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RELIAS MEDIA

Code Melancholia: A Review of Depression for Emergency Physicians

Depression is a multifaceted recurrent disease of growing prevalence. The World Health Organization reports that depression will be the second leading cause of disability worldwide by 2020.[1] Although the formal diagnosis of depression seldom is made in the emergency department (ED), emergency clinicians must understand the nature of depression and be prepared to deal with its complications, including suicidality and the toxicity of many antidepressant medications, which are among the most widely prescribed of modern medications. When depression isn't the primary driver of an ED visit — as opposed to the patient who has attempted suicide — it may present as either an underlying feature or a masking element of many vague and puzzling conditions.

Along with discussing the current classification, differential diagnosis, and treatment modalities of depressive disorders, this article examines the conundrum of suicide risk assessment. This article also reviews the toxicity of antidepressant medications, highlighting the subject of selective serotonin reuptake inhibitor (SSRI) withdrawal — a condition that is easy to miss on initial presentation. The article also includes a new mnemonic to simplify the process of recognizing possible serotonin toxicity. Finally, the article discusses the new and surprisingly effective use of ketamine.

The Nature of Depression

Owing to the universal human emotion of sadness, clinicians are all personally familiar with the general symptoms of depression, such as apathy, fatigue, irritability, and anhedonia. The line between normal, everyday sadness and pathologic clinical depression can be subtle and variable — an issue of degree more than quality. The question of why people sometimes slide from normal sadness into a debilitating state of depression is an ancient one. Hippocrates (450 to 357 BCE), who described patients with an aversion to food, feelings of despondency, difficulty sleeping, restlessness, and irritability, posited a biochemical explanation. He wrote that black bile (melancholia) is secreted by the spleen in excessive amounts under the influence of Saturn. It then circulates and darkens the brain. He noted that patients with longstanding fearfulness were prey to melancholia. Galen and medieval Persian physicians offered theories involving cerebral pathology and natural balance gone awry.[3] Galen also observed that too much wine, too much passion, and too little sleep could breed a discontent with living, a hatred of others, and the desire to die.[2]

EXECUTIVE SUMMARY

- Depression is a clinical diagnosis that must be present for at least two weeks. It may be associated with suicidal thoughts.
- Antidepressants generally are started by outpatient physicians, but they can be started in the ED if there is communication with an outpatient physician.
- SNAGGLE is a mnemonic for serotonin syndrome, which can be seen after overdose (monoamine oxidase inhibitors) or with a combination of medications.
- Ketamine appears to have antidepressant activity that starts shortly after infusion. In the future, this may become an ED medication.

Modern Classification of Depressive Disorders

Given that psychiatric nomenclature is under continuous evolution, branching, and debate[7] (the *Diagnostic and Statistical Manual of Mental Disorders* [DSM] is growing larger with each edition), the current classification and diagnostic criteria for depression warrant a brief discussion here. The National Institute of Mental Health (NIMH) considers the terms depression, major depressive disorder, and clinical depression to be interchangeable.[4] Other synonymous terms found in the literature include unipolar depression and major depression.[5] For clarity's sake, this article will use the term major depressive disorder (MDD).

The diagnosis of depression requires the presence of depressed mood or anhedonia (loss of interest or pleasure) along with four or more of the following symptoms: suicidal ideation (with or without a plan); insomnia, early awakening, or hypersomnia; psychomotor retardation; agitation and restlessness; fatigue and loss of energy; feelings of worthlessness; a free-floating sense of guilt; significant weight loss or weight gain; and difficulty concentrating.

Additionally, for the diagnosis of MDD, these symptoms must not be attributable to a substance use disorder or a major medical condition and must represent a challenge to the patient's normal level of function.[6] (*See Table 1.*)

The current edition of the DSM (DSM-5), released in May 2013, describes the additional depressive disorders that follow.[4] (*See Table 2.*)

Persistent Depressive Disorder. Also referred to as dysthymia, this condition involves a continuous depressed mood lasting longer than two years during which patients may or may not have episodes of MDD.

Postpartum Depression. This is not the typical "baby blues" that affects many mothers and involves minor depression or anxiety symptoms, usually clearing within two weeks post-delivery. True postpartum depression displays the much more significant symptom pattern of MDD. Risk factors include prior history of depression, younger age, domestic abuse, and lower socioeconomic situation.

Psychotic Depression. Patients with MDD accompanied by psychotic features, such as delusions (frequently of guilt, poverty, or illness), or hallucinations, are classified as having psychotic depression.

Seasonal Affective Disorder. This condition involves the predictable, recurrent onset of MDD symptoms during the winter months.

The DSM-5 includes two new depressive disorders:

Disruptive Mood Dysregulation Disorder. This diagnosis is applied to children between the ages of 6 and 18 years of age who display persistent irritability and episodes of out-of-control behavior, and who previously were included in the category of bipolar disorder.

Premenstrual Dysphoric Disorder. This diagnosis applies to women who experience potentially disabling affective lability and other severe depressive symptoms during the last week of the luteal phase.

The DSM-5 also adds two specifiers allowing psychiatrists to detail a patient's condition further. MDD "with mixed features" indicates that the patient has some manic features, which do not reach the threshold of full-blown mania; MDD "with anxious distress" specifies that the patient's level of anxiety is such that additional treatment with specific anti-anxiety medication may be indicated.

