary lecture at the American College of Neuropsychopharmacology in December 2009, researcher Andrew Feinberg suggested that this process may not only be routinely possible, but might shed light on theories of evolution. Darwin had developed the principle of selection of the fittest based on the occurrence of rare mutations in the DNA sequence. Feinberg suggests that evolutionary theory be revised to include the adaptive selection of those with the best epigenetically-based adaptations to the environment. This concept relies on the possibility that epigenetic mechanisms are accurately transferred across generations, a process originally proposed by French scientist Jean-Baptiste Lamarck around the turn of the 19th century and subsequently scorned by the rest of neuroscience.

In contrast to Lamarck's ideas, the epigenetic mechanisms posited by Feinberg are based on the selection for positive adaptations, which Feinberg believes occur on a frequent or random (stochastic) basis. Positive epigenetic adaptations to the environment would be selected for, explaining the more rapid evolution of many species than would be expected based on rare genetic mutations alone.

Should these views of epigenetics prove valid, they would not only change the field of genetics and evolutionary neurobiology profoundly, but they would also forge a new understanding of environmental impacts on the development of mental illnesses and suggest the potential for radically new conceptions of treatment. There are known substances that prevent DNA methylation, and some histone de-acetylase inhibitors are even routinely available in clinical practice in the form of valproate and butyrate. Therefore, there is great opportunity for attempting to modulate and alter

what were previously considered lifelong epigenetic vulnerabilities contributing to the onset and progression of the major mental disorders.

Events in the environment can't change inherited gene sequences, but they can put chemical markers on DNA that make it easier or harder to turn on genes.

None of our currently available treatments to date has reversed any of the primary pathophysiological aspects of illness vulnerability, and patients with the recurrent unipolar and bipolar affective disorders and with schizophrenia require lifelong treatment in an attempt to suppress illness and prevent recurrence. **The new conception of the role of epigenetics opens up the possibility of considering treatments that may ultimately reverse some of the basic illness vulnerabilities (based on the environment and epigenetics) and lead to what might be considered curative treatments.**

An early example of potential therapeutic approaches using epigenetic manipulations was noted in the last issue of the *BNN* in the study reporting positive effects of the histone de-acetylase inhibitor valproate on a variety of target symptoms in autism.

In fragile X and a variety of other genetic illnesses with major psychiatric manifestations, there is an excess in activity of the methylating enzyme MECP2. This excess results in a life-long alteration in the set point of the ratio of excitatory (glutamatergic) to inhibitory (GABAergic) activity in the central nervous system in the direction

Continued on Page 3

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.

Although the editors of the BNN have made every effort to report accurate information, much of the work detailed here is in abstract or pre-publication form, and therefore cannot be taken as verified data. The BNN can thus assume no liability for errors of fact, omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the BNN.

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New Data Indicate Inflammation Occurs In The Affective Disorders

Bipolar children exhibit more inflammation than healthy children, according to a paper presented by Pandey, Dwivedi, and Pavuluri from the University of Illinois at the American College of Neuropsychopharmacology in December 2009. In "Pro-inflammatory cytokines in plasma of patients with pediatric bipolar disorder," the researchers described their study in which 21 normal controls were compared with 22 children with pediatric bipolar disorder who were unmedicated for a period of at least two weeks. The level of the inflammatory cytokine interleukin-1b (IL-1b) was significantly higher in the pediatric bipolar patients compared with controls, and levels of TNF alpha, another inflammatory marker, were significantly higher as well. Not only is this evidence of increased inflammatory processes in pediatric bipolar disorder, but TNF alpha is associated with activation of transcription

factors and the initiation of preprogrammed cell death or apoptosis.

Natalie Rasgon of Stanford University studied neurotrophins and inflammatory markers in women with bipolar disorder. She found that women with bipolar disorder compared with controls had higher levels of C-reactive protein (CRP, a marker of inflammation) although BDNF and inflammatory markers TNF, beta-1 and interleukin-2 did not differ significantly from controls. She did find a negative correlation between BDNF concentrations and depression scores on the Montgomery-Asberg Depression Rating Scale (MADRS), again replicating the findings from multiple studies that show lower BDNF levels are associated with greater severity of depression.

Inflammation compounds the medical problems faced by people with affective disorders. Both markers of inflammation and also insulin

resistance (which can lead to Type 2 diabetes) are altered in women with bipolar disorder compared with controls. CRP was highly correlated with body mass index (BMI) and all biomarkers of insulin resistance in women with bipolar disorder while, in the control group, CRP correlated only with BMI. Interleukin-2 was significantly correlated with insulin area under the curve in women with bipolar disorder, but not in controls.

Editors Note: Increases in inflammation may not only be a marker for patients with affective disorders (along with decreases in BDNF and other neurotrophic factors), but cytokines and other factors may also explain some symptoms (such as fatigue) and contribute to other pathological processes which can disrupt normal neuronal functioning.

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Epigenetics: Genes Affected by the Environment

Continued from Page 2

of deficient excitation and increased inhibition. To the extent that this epigenetic mark could be inhibited, there is potential for amelioration of many of the symptoms of fragile X-related syndromes, even in adults who have experienced long-term psychological and mental deficiencies. This also raises the possibility of primary prevention in those who might be tested and found vulnerable to the development of a fragile X-related syndrome. Early application of inhibitors of the hyperactive methylating process could prevent the major manifestations of these syndromes altogether.

