Untangling Depression and Anxiety: Clinical Challenges

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference "Untangling Depression and Anxiety: Clinical Challenges," which was held July 12, 2005. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Forest Pharmaceuticals, Inc.*

The planning teleconference was chaired by ***Martin B. Keller****, M.D., Department of Psychiatry and Human Behavior, Brown University School of Medicine, Providence, R.I. The faculty were* ***John H. Krystal****, M.D., Department of Psychiatry, Yale University School of Medicine, West Haven, Conn.;* ***René Hen****, Ph.D., Center for Neurobiology & Behavior and Department of Pharmacology, Columbia University, and the College of Physicians & Surgeons, New York State Psychiatric Institute, New York, N.Y.;* ***Alexander Neumeister****, M.D., Department of Psychiatry, Yale University School of Medicine, West Haven, Conn.; and* ***Naomi M. Simon****, M.D., M.Sc., Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital, Boston.*

Faculty disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., a proprietary entity producing health care goods or services) occurring within the 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows: ***Dr. Keller*** *is a consultant for and has received honoraria from Bristol-Myers Squibb, Collegium, Cypress Bioscience, Cyberonics, Eli Lilly, Forest, Janssen, Merck, Organon, Otsuka, Pfizer, Pharmastar, Sepracor, Vela Pharmaceuticals, and Wyeth; has received grant/research support from Eli Lilly, Forest, Merck, Organon, Pfizer, and Wyeth; and is on the advisory boards for Abbott, Bristol-Myers Squibb, Cephalon, Cyberonics, Cypress Bioscience, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Merck, Mitsubishi Pharma, Novartis, Organon, Pfizer, Sanofi-Synthelabo, Scirex, Sepracor, Somerset, Vela, and Wyeth.* ***Dr. Krystal*** *is a consultant for Alkermes, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Merz, Pfizer, Shire, Sumitomo, Takeda, Titan, and UCB Pharma.* ***Dr. Neumeister*** *has received grant/research support from Pfizer and UCB Pharma.* ***Dr. Simon*** *has received grant/research support from AstraZeneca, Cephalon, Forest, GlaxoSmithKline, and Eli Lilly; is a member of the speakers bureau for Forest and Pfizer; has participated in trials sponsored by Cephalon, Janssen, and UCB Pharma; and is a consultant for Paramount Biosciences.* ***Dr. Hen*** *has no significant commercial relationships to disclose relative to the presentation.*

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Martin B. Keller, M.D., began by stating that the goals of the program included providing an update on current knowledge about and clinical findings on anxiety and depression, with an emphasis on trying to distinguish between these disorders. Discussions among the speakers on neuroanatomical pathways, genetic models, and serotonergic targets of anxiety and depression were followed by commentaries on the presentation, diagnosis, and treatment of anxiety and depression.

Neuroanatomical Pathways Underlying Depression and Anxiety Disorders

John H. Krystal, M.D., introduced the brain neural circuitry of mood and anxiety disorders by highlighting the regions of the brain that work together to regulate emotion: the ventral prefrontal cortex, the cingulate cortex, the amygdala, and the hippocampus (Figure 1). Each component receives extensive input from serotonin and, although each has a distinctive role within the network, collectively they regulate mood. In individuals with mood and anxiety disorders, each of these regions changes structurally and functionally.

Ventral Prefrontal Cortex and Cingulate Cortex

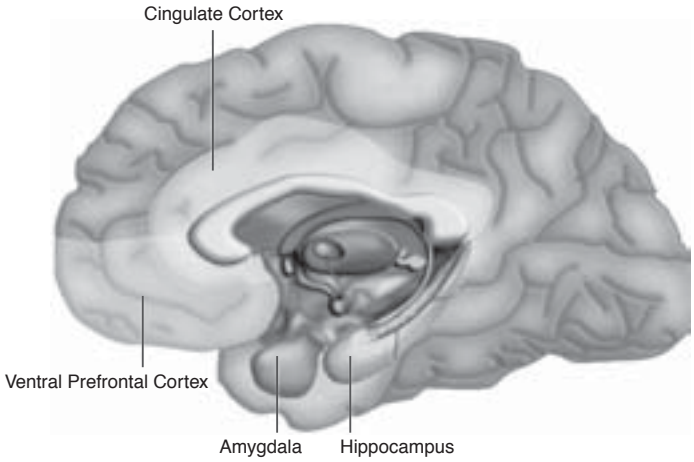
Dr. Krystal explained that the ventral prefrontal cortex plays an executive role in the regulation of emotion, coordinating the activity of the other regions and providing higher-order information (related to behavioral significance). In depression, cellular abnormalities in this area have been identified in postmortem brain tissue and include reductions in number and density of glial cells[1] and reductions in the number of γ-aminobutyric acid (GABA)-ergic neurons,[2] both of which may contribute to the overall reduction in volume of the ventral prefrontal cortex[3] in mood disorders.