Differences Between MDD and Bipolar Disorder

MDD and bipolar disorder constitute the two major human mood disorders. Bipolar disorder involves a cycling of mood states between mania (characterized by elevation, irritability, and expansiveness that lasts more than a week) and depression. Bipolar disorder is divided further into several subclasses. Bipolar type I involves episodic mania that may or may not be interwoven with periods of MDD. Bipolar type II is defined as having spells of milder mania (hypomania) cycling with episodes of more significant depression. Cyclothymia refers to a condition of recurrent hypomania alternating with milder depression (dysthymia).[2,5] These diagnoses will not be made in the ED. Emergency clinicians simply need to appreciate the fact that mood disorders represent a multidimensional continuum of characteristics.

Etiology and Pathophysiology

Although the ultimate cause of depression is unknown, the effectiveness of standard antidepressant medications suggests that a dysregulation of monoamine neurotransmitters (serotonin, norepinephrine, dopamine) and/or their receptors plays a major role. The situation is complex. Certain signaling proteins also appear to have a mood-modulating effect.[12] Researchers have discovered that anatomic changes in certain brain structures, such as the hippocampus, amygdala, anterior cingulate cortex, and prefrontal cortex, may play a role.[13] Based on twin and adoption studies, there is a 30-40% genetic influence on the development of MDD.[8] The remaining depression cases appear to be related to environmental, psychosocial, physiologic, and epigenetic elements.

Table 1. Diagnosing Major Depressive Disorder

Two or more weeks of depressed mood/anhedonia plus four or more symptoms from this list that are not attributable to either a substance use disorder or a major medical condition, and that must challenge a patient's normal level of function:

- Suicidal ideation
- Insomnia, early morning awakening, hypersomnia
- Psychomotor retardation
- Agitation/restlessness
- Fatigue/loss of energy
- Feelings of worthlessness
- Free-floating guilt
- Appetite changes with significant weight loss or gain
- Difficulty concentrating

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

Table 2. Depressive Disorders — DSM-5

- Major depressive disorder (MDD)
- Persistent depressive disorder (dysthymia)
- Postpartum depression
- Psychotic depression
- Seasonal affective disorder (SAD)
- Disruptive mood dysregulation disorder
- Premenstrual dysphoric disorder

Source: National Institute of Mental Health. Depression. Available at: www.nimh.nih.gov/health/topics/depression. Accessed Dec. 27, 2018.

Medications, including proton-pump inhibitors and beta-blockers, prescribed for other conditions also can induce the symptoms of depression. In a recent representative cross-sectional study of more than 26,000 adults, 9.5% were taking three or more concurrent medications, excluding psychotropic agents, that listed depression as a potential side effect. Of that group, the prevalence of depression was more than three times as great as in those not using such medications.[14]

Risk factors for developing MDD include low social support, divorce, substance use disorder, and chronic medical conditions.[9,10] The process may be bidirectional in that patients with MDD appear to have a higher risk of developing diabetes and coronary artery disease and a lowered pain tolerance.[15] Adverse events in childhood, including physical and sexual abuse, increase the risk of an individual developing MDD, possibly by permanently altering corticotropin-releasing cells in the hypothalamus, causing exaggerated responses to future stress.[5,11]

Epidemiology

Estimates of depression's societal impact are staggering. At one time or another, depression may affect as much as 10% of the population worldwide, or about 300 million people, and is a leading cause of disability.[16,17] The ratio of females to males affected is approximately two to one.[2] In contrast, bipolar disorder affects males and females in equal proportion. Although bipolar disorder tends to begin in an individual's 30s, the onset of MDD occurs in the 40s, on average. Approximately half of all cases of MDD involve patients with underlying bipolar disorder.[2] Estimates indicate that about half of all cases of depression are undetected or not adequately controlled.[2] Suicide is the second most common cause of death in people between 10 and 24 years of age, and it results in more than 5,000 deaths each year in the United States.[18] Anywhere from 50% to 75% of suicides are related to depression.

Differential Diagnosis

Many factors can generate mood alterations and psychomotor change that resemble the symptoms of primary MDD. These situations include substance use disorders, corticosteroid use, central nervous system (CNS) infections, hyper- and hypothyroidism, hypoglycemia, and many others.[5] Elderly patients, especially those with a new onset of depressive symptoms, require careful screening for occult infections or metabolic and endocrine derangements. Chronic illness can trigger an episode of MDD. Conversely, MDD sometimes may manifest in the form of multiple unexplained somatic complaints.[19] In a recent study, researchers showed an association between repeated ED visits for unexplained abdominal pain and moderate to severe depressive disorder.[20] Consider screening for depression in such patients, who often receive multiple, resource-intensive, negative workups over the course of months and years. In one study, patients with non-ST-segment elevation myocardial infarction and unstable angina who screened positive for depression spent an average of five hours longer in the ED.[21] The investigators speculated that this effect may be related partly to the fact that symptom patterns in patients with depressive disorder can be clouded by the depressive symptomatology.

Treatment of Depression

Antidepressant Medications

Modern pharmacologic treatment for depression dates back to the early 1950s, when researchers noticed that certain new antituberculosis agents that possessed monoamine oxidase inhibitory properties appeared to alleviate depressive symptoms.[22] Investigators speculated that this salutary effect might be due to a bump in monoamine neurotransmitters (serotonin, norepinephrine, dopamine) at CNS synapses. A flood of research began and has resulted in the development of several subsequent generations of continually safer agents that all act through various mechanisms to enhance the synaptic availability of monoamine neurotransmitters. Antidepressant medications (ADMs) now fall into the following categories: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs),

and atypical antidepressants.[5] (*See Table 3.*)

Hundreds of clinical trials since the 1950s have demonstrated that ADMs relieve symptoms to an extent 20-30% greater than placebo.[23] The beneficial effect appears stronger in moderate to severe depression than in milder forms of the disease.[23] The choice of an optimal agent for a given patient involves a knowledge of side effects, interactions, and comorbidities, and often involves a period of trial and error.[24] Some ADMs have indications for other conditions, including chronic pain and anxiety disorder. (*See Table 3.*)

Currently, antidepressant medications seldom are initiated by emergency physicians, partly because most emergency physicians are neither trained in making the initial diagnosis nor familiar with the nuances of which ADM might be best for a given patient. SSRIs generally require two weeks to become effective, and patients need primary care physician (PCP) or psychiatry follow-up for dosage adjustment and to monitor for side effects, including the potential for a transient increase in suicidal ideation. However, given the excellent therapeutic to toxicity ratios of SSRIs and SNRIs, certain patients would benefit from having an ADM started in the ED by the emergency physician.