Environmentally-induced epigenetic alterations leading to the development of psychiatric disorders would offer a potential explanation for why no genes of large effect have been identified in

the major psychiatric disorders despite an expensive and wide search across the entire human genome. While some mental illness vulnerability factors may, in fact, be encoded in the inherited variations in gene sequence, epigenetic processes may play an important role as well. There is increasing agreement that most complex psychiatric illness involve interaction of multiple gene and environmental vulnerability factors.

The powerful nature of epigenetic alterations in the developing animal is most readily seen in the differentiation of different organ systems in a developing fetus. That is, every cell in the body has the same DNA sequence, so it is by some other mechanism that some cells become liver cells and others become muscle or brain cells and these cells remain liver, muscle, or brain cells each time they divide

and replicate. Thus, cell fate appears to have a primary epigenetic mechanism and epigenetic mechanisms now appear to have a major role to play in adult learning and memory.

While this new view of epigenetics yields further evidence of the positive viewpoint that one's genetic inheritance is far from an absolute determinant of ultimate behavior, there may be a darker side to this equation as well. While the idea that adverse interactions with the environment may be transmittable across generations in the form of epigenetic mechanisms can offer greater hope for ultimate therapeutic interventions, it also allows for the possibility that aberrant behaviors could be passed down through multiple generations.

Neuroscience Update: Episodic Versus Continuous Social Stress Results in Different Behavioral and Biochemical Outcomes

At the American College of Neuropsychopharmacology meeting in December 2009, Klaus Miczek and colleagues from Tufts University in Boston presented a fascinating study indicating that the temporal aspects of the experience of social stress may have dramatic impact not only on defeat stress behaviors and the associated biochemistry, but also on the likelihood that an animal adopts cocaine self-administration. These investigators compared episodic versus chronic defeat stress in rodents.

Episodic social defeat stress consisted of four brief confrontations between an intruding animal and an aggressive resident rat over the course of a period of ten days. In contrast, chronic subordination stress involved the continuous exposure of the intruder rat to an aggressive resident over five weeks, during which time the intruder lived in a protective cage within the resident's home cage.

The episodically defeated intruder rats showed increases in intravenous cocaine self-administration and prolonged binge-like episodes, along with increases in brain-derived neurotrophic factor (BDNF), which is necessary for long-term learning and memory, in the midbrain ventral-tegmental area (VTA) and increased dopamine release in the nucleus accumbens, the reward area of the brain. **In contrast, the continuously subordinate rats showed the opposite pattern of suppressed cocaine intake**, suppression of dopamine release in the n. accumbens, and reduced BDNF in the VTA.

EDITOR'S NOTE: *These data are of considerable interest in indicating that the time course of stressors, including their frequency, duration, and timing during development, in addition to their severity, may have robust implications for behavior and biochemistry. In 1992, in an article in the American Journal of Psychiatry entitled, "Transduction of psychosocial*

stress into the neurobiology of affective illness," this editor indicated that it is the intermittency of cocaine and stressors that appears to lead to increased responsivity over time (sensitization), as opposed to the chronicity of the stressors, which leads to adaptive down-regulation and tolerance.

The opposite effects of intermittency versus continuousness for both cocaine and stressors is also reminiscent of the phenomenon of amygdala-kindling in which repeated intermittent (usually once a day) stimulation of the amygdala results in increasing severity of effects and ultimately full-blown behavioral seizures, while chronic continuous stimulation of the amygdala never leads to these seizures.

The data on cocaine from Everett Ellinwood of the University of North Carolina are particularly cogent. He unequivocally demonstrated that repeated intermittent cocaine administration led to marked cocaine sensitization of behaviors and biochemistry, while chronic continuous administration of cocaine through a small pump resulted in suppression of motor activity and biochemical variables. The data from Miczek noted above now extend this viewpoint to intermittent versus continuous stress, resulting in opposing effects on a variety of behavioral and biochemical outcomes.

Intermittency of stimulation, drugs, and stressors thus appears to be related to increases in responsivity or sensitization and kindling-like effects in many different models. Such findings must be studied more specifically in clinical situations, but should this principle pertain to people, it could explain some of the great variety in behavioral and neurochemical alterations that are associated with stressful life experiences.

While chronic stress exposure can often be adapted to, it may turn out that repeated intermittent stressors are more potent in evoking increased or sensitized behavioral responses over time. This perspective may not only be of interest in understanding pathophysiological

mechanisms of different types of stressful situations, but may ultimately be of importance in applying appropriate therapeutic maneuvers, which may differ as a function of the initial intermittency or continuousness of social support, drug treatment, or stimulation of the brain.

In particular, rTMS and electroconvulsive therapy (ECT) are both brain stimulations given in an intermittent fashion, as opposed to vagal nerve stimulation (VNS), which is delivered more continuously. It is noteworthy that both rTMS and ECT can be associated with tolerance phenomena and loss of effectiveness with repeated administration in a subgroup of patients. In contrast, the continuous stimulation of the vagus is associated with the unique phenomenon of increased clinical responsivity in individual depressed patients over a year of stimulation, and an increased number of responders seen at one year compared with initially at three months. Whether this difference in intermittency of stimulation is the key difference in long-term outcome (tolerance and fading of clinical efficacy with ECT and rTMS compared with increasing antidepressant efficacy over time with VNS) remains to be studied more directly.