According to Dr. Krystal, not only are the ventral prefrontal cortex and the cingulate cortex structurally abnormal in mood disorders, but they also function abnormally. Positron emission tomography (PET) scans[4] have shown hyperactivity in the left ventral prefrontal cortex with sadness and depression. On the other hand, activity was reduced in the posterior cingulate cortex with these emotions, suggesting a bidirectional, coordinated change in specific regions of the limbic system.

The lateralization of brain dysfunction, that is, the affected side of the brain, is also important in mood regulation. Dr. Krystal reported results from Blumberg et al.,[5] who found that depression appears to be associated with increased activity in the left ventral prefrontal cortex, whereas mania appears to be associated with reduced activity on the right side. These regions, which receive input from the serotonin and norepinephrine systems, change during treatment with antidepressants.

A partial overlap of regional brain changes has been observed in depressed patients treated with paroxetine versus interpersonal psychotherapy.[6] Paroxetine affected the left side of the brain and increased me-

Figure 1. The Emotion Circuit



tabolism in the lateral frontal cortex and in the anterior cingulate cortex. Only the anterior cingulate cortex was activated with interpersonal psychotherapy.

Dr. Krystal then related that several studies[7–10] implicate abnormalities in the ventral prefrontal cortex in anxiety disorders, including posttraumatic stress disorder (PTSD) and panic disorder. Reduced inhibition in the ventral prefrontal cortex is suggested by reduced ligand binding to $GABA_A$ receptors in both panic disorder and PTSD. Those with PTSD or panic disorder showed enhanced norepinephrine release and activation of the noradrenergic systems compared with healthy subjects when exposed to traumatic reminders, phobic stimuli, or yohimbine.[7] The orbital frontal cortex was one of the areas in the brain that distinguished patients with PTSD or panic disorder from healthy subjects. Dr. Krystal summarized the role of the ventral prefrontal cortex and cingulate cortex as using emotional input to guide behavior. The ventral prefrontal cortex is an emotional executive area that exhibits structural, chemical, and functional abnormalities in both depression and anxiety disorders. Ventral prefrontal cortical abnormalities may be important treatment targets for depression and anxiety disorders and may respond to both medication and psychotherapy.

Amygdala

According to Dr. Krystal, the amygdala has a direct connection to the orbital frontal cortex and is ideally situated in the brain to coordinate the regulation of emotional expression. Several brain regions that control some aspect of the physiologic, hormonal, or cognitive expression of emotion are connected to the amygdala. Although the amygdala has been labeled the "fear center" of the brain, the amygdala also responds to other emotional stimuli such as others' facial expressions registering disgust, happiness, and even neutrality.[11] Social relationships evoke some of the strongest human emotions, and viewing emotional expression in other people strongly activates the amygdala.

Dr. Krystal pointed out that depression and anxiety, which distort our emotional experience of the world, also change the activities of the emotional circuitry of the brain. Happy stimuli elicit decreased activation of the right and left posterior cingulate, while sad stimuli elicit exaggerated activity in the left amygdala and the left parahippocampus. People who are depressed show reduced amygdala activation associated with positive stimuli and exaggerated circuit responses to negative stimuli.[12] Anxiety disorders are also associated with changes in these emotional circuits. Exaggerated activity in the amygdala has been recorded when people with PTSD were exposed to reminders of their traumas.[13]

Hippocampus

The hippocampus is an area of the brain that is well-known for its involvement in the encoding of memory but less commonly known for its role in establishing emotional context or mood, that is, how people feel when they enter a particular environment even in the absence of specific cues that would elicit anxiety or happiness.

Dr. Krystal described postmortem data[14] from people with depression that suggest that this disorder is associated with atrophy of the hippocampus. This atrophy may be reflected in reduced neuronal size and increased neuronal packing density in hippocampal tissue. One explanation for hippocampal atrophy is that neurochemical responses associated with depression may damage the hippocampus. A review[15] of structural and functional neuroimaging studies showed that the hippocampus was reduced on both the left and right sides in depressed patients compared with healthy individuals. Other studies[16,17] reported no correlation between hippocampal volume and age in postdepressive or control subjects. One factor that may vary between studies is the duration of untreated depression. The size of hippocampi in people with depression was correlated with a longer duration of untreated depression.[16]

Evidence suggests that exposure to severe and chronic stress can damage the hippocampus,[17–19] and smaller hippocampal volume has been reported in people with severe PTSD.[20] However, Dr. Krystal cited a study[21] of monozygotic twins that suggests reduced hippocampal volume is a preexisting condition making one vulnerable to PTSD, rather than solely a consequence of exposure to trauma. Gilbertson and colleagues[21] found that the PTSD severity of the traumatized twin was correlated with the smaller

volume of the hippocampus in the twin who had never been exposed to the trauma and did not have PTSD. More research is needed to determine whether hippocampus deficits are a risk factor for vulnerability to stress or a consequence of chronic stress.

Antidepressant treatments, particularly selective serotonin reuptake inhibitors (SSRIs), may address some of the structural and functional abnormalities associated with the hippocampi in people with PTSD or depression.[16,22] Improvement in memory function as well as increases in the volume of the hippocampus have been demonstrated with SSRIs.[22] Dr. Krystal speculated that structural change may become a target of some treatments.