For an emergency physician to initiate ADM treatment, the following conditions should be met: 1) medical causes of depressive symptoms have been ruled out; 2) the patient has been screened for suicidality and found to be at low to no risk; 3) there are no concurrent medications with potential adverse reactions (especially serotonin toxicity); and 4) the emergency physician has spoken with the follow-up PCP or psychiatrist, who is aware of the medication and agrees to follow up in a specified time frame, ideally a week or less. The initial medication usually selected for a patient with straightforward MDD will be an SSRI, such as paroxetine.[24] For an adult, the starting dose of paroxetine is usually 20 mg, once a day, taken in the morning. Dosages will be increased weekly as needed in increments of 10 mg, up to a maximum of 50 mg per day. For patients who have a chronic pain syndrome along with MDD, SNRIs often are the initial ADM.[24] Venlafaxine is a representative SNRI, and can be initiated at 25 mg three times per day, with upward titration begun by the follow-up physician in approximately one week. Patients with MDD and anxiety symptoms often are started on either an SSRI or an SNRI.[24] In the face of worsening depression symptoms or SSRI withdrawal symptoms (discussed later), it also would be reasonable for an emergency physician to consider restarting a well-tolerated antidepressant that a patient recently had stopped taking on his or her own.[5]

Another agent — one that emergency physicians use on a daily basis for other indications — is rising to prominence rapidly as an acute treatment for depression and suicidality. Low-dose ketamine shows tremendous promise for treating depression and will be discussed in greater depth at the end of this article.

Other Treatments for Depression

Cognitive behavioral therapy (CBT) is a well-studied treatment modality for patients with depression. For many patients, it can be an effective standalone treatment, or it can serve as a useful adjunct with ADMs.[25] CBT aims to help individuals identify cognitive distortions and maladaptive behaviors and to replace them with more positive habits, skills, and coping strategies. Some authors consider CBT to be the gold standard for modern psychotherapy, and to be useful in treating many conditions other than depression, including post-traumatic stress disorder, eating disorders, substance use disorders, and borderline personality disorder.[26]

Electroconvulsive therapy (ECT) is a safe and time-tested treatment for individuals with MDD who have failed other forms of treatment. ECT also can be efficacious for other disorders, including catatonia and treatment-resistant schizophrenia.[27] The mechanism by which inducing a seizure can ameliorate psychiatric conditions is not fully understood, but it may involve changes in regional cerebral blood flow, transient breaches in the blood-brain barrier, and neurochemical release and metabolism.[27] The need for a backup treatment modality such as ECT remains significant. Approximately two-thirds of patients in one series did not respond to a three-month regimen of antidepressant medication,[28] and approximately half of the patients in another study who did not respond to antidepressants also did not respond to CBT.[29]

Transcranial magnetic stimulation (TMS) involves a noninvasive exposure of areas of the brain to a changing magnetic field that induces current flow via electromagnetic induction within the tissue thus exposed. There is substantial evidence that it can be effective in improving the symptoms of treatment-resistant depression,[30] with minimal side effects. TMS also appears to be useful in patients with neuropathic pain.[31] As is the case with ECT, a precise biochemical explanation for its efficacy still is unknown.

Herbal medications (particularly St. John's wort) have long been touted for the treatment of various psychiatric disorders, including MDD, anxiety, and insomnia, and researchers have explored possible neuropharmacologic mechanisms.[32,33,34,35] A recent systematic review of 35 efficacy studies found evidence that St. John's wort is superior to placebo in the treatment of mild to moderate depression, and that it is neither superior nor inferior to the standard antidepressants, although with fewer adverse effects.[36] However, there was considerable heterogenicity among the studies reviewed, and data were lacking to allow conclusions regarding its value in treating severe depression.

Complications of Antidepressant Medications

Toxicity of ADMs

Emergency clinicians in practice for more than a couple of decades will recall treating many cases of serious and often fatal tricyclic antidepressant overdose. Patients would be awake and cooperative, then rapidly deteriorate, becoming obtunded and developing difficult-to-manage tachydysrhythmias and brady-dysrhythmias with widening QRS and QT intervals. The scenario would be complicated by refractory hypotension and seizures. TCAs still are in use, and examples include amitriptyline, used primarily as an adjunct for the treatment

Table 3. Antidepressant Medications[23,24,37,41,43,44]

