

## ACADEMIC HIGHLIGHTS

# Enhancing Treatment Response in Depression

**T**his ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry presents the highlights of the teleconference "Enhancing Treatment Response in Depression" held May 18, 2004, and supported by an unrestricted educational grant from Cephalon, Inc.

This teleconference was chaired by **Philip T. Ninan, M.D.**, Mood and Anxiety Disorders Program, Emory University School of Medicine, Atlanta, Ga. The faculty were **Maurizio Fava, M.D.**, Depression Clinical and Research Program, Massachusetts General Hospital, Boston, and **Kerry J. Ressler, M.D., Ph.D.**, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, and the Yerkes Primate Research Center, Atlanta, Ga.

### Continuing Medical Education Faculty Disclosure

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The information received is as follows:

**Dr. Ninan** is an employee of Emory University; is a consultant for Cephalon, Eli Lilly, Forest, Janssen, Solvay, Wyeth, and UCB Pharma; has received research grant support from Cephalon, Cyberonics, Eli Lilly, Forest, Janssen, and Glaxo; and has received honoraria from and is on the speakers or advisory board for Cephalon, Forest, GlaxoSmithKline, Janssen, Pfizer, and Wyeth. **Dr. Ressler** has received research grant support from Pfizer and has received honoraria from Cephalon. **Dr. Fava** has received research support from Abbott, Lichtwer Pharma GmbH, and Lorex; has received honoraria from Bayer AG, Compellis, Janssen, Knoll Pharmaceutical, Lundbeck, and Somerset; and has received both research grant support and honoraria from Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Novartis, Organon, Pharmavite, Pfizer, Roche, Sanofi-Synthelabo, Solvay, and Wyeth.

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## Monoamines, Neuropeptides, and Neurotrophins in the Pathophysiology of Depression

Kerry J. Ressler, M.D., Ph.D., opened with the statement that the symptoms of major depressive disorder can be viewed as a result of brain circuit dysfunction. Three classes of molecules involved in depressive symptoms include the monoamines, which regulate broad functioning of neural circuits; neuropeptides, which mediate behavior-specific components of neural circuits; and neurotrophins, which allow for plasticity of the brain and maintenance of neural circuits.

### Monoamines

The neurotransmitters that have received the most attention in depression, according to Dr. Ressler, are the biogenic monoamines norepinephrine, serotonin, and dopamine. The role of dopamine in motivation and drive and the role of norepinephrine in arousal and vigilance are well understood. Other symptom pathways are more speculative, such as the role of serotonin in impulsivity. Some symptoms require multiple neurotransmitter systems; for example, norepinephrine and serotonin both play a role in anxiety symptoms of depression.

Dr. Ressler explained that the neurotransmitter system that produces the monoamines was originally called the reticular activating system but is now called the ascending arousal system of the midbrain. The raphe nucleus produces serotonin, the locus ceruleus produces norepinephrine, and the tuberomammillary nucleus produces

histamine. In addition, the ventral tegmental area produces dopamine while areas such as the laterodorsal and pedunculopontine tegmental nuclei produce acetylcholine.

All of these neurotransmitters project broadly through the brain and are thought to regulate multiple behavioral circuits. Norepinephrine and serotonin in particular have been shown to be involved in regulating the amygdala, the bed nucleus of the stria terminalis, and the hippocampal systems. These areas and systems contribute to the fear and stress response as well as anxiety symptoms and emotional memory. Dopamine has been shown to be involved in regulation of the nucleus accumbens and its roles in reward, pleasure, drive, and motivation.

Several other regions of the brain are regulated by monoamines as well. The hypothalamus is regulated by all of the monoamine systems, and it plays a critical role as the leader of the endocrine system in stress response and sleep, wake, and appetite regulation. The thalamus is known to be involved in arousal and sleep, as well as sensorimotor gating. Finally, multiple cortical areas, principally the prefrontal cortical areas, are known to be involved in executive functioning, cognition, and working memory.

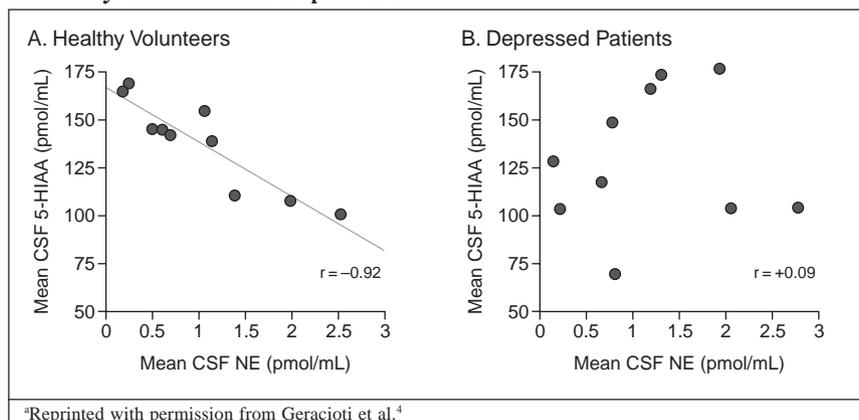
Dr. Ressler posed the question, what is the evidence for these neurotransmitter systems in depression? The serotonin system is well understood; evidence suggests decreased activity of

the serotonin system in depression. The norepinephrine system appears more complicated, related Dr. Ressler, in that depression probably does not involve grossly increased or decreased static levels of this neurotransmitter. Rather, it probably involves dysregulation of dynamic levels of norepinephrine, such as an overactivation of norepinephrine release or a hypersensitivity of the norepinephrine receptor systems.

Understanding what norepinephrine and serotonin do in the awake, normally behaving animal can illuminate the dysfunction of these neurotransmitters in depression. Aston-Jones and colleagues<sup>1</sup> have shown that norepinephrine plays a crucial role in organizing the behavioral state of an animal. Activity of the locus ceruleus was measured in monkeys that were trained to respond in a specific way to a specific, randomly given cue. The authors found that immediately after this cue, there was a burst of firing of the locus ceruleus neurons, indicating that norepinephrine was being released by the axon terminals during the switch from a calm, wakeful state to a state of vigilance and attention. When a different cue was given, one that the animals were not trained to respond to, no extra activity was seen in the locus ceruleus. These results suggest that the norepinephrine system plays a critical role in the arousal, vigilance, and stress response system.