Summary

A high degree of overlap exists between the structural changes that occur in depression and anxiety disorders, yet there are observable differences. Both functional and structural abnormalities are possible targets of both pharmacologic and nonpharmacologic antidepressant treatment.

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Genetic Models of Depression and Anxiety

Building on the foundation of neurotropic processes described by Dr. Krystal, René Hen, Ph.D., focused on the functions of the hippocampus, specifically, in modulating emotions and the response to drugs used to treat depression and anxiety. The fact that both depression and anxiety respond to treatment with SSRIs suggests that common circuits and molecules underlie both types of disorders.

Dr. Hen stated that the mechanisms of action of SSRIs are being studied in rodents to observe what changes they impart on the brain and specific molecules. However, SSRIs have well-known neurochemical functions, that is, they change the onset of monoaminergic transmission, primarily serotonin and to a lesser extent norepinephrine and dopamine. Yet, despite a rather rapid onset of change in monoamines, onset of therapeutic efficacy is delayed. This phenomenon has led some investigators to speculate that downstream of the increases of serotonin and/or epinephrine are a number of cell growth–related changes that underlie the long-term effects of antidepressants and their delayed onset of therapeutic action.

Hippocampus: Halting Atrophy and Increasing Neurogenesis

Dr. Hen cited a study[1] that showed that a reversal of the dendritic shrinkages in certain hippocampal subfields, in particular the C3 hippocampus subfield, is being achieved by some antidepressants. Some studies[2,3] have

Table 1. Compounds Known to Stimulate Neurogenesis in the Hippocampus (as of May 2005)

Selective serotonin reuptake inhibitors
Tricyclic antidepressants
Norepinephrine reuptake inhibitors
Phosphodiesterase (PDE4) inhibitor
Atypical antidepressants
Neurokinin 1 (NK1) inhibitor
Vasopressin (V1B) receptor inhibitor

shown that antidepressants can stimulate neurogenesis in the hippocampus, and the mechanism of action of antidepressants has become of greater interest. Dr. Hen explained that the general cell growth–related effects on the hippocampus stimulated by SSRIs involve a series of signal transduction changes that affect the transcription and translation of novel genes. These signaling cascades may turn on a collection of growth factors as well as impact several cellular processes.

Evidence from preclinical models suggests that the changes in hippocampal neurogenesis related to antidepressant treatment can have an impact on anxiety and depression. Neurogenesis is not a static phenomenon but is modulated by environmental challenges, particularly chronic stress, which has been shown to decrease neurogenesis specifically in the hippocampus.[4] Conversely, stated Dr. Hen, enriched environment and learning have been shown to stimulate neurogenesis in the hippocampus.[5]

Adult neurogenesis has been demonstrated in birds, rodents, and primates. In humans, neurogenesis occurs into late adulthood and takes place primarily in the hippocampus and olfactory bulb. In the hippocampus, neurogenesis takes place in both the dorsal (posterior) and the ventral (anterior) part of the hippocampus, which Dr. Hen emphasized because a current hypothesis[6] states that the dorsal part is more involved in spatial learning and that the ventral part is more important in limbic functions, primarily because of its connections with the amygdala, the nucleus accumbens, and the prefrontal cortex. The amygdala and the prefrontal cortex have been described as part of the emotion circuit (see Neuroanatomical Pathways Underlying Depression and Anxiety Disorders). It is possible that neurogenesis in the ventral hippocampus is a primary component of mood-related functions.

In addition to antidepressants, other compounds with antidepressant-like effects stimulate neurogenesis (Table 1). Somatic treatments such as electroconvulsive shock therapy and exercise as well as an enriched environment have also produced antidepressant-like effects in both preclinical models and humans and have also been shown to stimulate neurogenesis.[7] Clearly, there is a correlation between the ability to increase neurogenesis and the ability to produce antidepressant effects in rodent models. The next step, argued Dr. Hen, is to establish causation.

Blocking Hippocampal Neurogenesis and Testing Antidepressant Effect

Dr. Hen then described several strategies that have been tested to block neurogenesis and assess whether or not the animals that have been subjected to such ablations still respond to antidepressants. Three strategies have been used: pharmacologic, genetic, and radiological.

A pharmacologic attempt by Shors and colleagues[8] showed that there may be a connection between neurogenesis in the hippocampus and the formation of particular types of memories. The study used a fear-conditioning paradigm sensitive to hippocampal lesions to demonstrate this connection. This study has been difficult to replicate because of the toxic nature of the compound used to block neurogenesis.

Dr. Hen explained that a radiological strategy aimed at blocking neurogenesis, specifically in the hippocampus, has been developed based on radiation therapies to treat cancer. Along with Santarelli and colleagues,[9] Dr. Hen designed a radiation paradigm to produce mice that no longer were capable of neurogenesis in their hippocampus. The next step was to test antidepressant action in these mice. In order to replicate what happens in humans subjected to chronic SSRI treatment, models of chronic response rather than acute response were used. Chronic response behavioral tests include learned helplessness, chronic mild stress, and novelty-suppressed feeding in which a mouse that has not eaten for 24 hours is transferred to an aversive area with food, such as in the center of an open field. Behavioral tests that measure acute response are more likely to capture rapid neurochemical changes elicited by the drug, rather than the cell growth–related changes.