Class	Examples	Toxicity
Monoamine oxidase inhibitors (MAOIs)	• Phenelzine (Nardil) • Selegiline (Eldepryl) • Tranylcypromine (Parnate)	• Hypertensive crisis with tyramine-containing substances (beer, wine, cheese) • Serotonin toxicity when mixed with other serotonergic agents
Tricyclic antidepressants (TCAs)	• Amitriptyline (Elavil) • Imipramine (Tofranil) • Clomipramine (Anafranil) • Nortriptyline (Pamelor, Aventyl) • Doxepin (Sinequan)	• Significant anticholinergic effects • Cardiotoxicity — lethal arrhythmias • Coma, seizures
Tetracyclics (TeCAs)	• Maprotiline (Ludiomil) • Amoxapine (Asendin)	• Similar toxicity to TCAs but generally milder
Selective serotonin reuptake inhibitors (SSRIs)	• Fluoxetine (Prozac) • Paroxetine (Paxil) • Sertraline (Zoloft) • Citalopram (Celexa) • Escitalopram (Lexapro)	• Mild toxicity • Potential for serotonin toxicity when mixed with other serotonergic agents
Serotonin norepinephrine uptake inhibitors (SNRIs)	• Duloxetine (Cymbalta) • Desvenlafaxine (Pristiq) • Nefazodone (Serzone) • Venlafaxine (Effexor)	• Toxic profiles similar to SSRIs
Atypical agents	• Bupropion (Wellbutrin, Zyban) • Mirtazapine (Remeron) • Trazodone (Desyrel)	• Generally mild toxicity • Bupropion associated with seizures

of chronic pain and recurrent migraines, and clomipramine, which has an indication for obsessive compulsive disorder.

Emergency providers continue to see occasional overdoses with these agents and must be aware of the classic presentation and pharmacologic mechanisms, which include the inhibition of norepinephrine and serotonin uptake, alpha-adrenergic blockade, a quinidine-like action on myocardial cells, along with strong anticholinergic properties.[37] Always consider TCA toxicity in overdose patients with obtundation and widening QRS complexes. Obtain early airway control, consider gastric lavage or activated charcoal if early in the course, use benzodiazepines for seizures, and administer sodium bicarbonate for rhythm control, whether acidosis is present or not. Avoid antiarrhythmics that block sodium channels, such as the class Ia agents (procainamide, quinidine, disopyramide), and class Ic (flecainide). Class II agents can worsen hypotension, and class III agents (amiodarone) can further prolong the QT interval. Lidocaine (class Ib), despite its effect on sodium channels, has properties that make it the best agent for arrhythmias that do not respond to sodium bicarbonate alone.[37] The strong anticholinergic effects of the TCAs lead to profound CNS effects and an initial tachycardia. The use of physostigmine has been shown to be beneficial in anticholinergic agent poisoning, reducing the need for intubation. However, its use in TCA overdose, especially if there is any sign of sodium channel blockade with QRS prolongation, is highly problematic and may lead to cardiac decompensation.[38] By general consensus, physostigmine should be avoided in suspected TCA overdose, unless expert toxicology consultation is available.

TeCAs have a toxicity profile similar to the TCAs, although significantly milder. Mirtazapine is among the most commonly prescribed TeCAs and often is used for depression accompanied by insomnia and anxiety. In overdose, the TeCAs have strong antihistaminic effects but are markedly less toxic than the TCAs and seldom cause cardiovascular issues. The overdose fatality rate of TeCAs is similar to that of the SSRIs.

The original class of antidepressant medications, MAOIs, still is used in the treatment of certain cases of resistant MDD, atypical depression,[39] panic disorder, social phobia, and other conditions. While they are effective, they have fallen out of favor because of widespread drug-drug interactions and dietary restrictions. Patients taking MAOIs can experience severe hypertensive crises when ingesting the tyramine contained in aged cheeses, beer, wine, and animal liver. Adverse reactions, including serotonin syndrome (discussed more later), can occur when patients taking MAOIs are exposed to other classes of antidepressants, as well as St. John's wort, tryptophan, L-Dopa, meperidine, tramadol, dextromethorphan, MDMA, and various adrenergic stimulants. MAOI-induced hypertensive crisis also can occur in patients taking alpha-2 agonist medications for glaucoma.[40]

Because of a much safer therapeutic to toxicity ratio, the SSRIs and SNRIs have become the predominant ADMs currently prescribed. Adverse effects are less common with these agents than with

Table 4. SSRI Discontinuation Syndrome[45-47]

Onset	Symptoms	Treatment
• Seldom seen if patients are on an SSRI less than a month • Begins one to three days after abrupt discontinuation	Flu-like symptoms, dizziness, disequilibrium, headache, nausea, insomnia, vivid dreams, electric shock feelings, occasional visual and auditory hallucinations	Restart SSRI (consider longer-acting agent) and slowly taper over one to two months

any other class of ADM. Side effects generally are mild and include headache, insomnia, restlessness, initial anxiety, and possible sexual dysfunction. Nausea, insomnia, dry mouth, and sometimes hypertension are more likely to be seen with the SNRIs than with the SSRIs.[41] SSRI/SNRI overdose is rarely fatal. Most cases of serious toxicities involve multi-substance ingestions.[42,43] There is evidence suggesting that the SNRI venlafaxine may be more likely to cause adverse cardiac effects than SSRIs.[44]

Abrupt cessation of treatment with SSRIs and SNRIs can cause a well-recognized withdrawal syndrome that begins within several days of discontinuation and may last two or more weeks and sometimes much longer.[45] Be aware that the clinical picture includes flu-like symptoms, headache, ataxia, tremors, nausea, diarrhea, possible auditory and visual hallucinations, confusion, electric shock sensations, and vivid dreams.[45] Symptoms are not as prominent with longer-acting agents like fluoxetine. Researchers have studied the phenomenon in ICU patients and have concluded that home ADM regimens should be continued in critically ill patients to avoid the added symptom burden.[46] Strategies to avoid or minimize the SSRI/SNRI withdrawal syndrome include gradual tapering, switching to a longer-acting agent before discontinuation, and the temporary reinstitution of the SSRI/SNRI followed by a slow taper.[47] (*See Table 4.*)

Bupropion, mirtazapine, and trazodone are among the ADMs classified as atypical antidepressants, and each has unique mechanisms of action that modulate monoamine neurotransmitters and/or receptors. Indications for bupropion, a dopamine and norepinephrine uptake inhibitor, include depression and smoking cessation. With more sedating properties than other AMDs, trazodone, a potent serotonin and alpha-2 antagonist, is a preferred agent by some clinicians for the treatment of insomnia instead of benzodiazepines. Mirtazapine, an alpha-2 antagonist, also is useful for depression complicated by insomnia or anxiety. It stimulates appetite and weight gain, aids in sleep, and often is used in the elderly population.[24] Like the SSRIs and SNRIs, the therapeutic to toxicity ratio of the atypical agents is quite high.