Serotonin, explained Dr. Ressler, seems to have an opposite response to external cues. Fornal and coworkers<sup>2</sup> have shown that, for the most part, serotonin fires in a rhythmic and relatively slow way, a few times per second, during quiet, internally directed activity. When an animal has a period of vigilance and attention to outside stimuli, serotonin completely shuts down for a second or two. The authors studied a cat in which raphe nucleus activity was recorded. During quiet, normal activities, such as bathing and grooming, serotonergic neurons were active. However, when an unexpected event occurred, in this case, the door

**Figure 1. Relationship Between Cerebrospinal Fluid (CSF) Levels of Norepinephrine (NE) and 5-Hydroxyindoleacetic Acid (5-HIAA) in Healthy Volunteers and Depressed Patients<sup>a</sup>**



<sup>a</sup>Reprinted with permission from Geraciotti et al.<sup>4</sup>

to the cat's room was opened and closed, serotonergic activity in the raphe nucleus shut down for 1 to 5 seconds.

Dr. Ressler then proposed an experiment in which the locus ceruleus and the raphe nucleus would be monitored in the same animal. He hypothesized that such an experiment might demonstrate different but complementary responses from the norepinephrine and serotonin systems, such that when the serotonin system shuts down in response to an external stimulus, the norepinephrine system fires in a burst of activity.

Dr. Ressler went on to address how normal norepinephrine and serotonin activity fits with what is understood about depression. While it is well established that decreased levels of serotonin and its metabolites are present in patients with depression and/or anxiety, only recently has robust evidence of norepinephrine's role in depression been provided by studies of tyrosine hydroxylase.

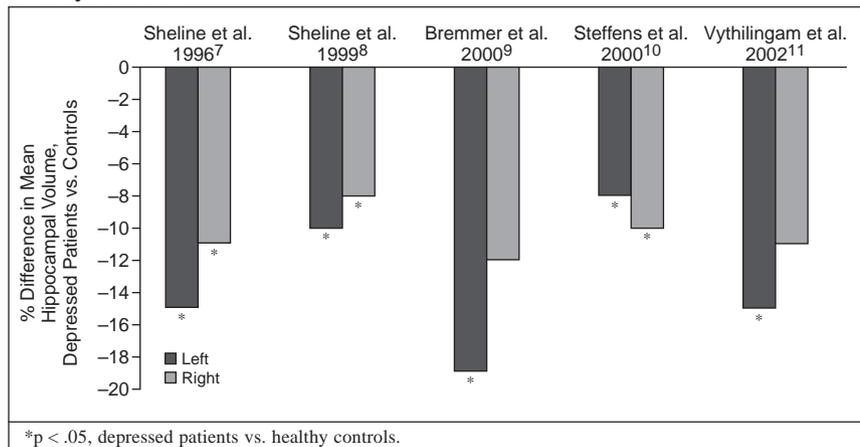
Tyrosine hydroxylase is an enzyme required for the production of norepinephrine, and levels of it have been shown to be increased in the locus ceruleus of patients with depression. Zhu and others<sup>3</sup> conducted a postmortem study of 13 patients with depression and 13 control subjects. They used antibodies to measure the levels of tyrosine hydroxylase within the

locus ceruleus of the deceased. They found higher levels of tyrosine hydroxylase in the patients with major depression compared with control subjects.

Dr. Ressler emphasized that recent theories point to the dynamic interplay between these neurotransmitter systems as being critically important in depression. Geraciotti and colleagues<sup>4</sup> found a negative linear relationship between serotonin (the metabolite 5-hydroxyindoleacetic acid [5-HIAA]) and norepinephrine levels in the cerebrospinal fluid (CSF) of healthy volunteers (Figure 1A). This finding is consistent with the results of the electrophysiologic studies<sup>1,2</sup> that imply that serotonin activity is quiet when norepinephrine activity increases and vice versa. In depressed participants, however, no relationship between 5-HIAA and norepinephrine levels was found (Figure 1B). Patients with major depression seem to experience a complete uncoupling of this normally regulated system. Dr. Ressler concluded that it may not be the static levels of neurotransmitters but the ways in which these different systems interact that is at the crux of depression.

### Neuropeptides

Dr. Ressler moved to a discussion of neuropeptide systems, such as those regulated by corticotropin-releasing

**Figure 2. Lower Hippocampal Volume Found in Depressed Patients Versus Healthy Controls**

hormone (CRH). CRH is released from the hypothalamus, which leads to increased adrenocorticotropic hormone (ACTH, also known as corticotropin) release from the pituitary gland, which then leads to increased cortisol release from the adrenal gland. Cortisol has multiple stress effects on the brain via the vagus nerve, including increasing norepinephrine release from the locus ceruleus. Dr. Ressler noted that CRH also has a direct projection from the amygdala, one of the principal sources of CRH in the brain, to the locus ceruleus, another way in which it may help modulate norepinephrine and thereby be indirectly involved in vigilance and arousal.

Depressed patients, according to Dr. Ressler, have increased levels of CSF CRH compared with people who are not depressed.<sup>5</sup> Because CRH affects so many parts of the brain that control stress, arousal, and depression, the dysregulation of CRH seen in depressed patients may be part of the pathophysiology of the disorder.

Dr. Ressler went on to discuss another neuropeptide from the hypothalamus, hypocretin. He noted that the hypothalamus has an important role in modulating sleep and arousal. The neurotransmitter  $\gamma$ -aminobutyric acid (GABA) is released from the hypothalamus and affects multiple monoamine systems in the midbrain that normally mediate arousal. Sleep is in-

duced in part via the shutting down of these different areas by the hypothalamus. Hypocretin, a recently discovered neuropeptide, is also released into these same areas; it appears to be required for normal modulation of sleep and wake cycles.

Preliminary evidence suggests that hypocretin is involved in depression. Salomon and colleagues<sup>6</sup> measured CSF hypocretin-1 levels in 14 control subjects and 15 depressed subjects. Diurnal hypocretin-1 levels varied during the course of the day in control subjects by 10%, whereas in depressed patients, levels varied only 3% during the day.

### Neuroplasticity and Neurotrophic Factors

Neurogenesis and neurotrophic factors have also been studied in depression, Dr. Ressler reported, especially since it is now known that new neurons are developed through adulthood. One of the most repeated findings in the depression literature is a decreased hippocampal size in patients with depression compared with control patients (Figure 2).<sup>7-11</sup> Dr. Ressler explained that CRH and/or cortisol may decrease hippocampal size by inducing atrophy or cell death.