This study[9] compared the effects of SSRIs on mice that had or had not been irradiated. In mice that were not irradiated, after a 30-day chronic regimen of the SSRI fluoxetine or the tricyclic antidepressant (TCA) imipramine, latency in the novelty-suppressed feeding test was reduced, which represents an anxiolytic or antidepressant-like effect. In tests of animals that were irradiated, that effect was completely absent. These tests indicated that hippocampal neurogenesis is required for the behavioral effects of antidepressants to occur.

Studies[10,11] have shown that young neurons produced in the adult hippocampus have different properties than the mature neurons. Young neurons are more excitable and display increased synaptic plasticity. Inspired by these studies, Santarelli and colleagues[9] applied electrophysiologic techniques to hippocampus slices from animals that had been treated with antidepressants or irradiated. They assessed long-term potentiation in the dentate gyrus, which is the part of the hippocampus that undergoes neurogenesis under normal conditions. Long-term potentiation, which is an induction of plasticity in the dentate gyrus, was completely abolished by irradiation and, conversely, was stimulated by fluoxetine. Dr. Hen stated that this form of long-term potentiation may be an electrophysiologic signa-

ture not just of the young neurons in the hippocampus but also of antidepressant action.

Using a genetic ablation model of the young neurons in the hippocampus, the same results were obtained as with radiation.[9] A further finding using the genetic model is that, unlike the irradiation model, which permanently ablates neurogenesis, the genetic model showed a reversible blockade of antidepressant action, and neurogenesis returned.

According to Dr. Hen, evidence such as this establishes a close temporal correlation among behavior, physiology, and the presence or absence of young neurons. Behavior and physiology recover when neurogenesis recovers. These studies suggest, therefore, a causal relationship between neurogenesis and antidepressant action.

Conclusion

Dr. Hen stressed 2 main ideas currently under investigation. First, by identifying neurogenesis as being a causal phenomenon in mediating the effects of antidepressants, the door is opened to the possibility that stimulating neurogenesis could lead to antidepressant action. Hippocampal neurogenesis may be stimulated by acting directly on hippocampal progenitors, thereby inducing antidepressant-like effects. Second, the electrophysiologic signature opens the door to the idea that stimulating long-term potentiation in the dentate gyrus of the hippocampus may produce antidepressant-like effects. By studying downstream targets of SSRIs and other antidepressants, new antidepressants that work faster and are more effective than the current ones may be developed.

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Serotonergic Targets as Mediators of Depression and Anxiety

Alexander Neumeister, M.D., explained that serotonergic pathways in the brain overlap with the network of cortical limbic regions implicated in depression and anxiety, as described by Drs. Krystal and Hen. Serotonergic dysfunction is well understood to be associated with mood disorders, and discerning whether the mechanisms of action in depression and anxiety have common or different pathophysiologic pathways may reveal new targets of interest for treatment and for drug development within the serotonergic system.

Two of the key structures that are involved in the regulation of serotonin transmission are the serotonin-1A (5-HT_{1A}) receptor and the serotonin transporter. These 2 structures talk with each other. If this talk is disrupted, which may be the case for many people with anxiety or depression, the serotonergic transmission is altered. If serotonin is detected by 5-HT_{1A} terminal autoreceptors, it binds to the receptors, which blocks 5-HT release. The role of the presynaptic 5-HT_{1A} receptor, then, is to fine-tune the further release of serotonin. As soon as serotonin is released into the synaptic cleft, another mechanism takes serotonin back into the neuron via serotonin transporter protein, which is located at the presynaptic neuron. Balanced serotonergic transmission occurs when the 5-HT_{1A} receptor and the serotonin transporter communicate with each other.

Acute or chronic stress can cause this communication to be disrupted and may trigger other pathways to get involved. Cortisol, for example, is an important stress hormone that can reduce the number of 5-HT_{1A} receptors, which ultimately causes dysfunctional serotonergic transmission.

5-HT_{1A} Receptor

Evidence suggests that the 5-HT_{1A} receptor is important in depression and anxiety disorders,[1] in particular, panic disorder.[2] Preclinical models of 5-HT_{1A} receptor knock-out mice show increased anxiety compared with healthy mice. Preclinical and clinical studies[3] have also shown that SSRIs mediate their effects via the 5-HT_{1A} receptor, and postmortem studies[1] and clinical studies[4] have shown that the number of 5-HT_{1A} receptors is altered in people with mood disorders.

Receptor function in vivo in a specific brain region can now be studied by superimposing PET images with magnetic resonance imaging (MRI). The resulting images further clarify the importance of the amygdala and the hippocampus for emotion control and anxiety regulation. Decreased 5-HT_{1A} receptors in cortico-limbic brain areas, including the mesiotemporal cortex, the anterior and posterior cingulate cortices, and the raphe, have been observed in patients with depression[5] and panic disorder[2] relative to controls. This suggests that there might be physiologic

pathways common to depression and in some anxiety disorders.