Serotonin Syndrome

Serotonin syndrome, more usefully called serotonin toxicity,[50,52] is a potentially fatal continuum of symptoms caused by an overactivation of peripheral and central postsynaptic serotonin receptors. These symptoms include neuromuscular hyperactivity, autonomic excess, altered mental status, and gastrointestinal (GI) disturbance. In brief, too much serotonin can be dangerous, and a major excess can kill.[48,49,50] The very long list of compounds that can raise serotonin levels includes SSRIs, SNRIs, MAOIs (including linezolid and methylene blue), opiates (tramadol, fentanyl, dextromethorphan), CNS stimulants, St. John's wort, lithium, risperidone, olanzapine, and metoclopramide.[5,48] Although mild and moderate cases of serotonin syndrome have been reported with single agents (after overdose or rapid upward therapeutic titration of an SSRI, for example), severe serotonin toxicity typically is triggered by a combination of substances that activate serotonin receptors through different mechanisms (e.g., serotonin precursors, agonists, reuptake inhibitors, MAOIs). Severe serotonin toxicity is rare in patients with solitary SSRI overdoses. The worst cases frequently involve an MAOI plus something else.[49,50]

Serotonin toxicity is a clinical diagnosis of exclusion, and its calling card is clonus. Spontaneous clonus alone, in the presence of known or suspected serotonin-raising chemicals, immediately narrows the differential. Serotonin toxicity tends to have an acute onset over hours and presents with the basic triad of neuromuscular symptoms (spontaneous clonus, induced clonus, ocular clonus, tremor, hyperreflexia, and possible rigidity); autonomic excess (hyperthermia, mydriasis, diaphoresis); and altered mental status (confusion, excitement, agitation, seizures). GI disturbances, such as nausea and diarrhea, also may occur. The worst cases often are marked by rapidly rising temperature and rigidity.[50] Another characteristic feature is that the clonus and hyperreflexia are more noticeable in the lower extremities. Remember that serotonin toxicity represents a continuum, with mild symptoms ranging from irritability, brisk reflexes, tremors, and nausea all the way to delirium, hyperthermia, sustained clonus, rigidity, rhabdomyolysis, and death. (*See Table 5.*)

The Hunter Criteria for Serotonin Toxicity (HCST) currently is the diagnostic gold standard, with a sensitivity of 84% and a specificity of 97%.[48] HCST is positive if a patient has been exposed to a serotonergic agent and has at least one of the following features: spontaneous clonus, inducible clonus plus agitation or diaphoresis, ocular clonus plus agitation or diaphoresis, tremor and hyperreflexia, or hypertonia and fever > 38° C plus ocular or inducible clonus.[51]

For the purposes of helping clinicians keep serotonin toxicity on the radar screen, remember the mnemonic SNAGGLE: sympathetic (autonomic) excess (fever, diaphoresis, tachycardia, mydriasis); neuromuscular hyperactivity (tremors, myoclonus, clonus,

Table 5. Serotonin Toxicity[48-51]

Presenting Symptoms	Differential Diagnosis	Treatment
• Autonomic excess (fever, diaphoresis, tachycardia, hypertension, mydriasis) • Neuromuscular hyperactivity (spontaneous clonus is pathognomonic, induced clonus, ocular clonus, hyperreflexia, rigidity) • Altered mental status (confusion, restlessness, excitement, headache, coma) • Gastrointestinal irritation (nausea, vomiting, diarrhea)	• Neuroleptic malignant syndrome (exposure to dopaminergic agent, slower onset, no clonus, more rigidity, bradyreflexia) • Malignant hyperthermia (exposure to inhalational anesthetic or depolarizing paralytic, mottled skin, rigidity, hyporeflexia) • Anticholinergic toxicity (dry skin, urinary retention, normal tone and reflexes) • Meningitis/encephalitis • Sedative-hypnotic withdrawal, including delirium tremens • Sympathomimetic toxicity	• Stop potential triggering agents • Supportive care • Benzodiazepines • Intravenous hydration • Check for rhabdomyolysis • Active cooling • Consider cyproheptadine (a serotonin antagonist) • Paralysis and airway control in severe cases

hyperreflexia, rigidity); altered mental status (excitement, restlessness, agitation, confusion); gastrointestinal upset (nausea, diarrhea); gait disturbance (and go look up the Hunter criteria); and LE, for the symptoms being more prominent in the lower extremities. (*See Table 6.*)

The differential diagnosis of serotonin toxicity includes neuroleptic malignant syndrome (NMS). However, unlike the more acute presentation of serotonin syndrome, NMS typically evolves over days, lacks the feature of clonus, and often is accompanied by extrapyramidal signs.[50] Other conditions to consider include anticholinergic toxicity, alcohol or benzodiazepine withdrawal, antidepressant discontinuation syndrome, meningitis/encephalitis, and malignant hyperthermia.[49] (*See Table 5.*)

