



FIGURE 29-1 Neurobiology of depression.

### Neurotransmitters

Although other neurotransmitters have also been implicated in the pathophysiology of depression, disturbances in serotonin and norepinephrine have been the most extensively scrutinized.

Cell bodies of origin for the serotonin pathways lie within the raphe nuclei located in the brain stem. Those for norepinephrine originate in the locus ceruleus. Projections for both neurotransmitters extend throughout the forebrain, prefrontal cortex, cerebellum, and limbic system.

### Areas of the Brain Affected

Areas of the brain affected by depression and the symptoms that they mediate include the following:

- Hippocampus: Memory impairments, feelings of worthlessness, hopelessness, and guilt
- Amygdala: Anhedonia, anxiety, reduced motivation
- Hypothalamus: Increased or decreased sleep and appetite; decreased energy and libido
- Other limbic structures: Emotional alterations
- Frontal cortex: Depressed mood; problems concentrating
- Cerebellum: Psychomotor retardation/agitation

### Medications and Their Effects on the Brain

All medications that increase serotonin, norepinephrine, or both can improve the emotional and vegetative symptoms of depression. Medications that produce these effects include those that block the presynaptic reuptake of the neurotransmitters or block receptors at nerve endings (tricyclics; SSRIs) and those that inhibit monoamine oxidase, an enzyme that is involved in the metabolism of the monoamines serotonin, norepinephrine, and dopamine (MAOIs).

Side effects of these medications relate to their specific neurotransmitter receptor-blocking action. Tricyclic and tetracyclic drugs (e.g., imipramine, amitriptyline, mirtazapine) block reuptake and/or receptors for serotonergic, noradrenergic, anticholinergic, and histamine. SSRIs are selective serotonergic reuptake inhibitors. Others, such as bupropion, venlafaxine, and duloxetine block serotonin and norepinephrine reuptake, and also are weak inhibitors of dopamine.

Blockade of norepinephrine reuptake results in side effects of tremors, cardiac arrhythmias, sexual dysfunction, and hypertension. Blockade of serotonin reuptake results in side effects of GI disturbances, increased agitation, and sexual dysfunction. Blockade of dopamine reuptake results in side effects of psychomotor activation. Blockade of acetylcholine reuptake results in dry mouth, blurred vision, constipation, and urinary retention. Blockade of histamine reuptake results in sedation and hypotension.