Serotonin Transporter

Dr. Neumeister reiterated that the serotonin transporter is key to regulating serotonin transmission in the brain. It is the primary target of SSRIs, which are important treatments for people with mood and anxiety disorders. Over the past few years, researchers have shown that the expression and the function of the serotonin transporter rely on the gene's promoter region. In animal studies, knocking out the promoter region leads to reduced expression of the serotonin transporters.[6,7] Without serotonin transporters, serotonin clearance is retarded, and serotonin accumulates in the synaptic cleft of knock-out mice.

Dr. Neumeister pointed out that regulating serotonin in the transporter may be also relevant for humans. A recent landmark study[8] showed 2 variants to the genetic environment of the serotonin promoter region: a so-called short (S) allele and a long (L) allele. The L allele appears to be more efficient than the S allele because more serotonin is taken up from the synapse into the presynaptic neuron in carriers of this allele. Individuals who carry 1 or 2 copies of the S allele, in the context of life stress, have an increased risk of developing depression during their lifetime over people who carry 2 L alleles. However, in the absence of life stress, the genotype groups do not discriminate. Therefore, their interaction is relevant to the pathogenesis of depression. Hariri et al.[9] showed that people who carry either 1 or 2 copies of this S allele also have increased amygdala reactivity to threat, which might be part of the pathogenesis of anxiety.

Tryptophan Depletion

Dr. Neumeister explained that research goals in his group have been to (1) characterize the role of serotonin transporters in depression in a model that considers the hypothesis of decreased serotonin function and (2) generate a model that integrates genetics, behavior, and brain function. Serotonin transporter polymorphism affects the behavioral response to tryptophan depletion and may help to identify people at risk for subsequent depressive episodes. Tryptophan depletion is a model in which brain serotonin function is dramatically but temporarily reduced over a period of several hours. Using this model on a behavioral level, patients with remitted depression can be returned to a mild depressive state in which the profound reduction of serotonin function can be studied.

Using the tryptophan depletion model, PET scans measuring glucose metabolism in healthy subjects were compared with those of subjects with a diagnosis of depression.[10] The study showed that glucose metabolism is altered in depressed people in brain regions which constitute a corticolimbic circuit even when these people are not suffering from symptoms of depression. This suggests persistent alterations in brain function in depressed people. Other data suggest that regulation of brain activity in this circuit is influenced by the 5HTTLPR polymorphim[11] and suggest that specific genetic variants not only modify 5-HT function but also brain activity. Consequently, it might be possible in the future to utilize both genetic information and brain imaging to identify people at risk for major depression.

Reaction to tryptophan depletion differentiates anxiety from depression. During tryptophan depletion, people who carry at least 1 copy of the L allele and have been depressed before respond with sadness, but healthy controls do not respond at all on measures of sadness.[12] However, tryptophan depletion increases amygdala function and induces anxiety in both patients with anxiety disorder and healthy controls if they carry at least 1 copy of the S allele.[9]

Dr. Neumeister continued with a model that explains the difference between anxiety and depression response to tryptophan depletion in controls. Healthy people who carry 2 copies of the S allele have a reduced number of 5-HT_{1A} receptors in the postsynaptic membrane compared with healthy people who carry 2 copies of the L allele. Reducing serotonin in the synaptic cleft creates a deficit in serotonin function, which is associated with an increased anxiety response in all people. However, depressogenic effects of tryptophan depletion do not occur in some people, that is, healthy people with 2 copies of the L allele, because these people have enough postsynaptic 5-HT_{1A} receptors available to compensate for the transient reduction of serotonin function.

Differences in response to tryptophan depletion also occur among depressed patients. Depressed people have a reduced number of 5-HT_{1A} receptors in the brain compared with healthy controls. Reduced intersynaptic serotonin function induces depressive symptoms during tryptophan depletion in patients who carry at least 1 copy of the L allele. On the other hand, depressed people with 2 copies of the S allele (the SS genotype) show no response to tryptophan depletion. Further, people with the SS genotype do not respond very well to SSRIs.[13,14] This lack of response in people with SS depression may indicate a different kind of depression not associated with serotonin function that is not yet understood.

Conclusion

Dr. Neumeister stated that although there are some differences, genetic and brain imaging studies suggest some overlap between depression and anxiety disorders in the pathophysiology and in the mechanisms involved in antianxiety/antidepressant treatment effects. Those studies also suggest that, in terms of brain imaging and brain function, some common final pathways are involved in both mood and anxiety disorders. Current research is focusing on identifying genetic determinants as well as gene-gene and gene-environment interac-

tions in the pathogenesis of depression and anxiety disorders. This knowledge may be a tool for identifying people at risk and predict effects of pharmacotherapy.