Mild and moderate cases of serotonin toxicity typically resolve within several days after discontinuing the agents involved. Patients with severe serotonin toxicity often require prolonged intensive care with intravenous hydration, benzodiazepine sedation, and active cooling. Complications include disseminated intravascular coagulation, rhabdomyolysis, adult respiratory distress syndrome, and multi-organ failure. A serotonin antagonist such as cyproheptadine often is used, but absolute evidence for their value is lacking.[50]

Be aware that some sources list ondansetron, a serotonin 5-HT3 receptor antagonist, along with metoclopramide as antiemetics associated with serotonin toxicity. Although these concerns are based solely on a small number of case reports, benzodiazepines might be considered as an alternative antiemetic for patients with serotonin toxicity.[52,53,54,55]

Suicide Risk Assessment

Screening for Depression and Suicidality

A significant public health problem across the world,[56] suicide has become the third leading cause of death among adolescents 14 to 19 years of age in the United States,[57] the second leading cause of mortality among young adults 20 to 29 years of age,[58] and the fourth leading cause of death for those between 10 to 65 years of age.[59] Evidence suggests that a disproportionate percentage of patients who attempt suicide have had an ED visit within the prior year, whereas no such correlation was found with primary care visits or hospitalizations.[58] Patients who are experiencing both severe anxiety and depression may visit the ED at twice the normal rate.[60] According to data from the National Hospital Ambulatory Medical Care Survey, between 2002 and 2008, an increasing percentage of patients with depression and suicidality presented to EDs rather than to outpatient clinics. Additionally, there is evidence that some patients presenting to the ED with low-acuity complaints and otherwise unidentified somatic complaints will screen positive for occult depression and suicidality, and that many patients desire to address these issues when identified.[61,62]

Given that the prevalence of depression and suicidality appears to be substantially higher in the ED than elsewhere, should emergency providers be screening for it more aggressively? In a study performed at an urban ED that has 80,000 annual visits, investigators screened 816 patients who presented with unrelated low-acuity chief complaints with one of two previously validated screening tools, the Patient Health Questionnaire for Depression and Anxiety (PHQ-4) and the Suicide Behaviors Questionnaire-Revised (SBQ-R). Of those 816 patients who presented for issues ostensibly unrelated to depression or suicidality, 11% screened positive as high risk for suicide.[62] Of those patients, a significant proportion were interested in addressing these issues during their ED stay. However, the ultimate effect of this finding remains to be explored.

Nowhere is suicide more tragic than in adolescents. A recent, small study showed the possible effectiveness of an intervention for adolescents at risk for suicide.[57] Forty-nine adolescents between 14 and 17 years of age who had presented to the ED for unrelated complaints, screened positive for suicide risk because of depression and alcohol use disorder or recent suicidal ideation or attempts. They were randomized into either a brief ED-based, personalized

Table 6. SNAGGLE Mnemonic for Serotonin Toxicity[45-47]

S	Sympathetic (autonomic) excess
N	Neuromuscular hyperactivity
A	Altered mental status
G	Gastrointestinal irritation
G	Gait disturbance (and Go check the Hunter Criteria)
L	Neuromuscular symptoms more prominent in the lower extremities
E	

counselling intervention known as Teen Options for Change (TOC) or treatment as usual. At the two-month follow-up, the TOC group showed a larger decrease in depression scores.

Much work is needed to determine what resources are required for such screening programs, what interventions could be mobilized, and what benefits may accrue. Such efforts would need to include logistical support for emergency physicians because a majority do not feel confident in their ability to create safety plans for depressed and suicidal patients.[63,64]

For a valuable in-depth discussion of suicide assessment and disposition, please refer to the Jan. 1, 2019 issue of *Emergency Medicine Reports*.[72]

Predicting the Risk of Suicide

Predicting the risk of suicide is challenging for both mental health professionals and emergency physicians. Factors that increase the risk include: suicidal intent and a plan; a history of attempts; a family history of suicide; recent stressors; and lack of social supports. Additional risk factors include a history of alcoholism or other substance use disorder, a chronic illness, age younger than 19 years or older than 45 years, current depressive symptoms, male sex, the contemplation of a highly lethal method of committing suicide, and a history of schizophrenia or bipolar disorder. Previous suicide attempts are highly predictive of future behavior.[65] The widely used SAD PERSONS Scale (SPS) incorporates these factors and provides a scoring scenario to help predict risk. The letters in the name of the scale stand for: sex (male > female); age (older white male at greater risk); depression; previous attempt; ethanol/other substance abuse; rational thinking loss; social support lacking; organized plan; no spouse; and sickness (medical or psychiatric). Five or more points on the scale may indicate a high risk of suicide.[5]

The use of the SPS by emergency physicians has shown some degree of concordance with subsequent psychiatric suicide risk assessments. Other researchers suggest that the SPS may be fairly specific regarding the identification of patients at risk for self-harm events, but it has a suicide risk prediction sensitivity of less than 10%.[67]

Because a single reliable method of excluding suicide risk is lacking, assessment in the ED remains an individualized process fraught with complexity. Other factors are involved. For example, observations indicate that patients with antisocial personality disorder appear to be at higher risk of suicide following the death of a spouse, and those with narcissistic personality disorder attempt suicide more frequently after being fired from a job.[68] An association also has been observed between the lifetime risk of suicide attempts and the presence of a history of severe headaches and chronic GI diseases.[58]

Emergency physicians should be aware of an excellent, online clinical resource developed by the American College of Emergency Physicians (www.acep.org/icar2e) that provides concise information on suicide risk assessment, red flags, screening tools, and communication tips. Consider creating a shortcut to this resource on every ED computer desktop.