This idea about intermittency is also of potential interest in relationship to the requirement of chronic administration of most antidepressant drugs, which often require several weeks or more to show maximum effectiveness. In contrast, intravenous administration of the glutamate antagonist ketamine or the acetylcholine antagonist scopolamine appears capable of inducing rapid onset of antidepressant effects. With ketamine, repeated intermittent application of the treatment is associated with a more sustained therapeutic response. This contrasted with the results when chronic administration of the glutamate antagonist riluzole was given and was ineffective in sustaining the acute antidepressant effects of ketamine. It is possible that mechanistically different

Continued on Page 5

Persistence of Low Levels of Depressive Symptoms Is a Risk Factor for Subsequent Relapse into a Full-Blown Episode in Bipolar Patients

Depression is three times more prevalent than manic symptoms in naturalistically treated bipolar patients (according to studies by Judd et al., Kupka et al., and Ezquiaga et al.). The occurrence of even residual depression or subsyndromal symptoms can be highly impairing, and is a predictor of increased likelihood for subsequent relapse, according to a poster presented by Gitlin et al. at the American Psychiatric Association meeting in San Francisco in May 2009.

These data support a large number of other investigators who have made similar observations, all indicating the importance of attempting to achieve remission as a major goal of clinical therapeutics and in order to decrease likelihood of relapse. Gitlin's study further indicated that impairment of quality of life in bipolar patients was closely related to the degree of their subsyndromal symptomatology.

Episodic v. Chronic Stress

Continued from Page 4

actions at the glutamate receptor were involved in this differential responsivity, but in light of the above discussion, it is also possible that intermittent blockade of the glutamatergic system with ketamine is an important therapeutic variable and that maintenance of the effect, even with other glutamate antagonists administered on a chronic basis, may be problematic. Parenthetically, ketamine is rapidly cleared from the body, yet its acute-onset clinical effects are seen after two hours and may last for a period of three to four days, i.e., long after the drug is out of the patient's system.

A Variety of Brain Stimulation Techniques May Help Treatment-Resistant Depression

Deep Brain Stimulation

At the American Psychiatric Association meeting in San Francisco in May 2009, Giacobbe et al. reported on the results of deep brain stimulation of an anterior-ventral part of the prefrontal cortex called the subgenual cingulate cortex in patients with refractory major depressive disorder. In deep brain stimulation, electrodes are inserted directly into the brain. Twenty-one patients received this treatment in an open study at sites in Canada at McGill University, the University of British Columbia, and the University of Toronto. This multi-center trial replicated results reported by Mayberg et al. (2005) with stimulation of what is also called Brodmann's area 25, or the part of the prefrontal cortex just under the anterior part of the corpus callosum (which carries fiber tracts between the left and right sides of the brain).

In the trial by Giacobbe et al., 13 of 21 patients achieved a 40% reduction in depressive symptoms, and an additional 4 out of the 21 had a partial response. At the last follow-up visit, two subjects had achieved full remission. The authors caution that verification of these findings in a placebo- or sham-controlled design (in which a procedure without real medical effects is performed for some period of time) is required before the effectiveness of deep brain stimulation in this area can be adequately assessed. While the 40% improvement rates are substantial in highly treatment-resistant patients, the finding that only two subjects achieved remission at the last follow-up demonstrates the relatively low rate of excellent or complete response with this highly invasive treatment intervention.

Less Invasive Approaches: Frontal Lobe and Vagal Nerve Stimulation

A variety of less invasive strategies in which the brain is not penetrated deserve further study. As we have reviewed in previous BNNs, other forms

of brain stimulation that are less invasive are currently being studied, including bilateral stimulation of the frontal lobes with subdural electrodes (which do not penetrate the brain substance), and vagal nerve stimulation (VNS), which requires an operation for the insertion of a stimulator in the chest wall and electrodes onto the left vagus nerve in the neck. VNS is FDA-approved for the treatment of both seizures and depression that have resisted other treatments.

Non-Invasive Approaches to Neurostimulation: rTMS

Repeated transcranial magnetic stimulation (rTMS) is also FDA-approved for treatment-resistant depression. It involves placing a magnet with a rapidly alternating magnetic field over the left prefrontal cortex while a person is awake. rTMS over the motor cortex produces movement in the hands or feet, but over the prefrontal area produces no motor effects.

Meta-analyses of a large series of relatively small placebo-controlled studies continue to indicate the efficacy of active rTMS compared with sham stimulation procedures, and a multi-center trial led to FDA approval of one type of rTMS apparatus, which is now increasingly becoming available to the public. A new NIMH replication study has just been published by Mark George et al. in the *Archives of General Psychiatry* and is described in the last BNN. In contrast to electroconvulsive therapy (ECT), rTMS does not require anesthesia or the induction of a seizure to be effective.

Right Unilateral Ultrabrief Pulse ECT

If one is contemplating the use of ECT, it may be prudent to discuss using the newly studied method using right unilateral ultra-brief pulse stimulation. Sackheim and colleagues reported in the journal *Brain*

Continued on Page 9

New Research on Quetiapine (Seroquel XR) Shows Efficacy Across A Spectrum Of Illnesses

Quetiapine as an adjunct to antidepressants in unipolar depression

Posters at the American Psychiatric Association meeting in San Francisco in May 2009 showed new data from a series of studies of quetiapine in unipolar depression that showed the drug in monotherapy (at 150mg & 300mg) was significantly more effective than placebo. Studies were also positive when quetiapine was used as an adjunct compared with placebo for patients showing inadequate or incomplete responses to antidepressants such as selective serotonin reuptake inhibitors (SSRIs).