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Presentation and Diagnosis of Comorbid Depression and Anxiety Disorders

Naomi M. Simon, M.D., M.Sc., opened with the statement that the rates of comorbid anxiety disorders like panic disorder, PTSD, simple phobia, social phobia, and generalized anxiety disorder (GAD) in patients with depression are impressively high.[1] In fact, comorbidity is more the rule than the exception. The study of the clinical phenomenology—the overall spectrum of symptoms—and the overlap between both disorders has been neglected.

Theories About Comorbidity

Dr. Simon suggested several clinical possibilities to explain the common comorbidity of these disorders.[1] One possibility is that anxiety and major depressive disorder (MDD) are 2 separate disorders coexisting with some overlapping symptoms. Another possibility is that patients have overlapping symptoms—subsyndromal or mixed symptoms—but do not actually meet the diagnostic criteria for either disorder. A third possibility is that patients who do have one disorder never fully meet the DSM criteria for the other disorder. Naturalistic studies[2,3] emphasize the differences among patients with MDD and patients with anxiety, which point to separate outcomes. Patients with anxiety disorders such as GAD are less likely to go into remission than patients with MDD, which, according to Dr. Simon, indicates that GAD and other anxiety disorders tend to be chronic.

To make an accurate diagnosis in the face of complications caused by comorbidity, physicians should regularly use a rating scale or tool such as the Structured Clinical Interview for Depression (SCID) when examining patients with depression to better detect overlapping anxiety disorders.[4] Many new patients themselves may not even realize they have an anxiety disorder, instead believing that their symptoms—such as those that characterize social anxiety disorder—are simply part of their personality. These patients may not realize treatment exists or even mention symptoms if not asked.

Research Findings

Dr. Simon stated that the effect of anxiety symptoms on the clinical course of MDD has been outlined in several studies (Table 2).[5,6] She explained that overall, these studies show that depression begins earlier and has a worse course in the presence of comorbid anxiety. In particular, suicide risk substantially increases in the combination of anxiety disorder and MDD.[7] Research[8] indicates that patients with panic disorder and MDD have a 15 times greater prevalence of suicidal ideation than those without panic or depression, and in another study[9] of depressed patients, anxiety at baseline was a significant predictor of suicide within 1 year. The studies also suggest that anxiety symptoms are associated with more severe depressive symptoms, longer episodes, and a more chronic course of MDD. These patients are more difficult to treat, more likely to be refractory, and require more medications and interventions to get them to remission than patients without this comorbidity. In addition, they

Table 2. Effect of Anxiety Symptoms on Clinical Course of Major Depressive Disorder[5,6]

Earlier age at onset of depression
More severe depressive symptoms
Longer episodes
Chronic course
Poorer response to medication
Worse psychosocial impairment
Less recovery from index episode
Increased risk of suicide

Table 3. Potential Causes of Major Depressive Disorder in Anxiety Disorders

Genetic risk/family history
Anxiety disorder as stressor triggering underlying neurologic vulnerability
Serotonergic dysregulation
Hypothalamic-pituitary-adrenal axis dysfunction (eg, cortisol dysfunction)
Work and social dysfunction
Demoralization

have worse psychosocial impairment, are less likely to recover from their first episode, and have an increased risk of suicide.

Physicians should, therefore, be watchful for the symptoms of comorbid depression and anxiety. Dr. Simon also suggested that researchers should consider comorbidity when performing biological studies. Few previous biological studies of depression or anxiety have assessed whether patients had a comorbid disorder or whether there was comorbid symptomatology. She cited a recent study[10] of anxiety and depression as a good example of biological research taking comorbidity into consideration. According to Dr. Simon, had the study not controlled for anxiety, it would have had different findings.

Potential Causes of MDD in Anxiety Disorders

Dr. Simon next explained what she believes are several potential causes of MDD in patients with anxiety disorders (Table 3). First, she explained that the association of MDD with anxiety disorders, including the overlapping of disorders, may be related to the presence of both disorders in a patient's family history. Family history can highlight genetic risks for these disorders. A second possible cause, given that the onset of anxiety disorder usually occurs earlier in life than depression, could be that the anxiety disorder itself may serve as a stressor that either amplifies or brings out underlying biological abnormalities such as serotonergic dysregulation and hypothalamic-pituitary-adrenal axis dysfunction that then lead to depression onset. In some cases, MDD may occur in patients with anxiety disorders as a response to social dysfunction, functional impairment, and demoralization due to the anxiety disorder itself.

Although data[11] indicate that the onset of anxiety disorders occurs first and the onset of depression second, it is not known whether the sequence of disorders occurs because the onset of depression is actually causally related to anxiety, or if anxiety disorder is just an artifact of differential ages of onset for the disorders. Dr. Simon pointed out that patients with primary anxiety disorders who are not currently depressed may still develop depression later in their lifetimes. Research[12] has suggested that patients with panic attacks, persistent avoidance, severe impairment, or multiple anxiety disorders have an increased likelihood of developing comorbid depression.