A Novel Treatment for Depression

If the increasing number of clinics that provide low-dose ketamine infusions for the treatment of depression, chronic pain, and migraines is any indication, ketamine may have the potential to become a game-changer in the realm of caring for profoundly depressed and suicidal patients in the ED.[73] There are relatively few ED-based studies on ketamine for depression, and those that do exist are small. However, the American Psychiatric Association found enough evidence from other settings to publish a 2017 consensus statement noting that ketamine produces a rapid and potent antidepressant effect in patients previously resistant to treatment.[69] Effects may be seen in an hour or less. In one randomized controlled trial,[57] patients with treatment-resistant depression were given single doses of either ketamine or midazolam. Approximately half of the ketamine group had suicide scales of zero at 24 hours compared to one-quarter of the midazolam group.[74] In another study, 33 patients with depression were administered a 0.5 mg/kg ketamine infusion. The investigators measured a significant decrease in all the employed suicide risk scales at 40 minutes.[75] Another small pilot study performed in a military ED showed dramatic decreases in suicidality within 40 minutes after an infusion of 0.2 mg/kg ketamine vs. no change in placebo controls.[76] Larger studies are currently ongoing.

Ketamine has multiple neurochemical properties. It is a high-affinity *N*-methyl-d-aspartate antagonist with glutaminergic properties and also has effects upon opioid receptors. One recent small and intriguing trial suggested that ketamine's opioid receptor properties may be involved in its antidepressant effects.[71] The investigators pretreated a group of depressed subjects with naloxone prior to administering ketamine and discovered a markedly attenuated antidepressant response.

It is not difficult to imagine a scenario in which a patient presents to the ED with symptoms of MDD and significant suicidality and, after appropriate medical screening, is administered a ketamine infusion, re-evaluated in a few hours, and discharged with an SSRI for close follow-up. Ketamine's long positive safety record as an anesthetic and procedural sedation agent is reassuring.[70]

Summary

Depression is a worldwide public health problem. A disproportionate number of patients experiencing depression will be seen in EDs, many of them for unrelated medical issues. The diagnosis of depression requires the presence

Table 7. High-Risk Factors for Suicide

- Highly lethal attempt mechanism
- Previous suicide attempts
- Plan for future attempt
- Access to lethal means
- Mental disorders, including depression and other mood disorders
- Male > female
- Age < 19 years or > 45 years
- Single, divorced, or widowed
- History of alcohol or other substance use disorder
- Lack of social supports
- Chronic medical conditions
- Family history of suicide, or history of suicide by a friend or acquaintance

Source: DeSelm TM. Mood and anxiety disorders. In: Tintinalli J, Stapczynski J, Ma O, et al, eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*. 8th ed. New York: McGraw-Hill; 2016:1963.

of depressed mood or anhedonia (loss of interest or pleasure) along with four or more of the following symptoms: suicidal ideation (with or without a plan); insomnia, early awakening, or hypersomnia; psychomotor retardation; agitation and restlessness; fatigue and loss of energy; feelings of worthlessness; a free-floating sense of guilt; significant weight loss or weight gain; and difficulty concentrating. One of the emergency physician's major roles in the care of patients with depression is to search for treatable medical conditions, such as occult infections, endocrinological disease, and toxic/metabolic disturbances.

Treatment for depression includes antidepressant medications and cognitive behavioral therapy. Treatment-resistant depression may respond to a change in antidepressant medication, electroconvulsive therapy, or transcranial magnetic stimulation. Low-dose ketamine infusions show great promise in rapidly relieving suicidal ideation and treatment-resistant depression.

Combinations of serotonergic compounds commonly used for depression can trigger serotonergic toxicity, manifested by neuromuscular hyperactivity, autonomic excess, and altered mental status. Severe serotonin toxicity is life-threatening and usually is caused by the combination of an MAOI and another medication such as an SSRI that raises synaptic serotonin levels via a different mechanism.

Suicide risk assessment remains challenging, even for seasoned mental health professionals. Factors that raise the likelihood of a patient attempting suicide include male sex, history of previous attempts, positive family history of suicide, age younger than 19 years or greater than 45 years, history of alcohol or other substance use disorder, and the presence of a suicide plan of high lethality. The SAD PERSONS scale commonly used in EDs to evaluate patients at risk for suicide attempts is specific but poorly sensitive. The same appears to hold true for clinical judgment alone. Better tools are needed.

Because of ketamine's apparent ability to rapidly reverse suicidal ideation and depression, it may be used someday by emergency physicians for more than procedural sedation and the treatment of pain.

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CME/CE Questions

1. Which of the following factors is most predictive of suicide?
   a. Alcoholism
   b. Family history
   c. Previous attempts
   d. Advanced age