Alternatively, neurotrophic factors such as brain-derived neurotrophic factor (BDNF) are thought to be involved in enhancing neuroplasticity and the

**Table 1. Changes in Pathophysiology Seen With Antidepressant Treatment**

Normalization of norepinephrine regulation
Normalization of serotonin function
Increase in brain-derived neurotrophic factor/neurotrophin levels
Increase in hippocampal size

number of neurons that are born within the hippocampus. Theoretically, argued Dr. Ressler, if depression is associated with a decrease in neuroplasticity and with neural atrophy, then increasing plasticity and growth may be associated with alleviation of depression, but much more research is needed in this area.

### Effects of Chronic Antidepressant Treatment on Pathophysiology

Dr. Ressler postulated that chronic antidepressant treatment, if effective, could begin to correct the pathophysiology associated with depression (Table 1). To test this theory, Nestler and colleagues<sup>12</sup> studied the effects of chronic antidepressant administration on tyrosine hydroxylase levels in the rat locus ceruleus. All major types of antidepressant treatment were studied, including electroconvulsive therapy, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and bupropion. No matter what the mechanism of treatment for depression was, tyrosine hydroxylase levels were decreased. Other psychotropic agents, such as haloperidol, diazepam, cocaine, and morphine, had no such effect. If antidepressants down-regulate the expression of tyrosine hydroxylase in rat brains, they may have the same effect in depressed patients whose levels of tyrosine hydroxylase are increased.

Another study<sup>13</sup> found that serotonin was increased in the hypothalamus, hippocampus, and frontal cortex of guinea pig brains during chronic SSRI treatment, again suggesting that antidepressant treatment may counteract the neurotransmitter dysfunction, in this case serotonin decrease, in patients with depression.

A similar effect has been reported in BDNF levels and neuroplasticity. Chen and colleagues<sup>14</sup> reported results from a postmortem study that examined BDNF activity in the brains of those who had been treated with antidepressants at the time of death compared with those who had not. The authors found increased BDNF expression in those who had been treated with antidepressants. This finding is consistent with that reported by Duman<sup>15</sup>: in animals with chronic stress, the total number of neurons was decreased, as was axon and dendrite morphology. Chronic antidepressant treatment was found to increase both the number of cells in the hippocampus and other brain areas and the amount of cell growth.

Santarelli and colleagues<sup>16</sup> found that hippocampal neurogenesis was required for antidepressants to be effective in mice. Neurogenesis was reported to be greater in animals who received an antidepressant (fluoxetine or imipramine) for 2 to 4 weeks versus those who did not receive an antidepressant. If the hippocampus is x-rayed, cell division is blocked; animals who received x-rays showed no alteration in grooming latency, whereas animals who received no x-rays experienced decreased grooming latency, suggestive of an antidepressant effect. Dr. Ressler suggested that hippocampal neurogenesis may be required for full antidepressant effect in humans as well.

### Summary

Dr. Ressler concluded by summarizing the data on the pathophysiology of depression and the different brain regions involved in depression. In euthymia, normal dynamic regulation by the dorsal prefrontal cortex involved in executive functioning seems to inhibit the amygdala in a counterexcitatory manner halfway from the ventral prefrontal cortex. The ventral prefrontal cortex is involved in exciting the amygdala as a result of emotional stimuli and is regulated by the hippocampus.

The normal role of the amygdala is to compare external sensory events with internal memory events. If something causes fear or is traumatic, the amygdala responds with stress and fear. However, the amygdala is also involved in learning tolerance to aversion. Pathways in the amygdala are modulated by serotonin from the raphe nucleus, which tends to decrease the amygdala's response to stress, and norepinephrine from the locus ceruleus, which, during burst firing, seems to increase the amygdala's response to stress.<sup>17</sup> All of these systems are interactive, explained Dr. Ressler, such that the amygdala can increase CRH release into the locus ceruleus, thereby increasing norepinephrine levels, and the locus ceruleus and raphe nucleus counterinhibit each other.

In states of depression, the amygdala appears to be hyperactive, with decreased activation of the dorsal prefrontal cortex, which normally inhibits the amygdala, and perhaps increased activation of the ventral prefrontal areas, which normally excite the amygdala. This dysregulation is consistent with decreased activation of the raphe, decreased serotonin release, and increased release of norepinephrine and CRH, all of which lead to a state in which external sensory information is encoded and responded to as being more stressful than it would be in a normal euthymic state, so the animal responds with a stressful or fearful reaction and is less likely to be tolerant to aversion.

Treatments for depression affect this pathophysiology in different ways. For example, SSRIs affect the system through the serotonin pathway, selective norepinephrine reuptake inhibitors through the norepinephrine pathway, and electroconvulsive therapy potentially through the interactions of the cortical areas with these limbic areas. It is also possible that psychotherapy plays a role in enhancing dorsal prefrontal cortex control over the amygdala.

Dr. Ressler concluded with the following hypothesis: remission from

major depression occurs when correction of one disrupted circuit, such as the serotonin system, with a specific treatment, such as an SSRI, leads to the correction of the dysregulation of the neural circuits. Treatment resistance and partial response occur when one disrupted circuit is corrected, but the other circuits fail to be normalized.

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## Managing Residual Symptoms in Depression

Maurizio Fava, M.D., focused on the pharmacologic approaches to the management of residual symptoms in major depressive disorder.

### Symptom Domains of Depression

Dr. Fava pointed out that when major depressive disorder is considered as a diagnosis, many clinicians may think only of the psychological symptoms. However, the most recent DSM criteria for major depressive disorder (DSM-IV-TR)<sup>1</sup> includes both psychological and physical or somatic symptoms (Table 2). Six of the 9 symptoms can be classified as psychological (symptoms 1, 2, 5, 7, 8, 9) and 3 of the criteria as somatic or physical (symptoms 3, 4, 6).

According to Dr. Fava, however, major depressive disorder includes a constellation of symptoms across 3 domains: behavioral, somatic/physical, and, of course, psychological.<sup>2</sup> Only one behavioral symptom is included in the DSM-IV-TR criteria for major depressive disorder—suicidal ideation or attempts. Other behavioral symptoms of depression include crying spells, interpersonal conflict, anger attacks, social withdrawal, avoidance of intimacy, substance use or abuse, and self-mutilation, among others. In terms of somatic or physical symptoms, the DSM-IV-TR criteria for major depressive disorder are clearly focused on sleep, appetite disturbances, and fatigue and have somewhat ignored other common physical/somatic symptoms such as headaches, muscle tension, gastrointestinal upset, aches and pains, and various symptoms of sexual dysfunction. Even though psychological symptoms are well represented in the

DSM-IV-TR criteria, some common ones are left out, such as hypersensitivity to rejection and criticism, hopelessness, helplessness, and cognitive distortions.