Quetiapine has previously been approved for monotherapy treatment of schizophrenia, acute mania, and acute bipolar depression, and is also approved to be used in combination with either lithium or valproate for prevention of both manic and depressive episodes.

Based on this new series of studies in unipolar (UP) depression, the FDA has approved quetiapine (Seroquel XR), but only as an adjunct to previously unsuccessful antidepressants for UP depression. The side effects demonstrated in these studies were similar to those previously reported in schizophrenia, mania, and bipolar depression. These included a moderate incidence of sedation and somnolence (sleepiness) with a 1kg to 2kg increase in weight in most of the studies. There was also a slightly increased risk for increases in some of the indices of the metabolic syndrome, including levels of fasting blood glucose, triglycerides, and the low-density lipoprotein component of cholesterol.

These studies were all performed with the extended release form of the drug (Seroquel XR), which it is recommended to administer three to

four hours prior to bedtime. With the XR preparation, blood levels reach a peak of 400ng/ml five or six hours after the administration of a single evening-time dose. With the original immediate release preparation, much higher blood levels (800ng/ml) occurred in the first hour after a dose, so it was recommended that the original preparation be administered immediately prior to bedtime.

The XR preparation comes in 50mg capsules, and it is recommended that the dose be titrated with 50mg increases each day until the target of 150mg (nighttime dose) is achieved on the third day. However, in those with problematic degrees of somnolence and sedation carrying over to the next morning, it is advisable to slow down the titration until these side effects wane. Since a few percent of patients will have difficulty getting up early in the morning after a single nighttime dose, a test dose on a Friday or Saturday night has been recommended by Dr. Joseph Calabrese for those with important morning work or school schedules.

Quetiapine in Generalized Anxiety Disorders (GAD)

Another poster described the effects of Seroquel XR in generalized anxiety disorder. Its use was associated with significant degrees of improvement on most outcome measures compared with placebo, including improvements in anxiety, somatic symptoms, and sleep. Doses administered were 75mg and 150mg given at night. Despite these positive efficacy data, the FDA advisory panel had concerns about its tolerability, and decided not to approve quetiapine for treatment of GAD.

Quetiapine in post-traumatic stress disorder (PTSD)

In a poster about the use of quetiapine (Seroquel XR) in post-traumatic stress disorder (PTSD), doses of 150mg and 300mg were both more effective than placebo. The range of improvement included the entire PTSD syndrome measured by the Clinician-Administered PTSD Scale (CAPS), and in each of its subscales, including paroxysmal events (such as nightmares and flashbacks), generalized level of anxiety, numbing, and sleep disturbances (which are often particularly problematic in PTSD).

Different doses of quetiapine for different illnesses

As illustrated in the figure, there appears to be an interesting relationship between receptor affinity and FDA-approved dose range of seroquel across different psychiatric syndromes, suggesting that different doses are effective for different illnesses. The conventional dose for treating acute mania or schizophrenia is 400mg to 800mg/day. In contrast, lower doses in the range of 300mg to 600mg/day are indicated for acute treatment of bipolar depression; however, the 600mg/day dose is not significantly superior to 300mg/day. The adjunctive prophylactic efficacy of quetiapine compared with placebo in preventing manic and depressive episodes in bipolar disorder was established at 400mg/day added to ongoing treatment with either lithium or valproate. Doses of quetiapine adequate for unipolar depression, generalized anxiety disorder, and PTSD appear to reside in a lower range (150mg to 300mg/day).

Continued on Page 7

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Quetiapine's Mechanisms of Action in Different Illnesses

Continued from Page 6

Mechanisms of action of quetiapine potentially related to its effectiveness

The wide range of efficacy of quetiapine across a number of psychotic syndromes (schizophrenia and mania) and mood and anxiety disorders makes one wonder about the mechanisms by which the drug works. While none of quetiapine's specific actions on different neurotransmitters has been definitively linked to efficacy in a given syndrome, a variety of hypotheses remain particularly appealing.

Weak blockade of dopamine receptors implicated in actions in mania and schizophrenia

The blockade of dopamine receptors has long been implicated in the mechanisms of antipsychotic and antimanic drugs, and this remains a likely mechanism for quetiapine's effects. However, quetiapine has a low affinity in blocking dopamine D_2 receptors, or a low degree of binding to those receptors, and its rapid dissociation from the receptor may be a reason that higher doses are needed for mania and schizophrenia. Even at these higher doses, it rarely causes acute Parkinsonian effects or increases plasma prolactin, which are both direct effects of potent D_2 receptor blockade.

New brain imaging data in humans also indicate that quetiapine (like clozapine, the most effective atypical antipsychotic that also features the least motor side effects) binds less tightly to dopamine receptors in

the motor areas of brain (striatum) than in extra-striatal areas, which could also explain its relative lack of Parkinsonian side effects.

Potential antidepressant mechanisms

Quetiapine's ability to block $5HT_2$ receptors is shared by most atypical antipsychotics and is thought to contribute to their benign motor side-effects profile. Such a blockade has also been implicated in antidepressant effectiveness and in enhancing slow wave sleep not only with the atypicals, but also with antidepressants such as trazodone and nefazodone.