Dr. Simon explained that some researchers believe that GAD and MDD overlap so much that they may not be separate disorders. One study[13] of twins found that many of the genetic risk factors for GAD and MDD are the same. However, differences in environmental risks exist that distinguish primary GAD from primary depression.[13] Further twin research[14] showed that life events like loss and humiliation were specifically associated with major depression, whereas danger had a much higher association with GAD. Dr. Simon suggested that the different types of life events could be used as predictors for the onset of either disorder. She then cited a study[15] that measured the influence of neuroticism with significant stressful life events on the onset of major depression. The study found that neuroticism, female sex, and greater adversity contributed to increased risk of the onset of MDD.

Unipolar Depression Versus Bipolar Disorder

Dr. Simon continued by explaining that not all depression is unipolar depression. Patients who see their physicians with complaints of depression may actually have bipolar disorder. The majority of patients with bipolar disorder, when symptomatic, are usually depressed and are only in manic, hypomanic, or mixed states for a short period of time.[16] She reminded her audience that physicians, when seeing patients with depression and anxiety comorbidity, should assess for the presence of bipolar disorder as well. Dr. Simon related a study[17] she conducted with colleagues that analyzed patients who sought treatment for depression or bipolar disorder. They compared rates of anxiety comorbidity in patients with unipolar depression versus patients with bipolar disorder. They found that rates of comorbid anxiety disorders were all at least as high in the group with bipolar disorder compared to those with depression, while GAD and panic were significantly more common in the bipolar group. Another study[18] found that anxiety comorbidity was frequently associated with poor outcome of bipolar disorder because of a longer time to remission.

Conclusion

Dr. Simon concluded by emphasizing that anxiety disorder comorbidity with depression is common, and anxiety often has an earlier onset than depression. Also, panic attacks and anxiety disorders in patients with de-

pression should trigger an evaluation for bipolar disorder, particularly if patients with comorbid depression and anxiety are not responding to or getting worse with antidepressant treatment. Dr. Simon highlighted that anxiety comorbidity with major depression results in greater severity, higher suicidality, and poorer outcomes than from either disorder alone. Finally, the etiology of anxiety disorder comorbidity with depression remains complex. Physicians should consider the interplay of the order of onset, genetics, biology, and environmental factors such as life stressors.

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Current and Future Treatments for Depression and Anxiety

Martin B. Keller, M.D., explained that a variety of U.S. Food and Drug Administration (FDA)–approved first-line treatments for depression and anxiety exist but have different indications for different anxiety disorders. He warned against assuming that a compound's treatment abilities are the same as those of other compounds in the same class of drugs. Using a compound for an indication that the FDA has not approved (off-label usage) means making a broader assumption about class effects than are warranted. No treatments have FDA approval for comorbid anxiety and depression. Dr. Keller then stated that he considers antidepressants as the first-line treatment for patients with comorbid anxiety and depressive disorders, but there is evidence that other agents and nonpharmacologic interventions or combinations are also effective (Table 4).

Pharmacologic Treatments

Monoamine oxidase inhibitors. Dr. Keller began his discussion of pharmacologic treatment by describing the advantages of monoamine oxidase inhibitors (MAOIs). He stated that their efficacy in treating depression is equal to that of any other class of compounds, although no head-to-head trials exist that show an advantage of the MAOIs over the other antidepressants. However, many physicians avoid the use of MAOIs because of dietary, tolerability, and lethality issues, which is the main reason they have fallen out of use.

Tricyclic antidepressants. Dr. Keller stated that tricyclic antidepressants (TCAs) are effective in alleviating symptoms of anxiety, are beneficial in major depression, and are inexpensive.[1] The disadvantages of TCAs include anticholinergic adverse effects, the possibility for worsening of activation effects, anxiety symptoms, cardiovascular risks, and the lack of published reports regarding rates of remission. The consequences of overdose are also severe; a 5- or 6-day supply is enough, if taken all at once, to put a patient into a comatose state.

Benzodiazepines. Benzodiazepines, according to Dr. Keller, make patients feel less anxious and can be used for acute exacerbations of anxiety symptoms, because they have a rapid onset, low cost, and high patient acceptance.[1] However, because benzodiazepines are depressogenic in the central nervous system, they can fail to reduce depression symptoms and in some instances can exacerbate depression. They can cause psychomotor and cognitive impairment, have a high potential for abuse, and have tolerance issues. Benzodiazepines are not recommended for long-term use, often require multiple daily doses, and have undetermined rates of remission. However, Dr. Keller stated his belief that combining benzodiazepines with antidepressants is a wise strategy in patients with severe

Table 4. Treatments for Depression and Comorbid Anxiety

Pharmacotherapy
Monoamine oxidase inhibitors
Tricyclic antidepressants
Benzodiazepines
Buspirone
Selective serotonin reuptake inhibitors
Serotonin-norepinephrine reuptake inhibitors
Psychotherapy
Cognitive-behavioral therapy (CBT) alone or in combination with medication for:
Refractory symptoms
Persistent cognitive factors, behavioral patterns
Comorbid conditions
CBT for help with medication discontinuation

anxiety. He also asserted that modest evidence[2] suggests that combination therapy is more beneficial for the prevention and treatment of GAD than benzodiazepine or antidepressant monotherapy.