Most clinicians have been taught to target disorders or syndromes, but given the wide variety of symptoms a depressed patient can experience, it may be more appropriate to focus treatment on the most troublesome symptoms or symptom domains rather than the disorder as a whole, argued Dr. Fava. The approach may please patients as well, who often simply want symptom relief.

If the clinician chooses to target specific symptoms or symptom domains of depression, he or she will still need to assess the effects of treatments. Dr. Fava explained that, unfortunately, the instruments that are typically used are somewhat limited. For example, clinician-rated instruments such as the Hamilton Rating Scale for Depression (HAM-D)<sup>3</sup> or the Montgomery-Asberg Depression Rating Scale<sup>4</sup> still reflect the DSM-IV nosology and focus primarily on psychological symptoms, although neither fully covers all the symptoms found in the DSM-IV-TR criteria for major depressive disorder. These scales only partially measure somatic symptoms. The Inventory of Depressive Symptomatology,<sup>5</sup> a more recent instrument, captures all the symptoms currently included in the major depressive disorder criteria, but it does not cover all the somatic or behavioral symptoms still outside the criteria.

Similar problems are encountered when considering patient-rated instruments, such as the Beck Depression

**Table 2. DSM-IV-TR Symptoms of Major Depressive Disorder<sup>a</sup>**

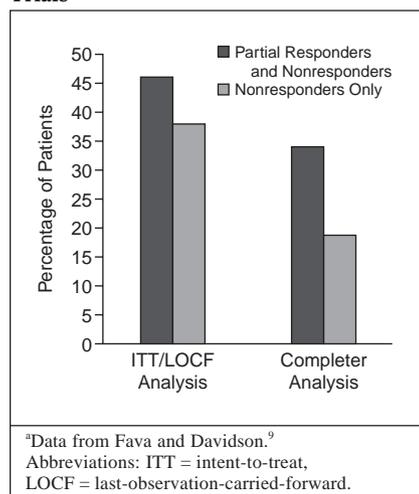
1. Depressed mood most of the day
2. Diminished interest or pleasure in all or almost all activities most of the day
3. Significant weight loss (when not dieting) or weight gain, or decrease or increase in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation observable by others
6. Fatigue or loss of energy
7. Feelings of worthlessness, excessive guilt, or inappropriate guilt
8. Indecisiveness or diminished ability to think or concentrate
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation with or without a specific plan or a suicide attempt

<sup>a</sup>Based on the DSM-IV-TR.<sup>1</sup> Five or more symptoms must be present every day or nearly every day for at least 2 weeks; one must be either depressed mood or loss of interest or pleasure.

Inventory,<sup>6</sup> the Zung Self-Rating Depression Scale,<sup>7</sup> and the HANDS Depression Rating Screening Tool.<sup>8</sup> All these tools are heavily weighted to measure psychological symptoms. However, these instruments can be useful in measuring symptom severity and improvement. How to classify symptom improvement is the next question, noted Dr. Fava.

### Response and Residual Symptoms

In clinical studies, Dr. Fava explained, researchers tend to divide treatment outcome into 3 groups based on degree of symptom improvement: nonresponse, partial response, and response. All categorizations assume an adequate antidepressant trial in terms of both dose and time. *Nonresponse* describes patients who experience < 25% improvement in depressive symptoms as measured by a rating scale such as the ones discussed above. *Partial response* typically indicates a clinically significant improvement that is not robust, such as a 25% to 49% improvement on a rating scale score. *Response*, then, describes patients who experience a robust improvement, e.g., ≥ 50% improvement according to a rating scale score with mild residual symptoms. Even a patient whose depression is described as being in *re-*

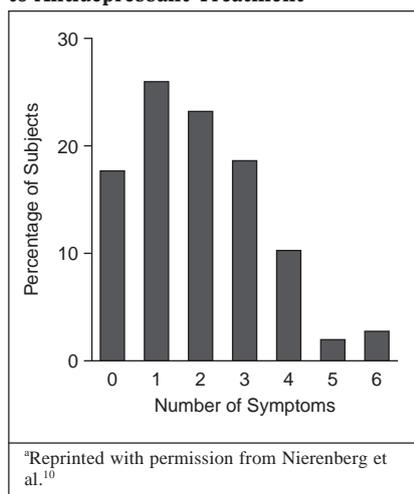
**Figure 3. Rates of Partial Response and Nonresponse in 36 Antidepressant Trials<sup>a</sup>**

mission, usually defined as the return to premorbid functioning, can experience some residual symptoms.

In a review of 36 clinical trials of antidepressants, Fava and Davidson<sup>9</sup> found that a significant proportion of treated patients were partial responders or nonresponders (Figure 3). In fact, many of the reviewed studies reported that 50% or more patients were partial or nonresponders.

Dr. Fava emphasized that, even among patients who have fully responded, many have at least 1 residual symptom. For example, Nierenberg and colleagues<sup>10</sup> assessed the presence and number of residual symptoms in 108 full responders (HAM-D score  $\leq 7$ , which is considered remission in many studies) to fluoxetine treatment. Fewer than 20% had no residual symptoms, and over half had 2 or more symptoms (Figure 4). The most common residual symptoms were sleep disturbances (44%), fatigue (38%), and diminished interest or pleasure (27%).

The importance of treating residual symptoms has been demonstrated, according to Dr. Fava. For example, Simon and colleagues<sup>11</sup> found that patients who have achieved remission and have greater clinical improvement take fewer sick days from work compared with patients who have not remitted and have a lesser degree of

**Figure 4. Distribution of Residual Symptoms Among 108 Responders to Antidepressant Treatment<sup>a</sup>**

clinical improvement. In addition, Paykel and colleagues<sup>12</sup> have shown that relapse and recurrence are more likely in patients with residual symptoms than in patients without residual symptoms—76% in patients with residual symptoms versus 25% in those without residual symptoms. Even among patients who recovered from their first depressive episode, according to a long-term study by Judd and coworkers,<sup>13</sup> those who had subthreshold residual symptoms were more likely to have experienced relapse or recurrence, relapsed more quickly, and had shorter well intervals than did recovered patients with no residual symptoms.