Quetiapine's active metabolite norquetiapine has extra actions not shared by the parent compound. Norquetiapine blocks the norepinephrine transporter, with potencies in a range similar to that of traditional noradrenergic-selective antidepressants such as desipramine, nortriptyline, and malprotiline. This action could account for some of quetiapine's antidepressant and anti-anxiety efficacy. In addition, norquetiapine is a $5HT_{1A}$ partial agonist and thus shares some of the effects of the more selective serotonin $5HT_{1A}$ agonist buspirone (Buspar), which exhibits some antidepressant and anti-anxiety effects.

Norquetiapine also blocks $5HT_{2C}$ receptors, which inhibit release of norepinephrine and dopamine into the prefrontal cortex. Since norquetiapine is an antagonist of these receptors, it increases dopamine and norepinephrine release in the prefrontal cortex via disinhibition (an action shared by ziprasidone (Geodon). Hypofunction of prefrontal cortex has been implicated in many primary and

secondary depressive syndromes, so it remains plausible that norquetiapine's action at the $5HT_{2C}$ receptors could be implicated in its antidepressant efficacy.

In animal studies, quetiapine increases levels of brain-derived neurotrophic factor (BDNF) in the hippocampus and prevents stress from decreasing BDNF. BDNF is necessary for long-term learning and memory as well as neural and glial health and survival. BDNF in patients' blood decreases with depressive episodes in proportion to their severity, and all known antidepressants appear to increase BDNF. Thus, effects on BDNF may also explain some of quetiapine's antidepressant actions.

Potential mechanisms related to side effects

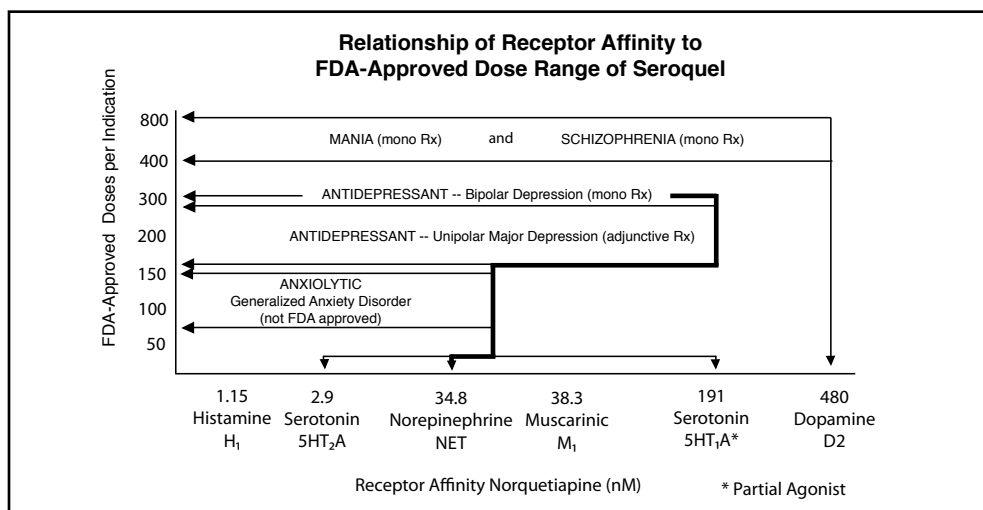
Quetiapine also potently blocks histamine (H_1) and muscarinic acetylcholinergic receptors (M_1), actions that could account for some of its side-effects profile, including sedation (via H_1 blockade), dry mouth and constipation (via M_1 blockade). Recent data indicate that intravenous doses of the selective blocker of muscarinic receptors scopolamine cause rapid antidepressant effects, so it is possible that quetiapine's ability to block M_1 could also contribute to its antidepressant effects. Quetiapine also blocks noradrenergic α_1 receptors, which could explain orthostatic hypertension (low blood pressure upon standing), an occasional side effect.

Overview:

Dose requirements correlate with receptor affinities

Quetiapine's blockade of the D_2 receptor is weak. To the extent that D_2 receptor blockade is implicated in antimanic and antipsychotic effects, higher doses of quetiapine are required to maximally exert this action. In contrast, the greater potency of norquetiapine for blockade of the norepinephrine reuptake transporter is in line with the lower doses required to treat depression.

The high potency of quetiapine in blocking histamine and cholinergic receptors would also be compatible with the high to moderate sedative and anticholinergic effects of the drug as well. For some patients, these side effects can be problematic even at the lowest doses.



An Update on Aripiprazole (Abilify), an Atypical Atypical Antipsychotic

Spectrum of Efficacy

Aripiprazole has now been approved for acute and maintenance treatment of pediatric patients with bipolar disorder from ages 10 to 17. It had already been approved for adult bipolar disorder, schizophrenia, and as an adjunctive treatment for acute unipolar depression inadequately responsive to antidepressants of the serotonin-selective class or the serotonin-norepinephrine reuptake inhibitor venlafaxine. Aripiprazole, along with risperidone, is one of only two drugs FDA-approved for the treatment of irritability in autism.

In a poster presented at the American Psychiatric Association meeting in San Francisco in May 2009, Whitehead and associates indicated that in these pediatric patients with bipolar disorder, not only did their Young Mania Rating score (YMRS) improve, but also their Clinical Global Impressions-Bipolar (CGI-BP) severity score and their quality of life assessments did as well. There was a moderate correlation between subjective improvement in quality of life as measured by the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQLESQ) and the degree of clinical improvement measured by YMRS and CGI-BP. The improvement occurred at both the aripiprazole 10mg/day dose and the 30 mg/day dose when compared with placebo.