Buspirone. Dr. Keller explained that despite criticism that buspirone is ineffective as an anxiolytic, several clinical trials do support its efficacy for patients with anxiety disorder.[3] However, drawbacks do exist. Buspirone has a slow onset of action that can take at least 1 to 2 weeks and a short half-life that may lead to dosing 3 times per day. Nonresponders to benzodiazepines tend not to respond to buspirone, and rates of response and remission are thought to be low, although data are minimal.

Serotonin and norepinephrine inhibitors. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) seem beneficial to patients in that they can alleviate anxiety symptoms.[1] Dr. Keller related that some SSRIs and SNRIs are FDA-approved for panic disorder, social anxiety disorder, obsessive-compulsive disorder, GAD, and PTSD, and their benefits in treating major depression are well documented. When compared with the SNRI venlafaxine extended release (XR), the SSRI fluoxetine had lower response rates in patients with comorbid depression and anxiety.[4] However, rates of remission with both drugs are modest. Dr. Keller opined that evidence is insufficient to conclude whether the SNRIs are more efficacious in producing a higher rate of remission than the SSRIs. In addition, SSRIs and SNRIs have a slow onset of action, are expensive, and have sexual adverse effects.

Dr. Keller concluded his discussion of pharmacologic treatment by stressing the importance of successful pharmacotherapy. He stated that treating patients with panic disorder, for example, tremendously reduced the likelihood of developing major depression.[3] Physicians should be proactive when confronted with a dominant disorder because effective treatment does appear to have a preventive effect for the secondary disorder.

Psychosocial Treatment

Dr. Keller reported that many psychosocial treatments are available and that cognitive-behavioral therapy (CBT) has undergone the most empirical testing and is a well-established treatment for MDD, panic disorder, GAD, and social anxiety disorder.[5] There are different versions of CBT for major depression and each of the anxiety disorders. They all include similar components such as psychoeducation regarding anxiety, restructuring of anxiety-related cognitions, exposure to avoided situations, and the possible use of relaxation techniques.[5] Dr. Keller also stated that CBT has high rates of efficacy and a lower relapse rate than medication when discontinued.[6] Most people like CBT, it is time-limited, it has an overall low price, and it has few side effects. However, CBT is harder to administer and takes more effort on the part of the patient than medication, and there are only a small proportion of experienced clinicians who perform CBT.

Dr. Keller related the results of a study[7] conducted to examine the use of imipramine, CBT, or combination therapies for patients with panic disorder. The study found that although both CBT and imipramine were highly effective, CBT was more effective than imipramine. Dr. Keller noted a review[8] of several studies that found that after initial treatment with psychotherapy for GAD, patients have a sustained response.

Treatments Under Development

New classes of pharmacologic treatment under development, according to Dr. Keller, include neuroactive peptides, selective GABA reuptake inhibitors, calcium channel modulators (α_2-δ ligands), $GABA_A$-receptor modulators, and newer 5-HT_{2A}-receptor agonists. None of these potential treatments have been approved by the FDA for the treatment of depression or anxiety. Neuroactive peptides such as the NK1 antagonist initially showed promise, but they ultimately were not differentiated from placebo on any measure during clinical trials. Selective GABA reuptake inhibitors might be used in treating anxiety and depression, but much of the preliminary excitement over glutamate receptors and modulators has quieted down because many early treatments in development failed to mature. α_2-δ Ligands, such as pregabalin, have shown promise in treating GAD. Placebo-controlled studies[9,10] showed positive results for pregabalin, which was recently not approved for GAD by the FDA for reasons not made public. These agents are structurally related to GABA, have biological activity that resembles L-leucine, and bind with high selectivity and affinity to the α_2-δ subunit of voltage-dependent Ca^{2+} channels.

Conclusion

The therapy options that Dr. Keller outlined include monotherapy with an

antidepressant or CBT or augmentation therapy with an antidepressant and an adjunctive anxiolytic or an antidepressant and CBT. Antidepressants are the first-line treatment in patients with anxiety or panic symptoms when depression is severe or recurrent.[11] However, anxiety symptoms may be caused or exacerbated by antidepressant therapy. Management of drug-induced anxiety symptoms includes dose reduction, an adjunctive anxiolytic, and antidepressant drug substitution.

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Drug names: *buspirone (BuSpar and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica), venlafaxine extended release (Effexor XR).*

Disclosure of off-label usage: *The chair has determined that, to the best of his knowledge, none of these drug treatments are approved by the U.S. Food and Drug Administration for the treatment of depression with comorbid anxiety or substance abuse. Any mention of use as treatment for depression with comorbid anxiety or substance abuse is considered off-label.*

To cite a section from this ACADEMIC HIGHLIGHTS, follow the format below:
Neumeister A. Serotonergic targets as mediators of depression and anxiety, pp 1481–1483. In: Keller MB, chair. Untangling Depression and Anxiety: Clinical Challenges [ACADEMIC HIGHLIGHTS]. J Clin Psychiatry 2005;66:1477–1487

For the CME Posttest for this report, see pages 1497–1499.