### Types of Residual Symptoms

Some residual symptoms are more common than others, stated Dr. Fava. For example, anxiety is a common residual symptom in depression.<sup>14</sup> Further, anxiety as a residual symptom in depression has also been associated with a short time to relapse or recurrence. In a study<sup>15</sup> of elderly patients with depression, those who were still anxious at the time of remission had a shorter time to relapse or recurrence, in spite of maintenance antidepressant medication.

Dr. Fava reported that most patients experience somatic symptoms as part

**Table 3. Strategies to Enhance the Chances of Achieving Remission of Depression**

Educate patients about depression and antidepressant treatment
Enhance treatment adherence
Ensure adequacy of antidepressant dose
Ensure adequacy of treatment duration
Choose antidepressant treatments with greater efficacy in specific subtypes or populations
Address residual symptoms and side effects

of depression. Denninger and colleagues<sup>16</sup> have found that residual somatic symptoms are significantly more common in responders who have not remitted than in remitters.

Sleep disturbances may also linger among responders to antidepressant treatment, as Nierenberg and coworkers<sup>10</sup> found. In a study by Reynolds et al.,<sup>17</sup> patients were maintained with antidepressant therapy or interpersonal psychotherapy. Among patients who received maintenance interpersonal psychotherapy, those patients with good sleep quality were more likely to remain well for at least 1 year (90%) compared with those with residual poor sleep quality (33%).

The presence of residual symptoms may be due to conditions other than depression, explained Dr. Fava, and a careful differential diagnosis is essential. Residual symptoms can be caused by concomitant medical conditions: fatigue, for example, may be due to hypothyroidism. Antidepressant-induced adverse effects may also cause a variety of symptoms that could be misinterpreted as residual symptoms of depression, such as sleepiness, fatigue, cognitive dysfunction, and apathy. It is important to distinguish residual symptoms from psychiatric or medical comorbidity or medication side effects.

### Achieving Remission and Managing Residual Symptoms

Several strategies can be used to help patients achieve remission, emphasized Dr. Fava (Table 3). One important strategy, and one that is often overlooked, is to manage residual

symptoms. Dr. Fava reviewed management strategies for 2 common residual symptoms: anxiety and hypersomnia/fatigue.

**Anxiety.** Anxiety, as Dr. Fava mentioned, is a common residual symptom. It is also a common side effect of antidepressant treatment. When patients report anxiety as a residual symptom or as a side effect, the clinician may want to consider switching the patient to a more sedating antidepressant. In many cases, however, switching may be inappropriate, since doing so would sacrifice the response the patient has already achieved. Because some anxiety disorders require higher doses than the ones used for depression, increasing the antidepressant dose may be an effective course of action.

More commonly, though, polypharmacy is used to address anxiety as a residual symptom or as a side effect. Augmenting agents such as benzodiazepines, anticonvulsants, buspirone, and even atypical antipsychotics have been used for this purpose, many of which are off label. Concomitant psychotherapy, such as cognitive-behavioral therapy, can also be quite helpful, particularly in patients with comorbid panic disorder or social phobia.

**Hypersomnia and fatigue.** According to Dr. Fava, when hypersomnia and fatigue are residual symptoms or drug side effects in major depressive disorder, the first step is to rule out concomitant substance abuse. Clinicians often experiment with the timing of the antidepressant doses. Reducing the antidepressant dose or switching antidepressants may help alleviate these symptoms, but then efficacy may be lost.

As in anxiety, adjunctive medications are often used to address hypersomnia and fatigue. If hypersomnia or fatigue is due to poor sleep quality, hypnotics or sedating antidepressants are often prescribed to be taken at bedtime. If hypersomnia or fatigue is not due to poor sleep quality, clinicians will often prescribe psychostimulants,

bupropion, a norepinephrine reuptake inhibitor such as atomoxetine, or modafinil.

Many of these augmenting strategies are used in an off-label fashion, stated Dr. Fava, and studies are clearly needed to prove their efficacy. In that respect, he presented preliminary results from a study<sup>18</sup> of modafinil as an adjunct to SSRIs in major depressive disorder. Nonresponders or partial responders to SSRI treatment who were experiencing persistent fatigue and sleepiness were randomly assigned to either modafinil (N = 135 completers) or placebo (N = 130 completers). Patients who received modafinil had significantly more improvement according to Clinical Global Impressions-Improvement scale scores ( $p < .05$  vs. placebo). In addition, modafinil was associated with a significant decrease in mean score on the Brief Fatigue Inventory item that asks patients to rate their worst level of fatigue in the previous 24 hours ( $p < .05$  vs. placebo).

### Conclusion

Dr. Fava said that incomplete response to antidepressant treatment is the rule, not the exception. Residual symptoms are common and may be psychological, behavioral, and/or physical and somatic in nature. Clinicians use many augmentation strategies for the management of residual symptoms, but clearly, further studies are needed to assess the efficacy of these strategies.

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## The Brain and the Mind in Depression

Philip T. Ninan, M.D., explored depression from the perspective of the brain and the mind. He emphasized the human brain as the organ at the core of mental disciplines and that without the brain, there could be no mind—no

ability for the conscious, executive capacity to make willful choices.

Dr. Ninan explained that the mind is the conscious product of brain function. The relationship is bidirectional: mental processes can also alter brain function. The challenge is to clarify the possibilities and boundaries of the mind's influence on the brain. Meeting this challenge requires moving beyond knowledge of structure and circuits to examining their dynamic relationships and postulating a framework that can form the basis for testable hypotheses.<sup>1</sup>

Consciousness provides a unique template to move beyond predetermined behavioral responses to volitional choice. The higher-order output of a system, remarkably, influences its own functioning—as an organ, the human brain is unique in that capacity. “Mind over matter” capacities would be expected to be prominent when the mind is fully developed and healthy. Such systems-level knowledge is a necessary foundation to understand “mental” illnesses like major depression and to critically guide the prescription of pharmacologic and psychotherapeutic treatments that can maximize the likelihood of achieving remission.

### Heterogeneity of Major Depression

To start at the diagnostic level, major depression is a clinical label. The DSM-IV criteria for major depressive disorder require a minimum 2-week period of at least 5 of potentially 9 symptoms, 1 being either sadness or anhedonia. Such a clinical diagnosis has subsumed under it several forms of the disorder. In attempts to address this heterogeneity, 2 broad types have emerged with some regularity in the literature: the *melancholic* type with persuasive neurobiological evidence of dysregulation of the hypothalamic-pituitary-adrenal (HPA) stress axis, and *atypical* depression marked by prominent anxiety, akin to major depression with comorbid anxiety disorder(s). An overactive anxiety neurocircuit has been suggested as the initiating pathophysiology in atypical

depression, with the subsequent development of depression.<sup>2</sup> These types of depression are often mutually exclusive in the diagnostic nomenclature (e.g., DSM-IV), although neurobiologically, they indicate originally different pathways that overlap with progression.