Mechanisms of Action

Aripiprazole is what is known as a partial agonist (stimulator) of dopamine D_1 , D_2 , and D_3 receptors, in contrast to all other typical and atypical antipsychotics, which are full antagonists (blockers) of dopamine receptors. The partial agonism means that when aripiprazole binds to the receptor, it activates the receptor only about 20%, but never any more, no matter how high the dose or blood levels of the drug are. Since aripiprazole "sits" on the receptor, any degree of excess

dopamine that may occur in mania or schizophrenia cannot reach these dopamine receptors, so aripiprazole effectively produces an 80% functional blockade. The 20% stimulation (agonism) of dopamine D_2 receptors is sufficient to make aripiprazole the only typical or atypical antipsychotic that significantly lowers prolactin levels. Aripiprazole is also a partial agonist at serotonin $5HT_{1A}$ receptors, like the drug buspirone (Buspar), which is known for its antidepressant and antianxiety

Aripiprazole is the only atypical that partially stimulates dopamine receptors. It also keeps them from being overstimulated and thus balances dopamine's impact on mood and side effects.

effects. Aripiprazole is a full blocker of $5HT_{2A}$ receptors, which might also contribute to its antidepressant effects, and (like the antidepressant Trazodone) its ability to increase the deeper phases of sleep known as slow wave sleep.

Side effects: weight gain, but no increases in other metabolic indices

At the American Psychiatric Association meeting in San Francisco in May 2009, Newcomer et al. presented a poster on metabolic measures in pediatric and adolescent patients in the studies that led to the FDA approval. In contrast with schizophrenic patients at six weeks and bipolar patients at four weeks who experienced negligible weight gain, among the bipolar children and adolescents treated with aripiprazole for 30 weeks, there was an approximate 3kg increase in weight compared with

1kg on placebo. However, none of the other indices of the metabolic syndrome showed significant changes when compared with placebo. These included total cholesterol, fasting triglycerides, and fasting glucose.

The metabolic syndrome is considered present if three of five following indices are abnormal. These include: 1. Fasting blood glucose or insulin resistance 2. Increased waist circumference (reflecting weight gain) 3. Increases in cholesterol 4. Increases in triglycerides and 5. Increases in blood pressure. Patients with both unipolar and bipolar affective disorders should take special precautions to have these indices carefully monitored and stabilized by their internist, family practitioner, or directly by their psychiatrist if other specialists are not available. Depression is a risk factor for type II diabetes and vice versa.

The authors of this poster on aripiprazole concluded that **these mild weight gain results should inform clinical decisions about the potential use of aripiprazole in children and adolescents**, and that the study supports the need for careful management of weight gain and metabolic monitoring of these youngsters.

An acute adjunctive treatment for unipolar patients inadequately responsive to their antidepressant, either an SSRI or an SNRI

Three randomized, placebo-controlled studies all have shown that when aripiprazole (compared with placebo) is added to previously inadequate antidepressant treatment, there is a rapid and highly statistically significant improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores. Even in studies of only six weeks' duration, quality of life on the Sheehan Disability Scale (SDS) tended to show improvement as well. There was

Continued on Page 9

Aripiprazole and Ziprasidone Are Two of the Best-Tolerated Atypicals

Continued from Page 8

minimal sedation (approximately 10% of patients on aripiprazole). Twenty-five percent of patients did experience akathisia (restless legs) and restlessness, but fewer than 2% of the patients discontinued aripiprazole because of these side effects. *This editor recommends starting children with bipolar disorder and adults with unipolar depression with 1mg to 2mg of aripiprazole in order to establish better initial tolerability and less akathisia.* The weight and metabolic profiles of this study mirror those reported above in the pediatric trials, in that there was significantly greater weight gain on aripiprazole than placebo, but this was of relatively small magnitude (1.3kg), and there was a lack of significant alterations in any of the metabolic indices, including cholesterol, triglycerides, and glucose.

EDITOR'S NOTE: The lack of increase in indices of the metabolic syndrome while on aripiprazole, with the exception of some weight gain, is of substantial clinical importance, because affectively ill patients are already prone to the metabolic syndrome and lose many years of life expectancy (compared with the general population) due to increased medical mortality, predominantly from cardiovascular disease. Thus, it becomes important not to prescribe medications that might exacerbate these problems, such as elevated cholesterol, triglycerides, blood sugar, or blood pressure.

Adjunctive Aripiprazole Affects Core Symptoms of Unipolar Depression

Adding aripiprazole to the drug regimen of a patient with major depression was significantly superior to adding placebo on most of the core symptom items of major depression in a pooled analysis of several studies. Martin et al. presented these data in a poster at the American Psychiatric Association meeting in San Francisco in May 2009. The improved areas included: trouble falling asleep, feeling sad, low mood, decreased appetite, view of the self, view of the future, thoughts about death/suicide, general interest, capacity for pleasure/enjoyment, interest in sex, and interpersonal sensitivity.

These improvements were accompanied by improvements at a trend or significance level in quality of life after just six weeks of treatment, as well as a generally good side-effects tolerability profile. The most common side effects are akathisia (restless legs) and restlessness, which appear to be less prominent if one starts with very low (pediatric) doses, i.e. 1mg to 2mg/day. The metabolic profile of the drug is relatively benign, with only weight gain occurring significantly more on aripiprazole than on placebo, while there were no significant changes in cholesterol or triglycerides.

with a wider pulse width that may be associated with more memory loss.

