The Psychopharmacology of Painful Physical Symptoms in Depression

Stephen M. Stahl, M.D., Ph.D.

Issue: *The painful physical symptoms, as well as the emotional and vegetative symptoms of depression, may all be regulated by specific pathways for serotonin and norepinephrine in the brain and spinal cord.*

Take-Home Points

- Serotonergic and noradrenergic projections from the brainstem ascend into the brain and mediate numerous emotional and vegetative functions, some of which may become dysfunctional in depression.
- Serotonergic and noradrenergic projections from the brainstem also descend down the spinal cord where they normally suppress painful input from the body, but may become dysfunctional in depression and lead to painful physical symptoms that have no organic pathology in the sites of these symptoms.
- Antidepressants that inhibit the reuptake of both serotonin and norepinephrine have the best chance to reduce all of these symptoms by targeting the multiple pathways that mediate them in both the brain and spinal cord.

Last month's BRAINSTORMS explored the pathophysiology and treatment of both the painful physical symptoms and the emotional and vegetative symptoms of depression.[1] Here we illustrate the pathophysiology of the various symptoms of depression.

Figure 1A: Both the serotonin and norepinephrine systems have their most important cell bodies in a small area of the brainstem that serves as a headquarters or command center for each. Axons project from these headquarters throughout the brain in specific pathways that mediate specific functions. Serotonin's cell bodies are located in the midbrain raphe, and its axons project to (1) frontal cortex where they may have important regulatory functions for mood, (2) basal ganglia where they may regulate movements, and (3) limbic areas where they may modulate emotions, particularly anxiety. Serotonergic projections also arrive in the hypothalamus where they can regulate eating, appetite, and weight as well as sex drive and pleasure and project to sleep centers where they regulate the sleep-wake cycle.

Figure 1B: Norepinephrine's cell bodies are located in the locus ceruleus. Some but not all norepinephrine pathways project to the same areas of the brain where serotonin pathways project. Thus, similar to serotonergic neurons, noradrenergic neurons project to (1) frontal cortex to regulate mood, (2) limbic areas to regulate emotions and anxiety, and (3) hypothalamus for regulation of eating, appetite, weight, sex drive, and pleasure. In addition, one unique norepinephrine projection to frontal cortex regulates cognition and attention, and another to cerebellum may modulate motor movements.

Figure 1C: Deficiencies in the activity of specific pathways for serotonin and norepinephrine have long been hypothesized to account for the symptoms of depression. Thus, depressed mood as well as problems concentrating may be linked to deficient functioning within the monoamine projections to frontal cortex, and emotional symptoms such as feelings of guilt and thoughts of death or suicide may be related to projections to the

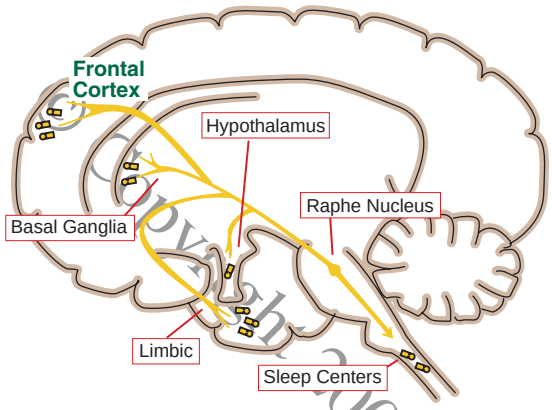
BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry *aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

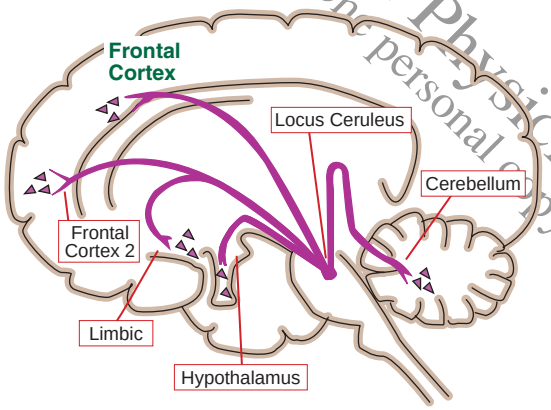
Corresponding author and reprints: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

Figure 1. Serotonin and Norepinephrine Pathways in the Brain and Associated Symptoms

A. Serotonin Pathways in the Brain



B. Norepinephrine Pathways in the Brain



C. Symptoms Associated With Serotonin and Norepinephrine Pathways

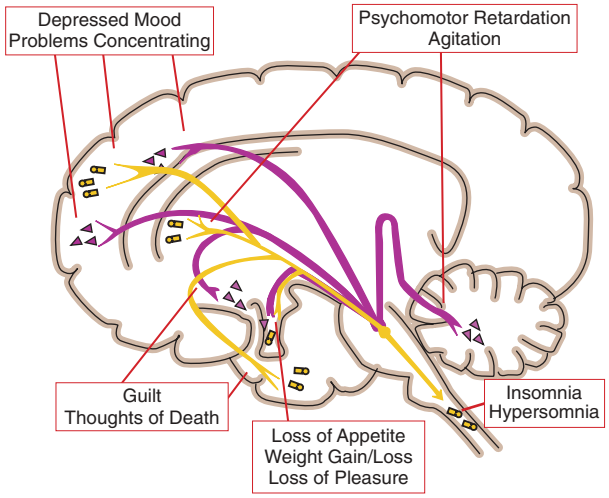
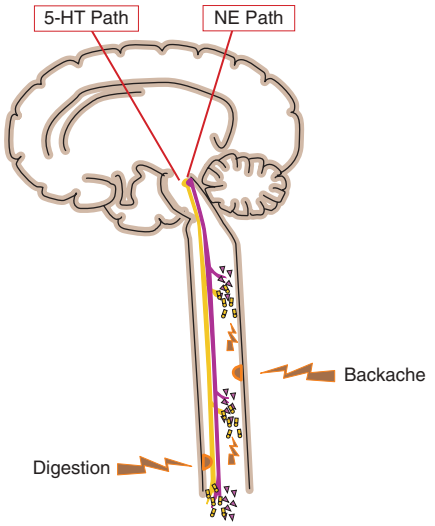


Figure 2. Actions of Descending Serotonin (5-HT) and Norepinephrine (NE) Pathways



limbic area. The symptoms of psychomotor retardation or agitation may be linked to problems in the various motor projections, whereas vegetative symptoms such as changes in appetite or weight, lack of pleasure, and sleep abnormalities may relate to dysfunctional hypothalamic or sleep centers. All drugs that boost serotonin, norepinephrine, or both can improve the emotional and vegetative symptoms of depression.

Figure 2: Normally, the sensations associated with the routine functioning of the body, such as digestion in the abdomen and routine inputs to the musculoskeletal system throughout the body, are suppressed from consciousness so that attention can be paid to more important events outside of the body. Descending serotonergic and noradrenergic pathways normally help to suppress such inputs even when they cause minor discomfort. However, when these monoaminergic systems malfunction, deficient inhibition from the descending spinal pathways may allow routine sensory input to be interpreted as uncomfortable or even painful physical symptoms.[1] ◆

REFERENCE

1. Stahl SM. Does depression hurt? [Brainstorms] J Clin Psychiatry 2002;63:273–274