How can one make sense of this complex dissociation between the clinical and neurobiological perspectives? Why is there not a one-to-one correlation between neurobiology and clinical presentations? For that, Dr. Ninan reported, one must examine the brain and its product, the mind.

### The Brain as a Cartographer

A fundamental capacity of the brain is its ability to make representations or maps. The brain makes several kinds of maps, such as sensory ones that represent information about the world derived through the senses. Such maps are patterns of neural activity that represent external reality, just like a conventional map is a pictorial representation of a geographical area. Visual information from the retina, for example, is dynamically processed through various relay stations and represented internally in the occipital cortex. However, for perception to occur, sensory representations have to be selectively received by or matched to complementary preexisting internal templates.<sup>3,4</sup> Thus, the miracle of subjective perception occurs when 2 maps coalesce—the map of visual representation created by “bottom-up” processing (the retina to the occipital cortex), and the internal template map resulting from “top-down” processing. What then forms such internal template maps? There is much to be discovered here, but the answer very likely is in the intrinsic properties of the relevant brain modules and their sculpting by experience.<sup>5</sup> Such a system allows the flexibility necessary for expectations to influence perception. As Yogi Berra purportedly said, “I would not have seen it if I hadn't believed it.”

Major depression may be conceptualized as the universe of “receptive”

internal templates being functionally dominated by negative affect, cognitions, and memories. Thus, only experiences consistent with the depressed state are perceived, which reinforces depression. A happy event may not have an available, complementary matching internal template for reception and therefore is not perceived—in other words, it does not exist in the internal theater of the mind. The benefits of cognitive therapy in major depression, for example, may arise from disputing such restrictions so that a larger repertoire of top-down internal template options becomes available for perception.

### Somatic Symptoms

The brain also maps or represents the body. The parietal lobe has a somatosensory representation of the body, the familiar homunculus that straddles the parietal ridge representing different anatomical areas. The insular cortex represents information from the internal organs for a visceral map.<sup>6</sup> The combination of the somatosensory and visceral representations forms the basis of the somatic self. Abnormal functioning in these maps can theoretically have profound influences. The somatic symptoms in illnesses like major depression may result from functional aberrations in these somatic representations. Patients often have difficulty accepting the mental nature of somatic symptoms, and clinicians become frustrated over their inability to detect an end-organ abnormality when the somatic map may be the one causing the experience.

A seizure affecting the somatosensory cortex results in the individual's losing awareness of the body, a condition called *asomatognosia*. Such an experience of nonexistence is terrifying because the boundaries of the self merge with the surroundings. *Asomatognosia* provides a model for exploring dissociative phenomena common in major depression, anxiety disorders, and somatoform disorders.

The somatic representation of the self is a necessary foundation for the

symbolic or psychological self. Object relations theory argues that the psychological self is critically influenced by relationships, particularly early in development.<sup>7</sup> Why do early relationships, such as with the mother, have such an overwhelming influence? Is it because developmental processes, such as myelination and synaptic pruning, are necessary for the formation of somatic maps? An infant, without a defined somatic boundary, may experience maternal emotions as one's own and lay down emotional memory traces of those experiences. With the development of somatic boundaries, the agent who is having the experience—the self or the other—can be distinguished, and the child can now be more sovereign. A failure of appropriate development in somatic representations may leave the individual without a sense of a stable psychic self. Such a person would be inordinately suggestible and excessively vulnerable to outside influences.

Psychoanalytically based therapies attempt to solidify the psychological self through the experiential, preverbal microcosm of the transference relationship. Their benefits in illnesses such as major depression may result from the greater buffering provided against the trials and tribulations of life experiences. Since the treatment is delivered later in life, the degree of modifiable plasticity in the relevant brain modules may define the potential for success of such treatments. A testable hypothesis is that patients who respond to psychoanalytically oriented therapy will develop a more stable representation of the self, which is measurable as somatic and psychological suggestibility.

### Levels of Response

Perceptions evoke action. Action can be reflexive (e.g., the blink of an eye), automatic (e.g., emotion), or executive (e.g., cognition) as well as self-generated. A reflex reaction happens quickly and requires limited information processing, involving only a few synaptic connections. The stimu-

lus induces a reaction without requiring an internal representation. A reflex response such as a blink can be potentiated by emotional states (e.g., anxiety) and can habituate with repetition. Reflex responses have limited functional significance in psychiatry compared with automatic and executive level responses that are of greatest relevance.

An evoked response beyond a reflexive one initially activates limbic sites where, if the input matches an internal template, it triggers a response. The responses are broadly valued as positive or negative and emerge to subjective awareness as emotions. Negative emotions include anxiety and sadness, while pleasure is of course positive. The central hub for negative emotions is the amygdala. Understanding the functional anatomy underlying emotions can help illuminate their characteristics.

Sensory information initially reaches the thalamus, where low-frequency components are forwarded to the amygdala and high-frequency information is simultaneously sent to the cortex. If the information reaching the amygdala matches previously stored threat templates, a fixed action pattern of responses is activated—fear for immediate, physical threats, and anxiety for anticipated and psychological threats. The amygdala serves as a central command switch that activates a cascade of events in the brain and the body that enhance survival.

The information sent to the cortex is processed in a parallel manner through various relay stations; it is ultimately identified consciously and forwarded to the amygdala. The coincidental arrival of the detailed information from the cortex with the automatic activation of the fear/anxiety response is stored by the strengthening of synapses that represent that experience—as an emotional memory.<sup>8</sup> Subsequent experiences, either actual or anticipated, that match components of that emotional memory now trigger the fear/anxiety response—fear and anxiety have become conditioned.