Low Level Magnetic Fields (LLMF)

Researchers at McLean Hospital in Boston have reported antidepressant effects of rapid pulse sequences of the low level magnetic fields of a magnetic resonance imaging (MRI) machine. This is the same machine widely used to image the brain, but a different pulse sequence is utilized. This strategy deserves further study because of its lack of invasiveness compared to some other types of brain stimulation.

Ziprasidone (Geodon) in pediatric patients with bipolar disorder

As noted in the previous volume of the *BNN*, ziprasidone has also shown efficacy in pediatric BP I disorder (ages 10 to 17). It's metabolic profile is the most benign of the atypical antipsychotics, including being the only one that does not produce weight gain in children. None of the other metabolic indices increased either.

This drug is currently rarely used in children because of concerns about its effects on electrocardiogram (EKG), which have rarely been seen in clinical practice. Perhaps the overall assessment of its risk/benefit ratio should be re-evaluated.

The Rationale for Dual Drug Treatment of Memory Disturbances in Alzheimer's Disease

The two main classes of drugs for the treatment of Alzheimer's disease currently include cholinesterase inhibitors, which increase brain acetylcholine levels, and memantine (Namenda), which is a partial blocker of glutamate receptors.

The brains of patients with Alzheimer's are deficient in acetylcholine. Acetylcholinesterase breaks down acetylcholine, so the first class of Alzheimer's drugs inhibits these esterases and makes more acetylcholine available.

Memantine works a different way. Glutamate is the major excitatory neurotransmitter in the brain. Excesses of glutamate may be toxic to cells, so memantine's ability to partially block

Brain Stimulation (con't)

Stimulation in 2008 that this type of unilateral ECT was associated with degrees of improvement equivalent to traditional bilateral electrode placements, but was associated with substantially reduced impairments in autobiographical memory. Thus, if one is considering ECT for the treatment of acute unipolar or bipolar depression, current data suggest the likely better tolerability of the ultra-brief pulse right unilateral parameters compared with bilateral stimulation or even unilateral stimulation

Continued on Page 11

Treatment with Lamotrigine Plus Valproate Superior to Lamotrigine Alone

In a study comparing valproate monotherapy with the combination of lamotrigine and divalproex (Valproate) extended release (ER), the combination appeared more effective in bipolar depression. At the American College of Neuropsychopharmacology meeting in December 2009, Vivek Singh, Charles Bowen, Richard Weisler, and colleagues from The University of California, San Diego reported on the randomized, double-blind, eight-month maintenance study of bipolar depressed patients.

Patients who could be stabilized for two consecutive weeks on the combination treatment of both lamotrigine and divalproex were then randomized to either lamotrigine alone or the combination for the duration of the study. Most of the data collected about these 87 subjects favored the treatment with the combination (lamotrigine plus divalproex) compared with lamotrigine alone. **Combination therapy was superior for manic symptomatology and resulted in lower rates of unanticipated worsening of depression** (greater than 20 points on the Montgomery-Asberg depression rating scale (MADRS)) that led to termination from the study than lamotrigine monotherapy did.

EDITOR'S NOTE: *These data are interesting for several reasons. One is the generally good tolerability of the combination. While divalproex added to lamotrigine will essentially double lamotrigine blood levels and can increase risk of a serious rash, the two drugs are widely used in combination in the treatment of patients with seizure disorders with both good efficacy and tolerability. This may be attributable in part to the fact that divalproex has the ability to increase brain GABA, while lamotrigine inhibits glutamate release, and the combination may thus be associated with dual mechanisms of increasing GABA inhibition and decreasing glutamatergic over-excitation which together would prevent too rapid cell firing and behavioral dysregulation.*

This study also has interesting parallels with the results of the large BALANCE study conducted recently in Europe, in which the combination of lithium and divalproex (Valproate) was found to be substantially more effective than divalproex alone and, to a lesser extent, more effective than lithium alone as well. These two studies add to the literature suggesting that treatment with combinations of mood stabilizers may be superior to monotherapy.

This conclusion is also supported by several studies from Case Western Reserve University in Cleveland of both adults and children with bipolar disorder who were initially stabilized on the combination of lithium and divalproex and then randomized to monotherapy with either agent. In both patient populations there was a very high relapse rate upon the switch to monotherapy and, at least in the children with bipolar disorder, a very high re-response rate once the combination of lithium and divalproex was reinstated.

Clinicians have long used combination therapy and, at times, complex combination therapy in order to establish more substantial long-term responses or remission, but until recently there was not an extensive controlled clinical trials literature to support this procedure. Now there is support for combination therapy in overall superior treatment outcome and the prevention of both manias and depressions with the combination of lithium and divalproex, and now in bipolar depression with the combination of divalproex and lamotrigine compared with lamotrigine alone.

Some clinicians and investigators, such as Paul Grof and colleagues, have extolled the virtues of monotherapy compared with combination therapy and, while there is a small subgroup of patients who do well on long-term lithium monotherapy, this appears, at least in the U.S., to be a very small minority of patients, and much more often combinations are required to achieve short- and long-term stability. Even in the current study of Singh and colleagues, only 87 of the 165 subjects originally enrolled were able to

be randomized, meaning that in a period of open treatment for up to eight weeks, only about half the patients treated with the divalproex/lamotrigine combination for a current depression or a depression within the past six months were able to sustain low depression scores for a period of two weeks.

Indirectly, this indicates that other combinations of treatments or additional augmenting agents would be required for this other half of the patients who failed to show initial mood stabilization. These

Combination therapy is often superior to monotherapy.

data are very much like those of Calabrese and colleagues who found that only about one-quarter of the patients evaluated on the combination of lithium and divalproex who had rapid cycling bipolar disorder were able to be stabilized for a short period of time on this combination. It appears that not only are monotherapies with mood stabilizers often much less satisfactory than combination therapy, but one-half to two-thirds of patients do not even respond satisfactorily enough to the combination in the first place, and would then need other and potentially more complicated treatment strategies from the outset.

The data with atypical antipsychotic augmentation would appear to conform with this same theory. Quetiapine (Seroquel) is FDA-approved as an adjunct to lithium or divalproex. Its addition has resulted in superior prevention of both manic and depressive episodes compared with continuation of lithium or valproate alone (and with the addition of a placebo). While there is now evidence (from the SPARKLE study described in the BNN (2009) Vol. 13, Issue 3) that quetiapine monotherapy is also more effective than placebo, it remains to be seen whether a mood stabilizer (lithium or divalproex)

Continued on Page 11

Update on the Treatment of GAD

Generalized anxiety disorder (GAD) is highly prevalent and often associated with considerable discomfort and dysfunction. It often co-occurs with bipolar disorder. Traditional treatments of the primary syndrome (occurring in the absence of bipolar disorder) involve serotonin-selective antidepressants and serotonin-norepinephrine reuptake inhibitors such as venlafaxine (Effexor) or duloxetine (Cymbalta). While these are often useful and lead to considerable improvement, they often do not lead to full remission of somatic or accompanying symptoms of insomnia.

Alternative treatment possibilities include the anticonvulsant pregabalin (Lyrica), which has been found effective in four placebo-controlled studies in GAD. A poster presentation by Joshi et al. at the American Psychiatric Association meeting in San Francisco in May 2009 also reported that pregabalin was more effective in reducing sleep disturbance than venlafaxine. Pregabalin is FDA-approved for seizures and fibromyalgia, but not for GAD or pain syndromes. Another treatment possibility is quetiapine (Seroquel) mentioned on pages 6-7, where not only have there been positive efficacy in placebo-controlled studies of patients with GAD, but the patients also experienced improvement in sleep.

Each of the different types of treatments of GAD have had small effect sizes when studied, which suggests

that several drugs may need to be used in combination in order to target the various components of generalized anxiety disorder, including persistent and excessive worry, a variety of somatic symptoms, and insomnia.

In the study of Joshi et al., pregabalin was used in the range of 300mg to 600mg/day compared with venlafaxine XR (75mg to 225mg/day) and compared with placebo. Both pregabalin and venlafaxine XR were significantly more effective than placebo for the treatment of GAD. The disturbances that improved on pregabalin included poor sleep adequacy, shortness of breath, and daytime sleepiness.

Micelli also reported on the addition of adjunctive pregabalin after partial response to other treatments for GAD. In this study, patients who were inadequately responsive to a course of an SSRI/SNRI or benzodiazepine after eight weeks were randomized to either pregabalin (150-600 mg/day) or placebo, in addition to continuation of the existing SSRI/SNRI. The change in the Hamilton Anxiety Scale scores (showing a 50% reduction in anxiety) were significantly greater on pregabalin compared with placebo, along with a significantly earlier time to sustained response compared with placebo as well. Common side effects included dizziness, headache, and somnolence, but discontinuations due to side effects were low (4.4%) on pregabalin and non-significantly different from placebo (3.4%).

Lamotrigine and Valproate Effective in Combination Therapy

Continued from Page 10

plus an atypical such as quetiapine would be more highly effective in selective patient populations compared with quetiapine alone. Quetiapine monotherapy in the SPARKLE study showed about equal efficacy to lithium monotherapy.

There is also a strong clinical-trials literature indicating the superiority of

the combination of an atypical plus a mood stabilizer in the treatment of acute mania. These data extend to almost all of the atypical antipsychotics studied in a controlled fashion. Since we and most other clinicians and investigators have endorsed the general principle that the treatments that are successful in achieving acute mood stabilization/remission are the ones most likely to sustain this response in long-term

Dual Drug Treatment May Be Best for Alzheimer's

Continued from Page 9

glutamate receptors may explain the drug's effectiveness in Alzheimer's.

An extended release formulation of memantine (28mg once daily) has now been shown to improve behavior in patients with moderate to severe Alzheimer's disease (in a poster by George Grossberg et al. at the American Psychiatric Association meeting in San Francisco in May 2009). In another poster, the same investigators reported that extended release memantine (28mg once daily) also improved attention and verbal fluency in patients with moderate to severe Alzheimer's disease.

Previous work had indicated that the combination of an anticholinergic such as donepezil (Aricept) with regular release memantine gave an additive improvement in cognitive function when both drugs were given from the outset of the treatment of Alzheimer's disease. With this additive improvement, the time it took a patient to fall below their baseline level of cognitive dysfunction was also extended for several years' greater duration than with either drug alone. These data would suggest that in contemplating pharmacotherapy for Alzheimer's disease, combination approaches should be carefully investigated and considered, rather than starting with either a cholinesterase inhibitor or memantine alone.

prophylaxis, there is further rationale for continuation of a mood stabilizer and an atypical during the maintenance phase, particularly if there is good tolerability and no problematic emergence of side effects. Thus, long-term tolerability, which varies considerably among the different atypicals, becomes an important variable in the choice of agents to be considered in acute treatment as well as long-term prophylaxis.

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