**Table 4. Conditioning of a Negative Emotional Response<sup>a</sup>**

Fear/sadness conditioning: involves specific nuclei of the amygdala that form emotional memories
Contextual conditioning: involves declarative memory circuits mediated through the hippocampus
Avoidance conditioning: involves prefrontal cortical and limbic interconnections

<sup>a</sup>Based on LeDoux,<sup>8</sup> Davis,<sup>9</sup> and McKernan and Shinnick-Gallagher.<sup>10</sup>

### Forms of Conditioned Emotional Responses

The literature postulates 3 distinct forms of conditioned emotional responses (Table 4). First is fear conditioning, discussed above. For example, if one is assaulted late at night, that experience will trigger a fear/anxiety response. The internal representation of the perpetrator will be indelibly associated with the activation of the fear/anxiety response. The maps representing these 2 components will be tied together by the strengthening of their overlapping synaptic maps in the basolateral nucleus of the amygdala. If one encounters the perpetrator again, even in a nonthreatening situation, fear/anxiety will be activated because of the previous association rooted in the amygdala, i.e., the emotional memory of the original event.

The conventional or explicit memory system also remembers the assault. What is remembered, though, is the context in which the assault occurred. Thus the darkness, for example, is now associated with the assault, and walking unprotected in the dark may indicate the potential for another assault. Going out at night will then result in a heightened sense of vigilance and anxiety, the result of contextual conditioning. Explicit memory involves the hippocampus as its central hub. Contextual conditioning serves to anticipate potentially threatening situations.

The third way in which negative emotional responses are conditioned is through avoidance. The anticipation of going out unprotected at night is

**Table 5. Classification of Emotions<sup>a</sup>**

Primary emotions: happiness, sadness, fear, anger, surprise, disgust
Background emotions: well-being/malaise, calmness/tension, pleasure/pain
Secondary (social) emotions: embarrassment, jealousy, guilt, pride
<sup>a</sup> Based on Damasio. <sup>11</sup>

dysphoric and therefore avoided. The functional anatomy of such avoidance involves the medial/orbital prefrontal cortex and its connections with the amygdala. Damage to these circuits prevents the learning of new information that may counter the initial association (extinction), and avoidance becomes permanent.

Dr. Ninan asked, what does emotional conditioning reveal about the nature of emotions? Emotions are automatic in that they are set off in the limbic circuits prior to conscious awareness or detailed recognition of the triggering stimulus. If emotions are triggered preconsciously, then they cannot be willfully chosen. What is within volition is whether an individual executively agrees with the emotion experienced and subsequently chooses to inhibit or intensify it. The consequences of conditioned anxiety result not only in a greater propensity for emotional anxiety but also enhanced anticipation and behavioral avoidance.

### The Nature of Emotions

Damasio<sup>11</sup> has argued that emotions are framed by the body—automated changes that occur in the internal milieu of the viscera and the musculoskeletal system. He classifies emotions as primary (negative ones such as anxiety and sadness), background emotions (more reflective of the nonevoked body state), and social (driven by interpersonal interactions) (Table 5).

Intense emotions are experiential, global, and overpowering because they are indelibly tied to the body. Intense emotions drive cognitions and behavior. They diminish the individual's capacity to make independent observations or executive decisions. Emotions

drain working memory capacity and the ability to plan a deliberate response. Thus, anxiety experienced at an emotional level commands catastrophic cognitions, called *worry*. Likewise, positive emotions such as pleasure result in cognitions that are lavish and behaviors that are expansive and inclusive.

Emotions also drive behavior. Anxiety, for example, results in physical tension, restlessness, the desire to flee, or defensive aggression. Therefore, anger and its associated behaviors are often a consequence of anxiety. Gender may be a critical variable that modifies the expression of anxiety toward defensive aggression.

Emotions are associative, such that a current emotion is typically associated with past events that induced similar responses. The life span of an experienced emotion generally stretches beyond the time frame of cognitive events. Hence, residual emotions from an experience influence subsequent events, even if they are independent and unrelated, for example, an individual who snarls at his or her spouse after a stressful day at work. Decisions based on emotions are intuitive because they are not deliberate. Given the complex and differential time frames for emotions, cognitive processing, and conscious awareness, such emotional decisions are vulnerable to post hoc rationalization.

Intense and sustained anxiety is the base criterion for anxiety disorders. Anxiety suppresses positive emotions such as pleasure, which leads to sadness and depression. Thus, many individuals with an anxiety disorder will, over time, develop major depression. Dr. Ninan posed the questions, do patients with major depression and a comorbid anxiety disorder have a unique pathophysiology different from melancholic depression? And do such distinctions have implications for treatment?

### Stress Reactivity

The melancholic type of major depression has been strongly associ-

**Table 6. Characteristics of Cognition<sup>a</sup>**

Is proportionate, logical, reasoned
Is processed serially from summation of precognitive parallel processing
Is time sequenced, serial, context provided by past or present
Is goal directed with simulations of future outcomes
Is dependent on language with the ability for nuanced differentiations
Allows willful control and choice
<sup>a</sup> Based on Ninan et al. <sup>13</sup>

ated with dysregulation of the HPA axis. The HPA axis is endocrine by nature and is driven by hypothalamic corticotropin-releasing hormone (CRH) that responds largely to physical threat. CRH is also present in non-hypothalamic sites that are responsive to psychological stress. CRH tone is particularly vulnerable to sensitization early in development when the system is calibrated by environmental experiences. Setting the system to have a high tone subjects the individual to exaggerated and sustained stress responses that ultimately result in feedback dysregulation and consequent major depression. Posttraumatic stress disorder, an anxiety disorder, is also associated with dysregulation of the HPA axis, although at a different level.

Major depression of the melancholic type appears to be less responsive to nonspecific components of treatment (e.g., placebo) and more responsive to medications that have potent norepinephrine reuptake effects. Patients with chronic major depression and early life stresses are more responsive to psychotherapy with strong cognitive and interpersonal components compared with the antidepressant nefazodone.<sup>12</sup>

### Cognition

Evoked responses in the brain move sequentially from emotions to cognition. Cognition is essentially the capacity to frame emotions and other information in different contexts and warp it proportionately so that the end product appears reasoned, balanced, and logical (Table 6). In other words, cognitive processes tally the votes and

declare a winner. For example, cognitive systems gather information about a current situation and relevant memories; run simulations of possible outcomes; frame them in the context of the self, ideals, goals, and so on; and choose a decision. Language allows cognitions to be nuanced, differentiated, and communicated to others. Cognitive processes allow human behavior to rise above predetermined responses toward willful choice.

Important neurobiological differences exist in the systems that underlie emotions and cognition. The neurocircuits mediating emotions are largely feed-forward systems, whereas cognition emerges from recursive circuits that prominently include feedback mechanisms. Thus executive functions move beyond the matching receptivity of representations that are at the core of emotions. Cognition has a richer pattern-matching capacity: the ability to hold and process information in working memory, access relevant memories, and inhibit automatic responses for social or other reasons. If an animal is provoked, its behavior is automatic and predetermined, like human emotions. Cognition allows greater choice. The degree of willful choice and volition that emanate from cognitive functions is another debate.<sup>14</sup> In major depression, cognitive processes often lose many of these abilities and become ruminatively repetitive, restricted in content focusing on guilt, hopelessness, and death.

Functional brain imaging studies support the postulated interactive relationship between emotions and cognition. Mayberg and colleagues<sup>15</sup> used positron emission tomography to measure brain changes in healthy volunteers who were asked to recount sad personal experiences and depressed patients who were subsequently treated with fluoxetine. Sad memories in healthy subjects increased blood flow in critical emotional centers and decreased them in executive regions that mediate cognitive processes. In successfully treated depressed patients, the opposite pattern was seen.

**Table 7. Characteristics of Consciousness<sup>a</sup>**

Is unitary and serial Is a recent evolutionary development Requires complex processing and time Requires self-representation
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<sup>a</sup>Based on Llinas<sup>16</sup> and Searle.<sup>17</sup>

These results suggest that with sadness or depression, overactivity of negative emotional systems is coupled with reduced executive and cognitive capacity. Successful pharmacologic treatment improves depressive symptoms and reestablishes the normal balance between emotions and cognition.

### Consciousness

Consciousness is a necessary property for the mind. Understanding the nature of consciousness is arguably the biggest challenge in neuroscience research. However, one can explore the characteristics of consciousness even if its nature is still a mystery (Table 7).

Consciousness is unitary—of all the possible states an individual can be conscious of at a point in time, one is chosen. That chosen state binds components experienced together into a single whole, so multiple conscious states do not occur at the same time. This unification makes conscious experiences serial. Preconscious processes may allow simultaneous, parallel processing, but consciousness forces them through a single, serial, bottleneck. Dr. Ninan wondered whether this aspect of consciousness is a fundamental limitation of human consciousness and whether future evolutionary advances will allow multiple simultaneous conscious states.

What one is currently conscious of is the center of one's awareness, but that does not make it the be-all and end-all of brain function. Much of what is processed in the brain happens below the threshold of conscious awareness. Therefore, there is the potential for major errors in conscious attribution.

Psychotherapy as a treatment for major depression works through the conscious mind to bring about changes

**Table 8. Possible Mechanisms of Pharmacotherapy Response**

Balancing negative value judgments (catecholamines and indoleamines) Enhancing inhibition of emotional response (GABAergic agents) Modulating excitation (glutamatergic agents) Inducing neurogenesis, thereby possibly enhancing working memory (neurotrophic agents) Enhancing cortical wakefulness (histamine)
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**Table 9. Possible Mechanisms of Psychotherapy Response**

Empathy (supportive psychotherapy) Reconsolidation (psychodynamic psychotherapy) Alteration of context (cognitive therapy) Extinction (behavioral therapy)
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in the brain. The fundamental sense of centrality arising from the conscious mind opens one to errors of interpretation and post hoc rationalization. The challenge is to endow appropriate weight to preconscious brain processes that drive behavior in the face of a consciously driven belief.

### Mechanisms of Treatment Response

There are several ways to treat major depression to remission. Can an understanding of pathophysiology guide augmentation strategies in a partial responder, or switching choices in a nonresponder?

Antidepressant pharmacotherapy can directly impact overactive or sensitized systems in depression (Table 8). For example, inhibiting negative emotional reactions consolidated in the amygdala may enable a depressed individual to rationally balance a current experience with opposing information. Increasing neurogenesis in the hippocampus might enhance working memory capacity so that a person is able to juggle more complex and multifaceted information simultaneously.

Several forms of psychotherapy exist, with potentially different mechanisms of action (Table 9). Empathy

perceived in supportive psychotherapy may involve circuits that represent social relationships; sharing and feeling emotionally connected to a compassionate individual can powerfully calm psychic distress. Psychodynamic psychotherapy may reawaken traumatic emotional memories so that they become labile again. The current therapeutic context, as well as the knowledge and experiences that the individual now has as an adult, can modify such memories during reconsolidation. The brain that now remembers is different from the brain that originally memorized the experience. The process of reconsolidation releases the traumatic memory from the context in which the trauma occurred.

Cognitive therapy allows the individual to alter the cognitive context, i.e., the automatic assumptions and belief systems that perpetuate negative emotional responses. Framing experiences in a healthier, more rational context opens the depressed individual to a variety of potentially corrective practices.

Behavioral treatments focus on avoidance using sustained exposure to generate extinction, a process by which exposure counters an original negative association with benign experiences and the reduction of anxiety.

Connecting preclinical neuroscientific knowledge with the core aspects of psychotherapies delivered will allow the development of testable hypotheses of brain changes resulting from specific psychotherapies. The prescription of a psychotherapy may one day be neither random nor based on the therapist's training, but instead based on the nature of the pathology and the evidence regarding which treatment is most likely to address it, just like the prescription of medications.

## Conclusion

The human brain is the most complicated structure known to us, said Dr. Ninan; thus, much can go awry in it. Information is the currency of the brain. The processing of information generates perception, emotions, cognition, and behavior. Conscious awareness occurs late in the governance of information. The interaction of these brain functions and their dysregulation form the basis of mental illnesses such as major depression.

A healthy, nondepressed individual is free to override a negative emotional response with a cognitive, rational decision. A depressed individual appears to have lost that choice. Executive control has shifted to a more primitive and emotional circuitry, leaving the individual captive to repetitive, negative, and fixed action patterns of behavior. Understanding the delicate balance between the brain and the mind and the critical junctions at which abnormalities can occur provides a heuristic basis for appreciating how treatments work. Such knowledge arms the practicing clinician with the ability to intelligently prescribe treatments, whether pharmacotherapy or psychotherapy, most likely to successfully target the pathology underlying the illness.

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*Drug names:* atomoxetine (Strattera), bupropion (Wellbutrin and others), buspirone (BuSpar and others), diazepam (Diastat, Valium, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), modafinil (Provigil), morphine (Duramorph, Oramorph, and others).

*Disclosure of off-label usage:* The chair has determined that, to the best of his knowledge, atomoxetine, buspirone, and modafinil are not approved by the U.S. Food and Drug Administration for augmentation of depression treatment. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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