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2. A 23-year-old female presents to the ED with a Glasgow Coma Score of 8 after an unknown suicidal overdose three hours previously. She is afebrile, has a blood pressure of 110/65, and heart rate of 122 beats per minute. Her clinical picture resembles an anticholinergic toxidrome with mydriatic pupils, dry membranes, and absent bowel sounds. An ECG shows sinus tachycardia with a widened QRS interval. Following airway control, which next step in treatment would be most appropriate?
   a. Gastric lavage
   b. Levetiracetam
   c. Physostigmine
   d. Sodium bicarbonate
3. In the same patient described in question 2, her rhythm deteriorates into ventricular tachycardia. Which of the following antiarrhythmic agents could be considered?
   a. Amiodarone
   b. Flecainide
   c. Lidocaine
   d. Quinidine
4. A 39-year-old female has recently moved into the area and is awaiting her first appointment with a new primary care provider. Several days ago, she ran out of the fluoxetine she had been taking for the previous three years and presents today with restlessness, flu-like symptoms, and a sense of intermittent electric shocks in her head. Which is the most appropriate medication to consider?
   a. Cyproheptadine
   b. Diazepam
   c. Fluoxetine
   d. Tamiflu
5. A low-dose ketamine infusion has shown promise in rapidly alleviating major depression symptoms including suicidal ideation.
   a. True
   b. False
6. A 32-year-old male presents with the acute onset over hours of delirium and severe restlessness. He has a history of hospitalizations for depression, is on an antidepressant medication, and may have taken an overdose of multiple substances. On initially examining the patient, you notice intermittent spontaneous clonus involving his lower extremities. Which additional finding can you expect to see?
   a. Dry skin
   b. Hyperthermia
   c. Miosis
   d. Oculogyric crisis
7. Which of the following naturally occurring herbal medications has been implicated in serotonin toxicity?
   a. Curare root
   b. Extract of chrysanthemum
   c. Thistle seed oil
   d. St. John's wort

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EMERGENCY MEDICINE REPORTS

Code Melancholia: A Review of Depression for Emergency Physicians

Diagnosing Major Depressive Disorder

Two or more weeks of depressed mood/anhedonia plus four or more symptoms from this list that are not attributable to either a substance use disorder or a major medical condition, and that must challenge a patient's normal level of function:

- Suicidal ideation
- Insomnia, early morning awakening, hypersomnia
- Psychomotor retardation
- Agitation/restlessness
- Fatigue/loss of energy
- Feelings of worthlessness
- Free-floating guilt
- Appetite changes with significant weight loss or gain
- Difficulty concentrating

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

Depressive Disorders — DSM-5

- Major depressive disorder (MDD)
- Persistent depressive disorder (dysthymia)
- Postpartum depression
- Psychotic depression
- Seasonal affective disorder (SAD)
- Disruptive mood dysregulation disorder
- Premenstrual dysphoric disorder

Source: National Institute of Mental Health. Depression. Available at: www.nimh.nih.gov/health/topics/depression. Accessed Dec. 27, 2018.

Antidepressant Medications[23,24,37,41,43,44]

Class	Examples	Toxicity
Monoamine oxidase inhibitors (MAOIs)	• Phenelzine (Nardil) • Selegiline (Eldepryl) • Tranylcypromine (Parnate)	• Hypertensive crisis with tyramine-containing substances (beer, wine, cheese) • Serotonin toxicity when mixed with other serotonergic agents
Tricyclic antidepressants (TCAs)	• Amitriptyline (Elavil) • Imipramine (Tofranil) • Clomipramine (Anafranil) • Nortriptyline (Pamelor, Aventyl) • Doxepin (Sinequan)	• Significant anticholinergic effects • Cardiotoxicity — lethal arrhythmias • Coma, seizures
Tetracyclics (TeCAs)	• Maprotiline (Ludiomil) • Amoxapine (Asendin)	• Similar toxicity to TCAs but generally milder
Selective serotonin reuptake inhibitors (SSRIs)	• Fluoxetine (Prozac) • Paroxetine (Paxil) • Sertraline (Zoloft) • Citalopram (Celexa) • Escitalopram (Lexapro)	• Mild toxicity • Potential for serotonin toxicity when mixed with other serotonergic agents
Serotonin norepinephrine uptake inhibitors (SNRIs)	• Duloxetine (Cymbalta) • Desvenlafaxine (Pristiq) • Nefazodone (Serzone) • Venlafaxine (Effexor)	• Toxic profiles similar to SSRIs
Atypical agents	• Bupropion (Wellbutrin, Zyban) • Mirtazapine (Remeron) • Trazodone (Desyrel)	• Generally mild toxicity • Bupropion associated with seizures

SSRI Discontinuation Syndrome[45-47]

Onset	Symptoms	Treatment
• Seldom seen if patients are on an SSRI less than a month • Begins one to three days after abrupt discontinuation	Flu-like symptoms, dizziness, disequilibrium, headache, nausea, insomnia, vivid dreams, electric shock feelings, occasional visual and auditory hallucinations	Restart SSRI (consider longer-acting agent) and slowly taper over one to two months

Serotonin Toxicity[48-51]

Presenting Symptoms	Differential Diagnosis	Treatment
• Autonomic excess (fever, diaphoresis, tachycardia, hypertension, mydriasis) • Neuromuscular hyperactivity (spontaneous clonus is pathognomonic, induced clonus, ocular clonus, hyperreflexia, rigidity) • Altered mental status (confusion, restlessness, excitement, headache, coma) • Gastrointestinal irritation (nausea, vomiting, diarrhea)	• Neuroleptic malignant syndrome (exposure to dopaminergic agent, slower onset, no clonus, more rigidity, bradyreflexia) • Malignant hyperthermia (exposure to inhalational anesthetic or depolarizing paralytic, mottled skin, rigidity, hyporeflexia) • Anticholinergic toxicity (dry skin, urinary retention, normal tone and reflexes) • Meningitis/encephalitis • Sedative-hypnotic withdrawal, including delirium tremens • Sympathomimetic toxicity	• Stop potential triggering agents • Supportive care • Benzodiazepines • Intravenous hydration • Check for rhabdomyolysis • Active cooling • Consider cyproheptadine (a serotonin antagonist) • Paralysis and airway control in severe cases

SNAGGLE Mnemonic for Serotonin Toxicity[45-47]	
S	Sympathetic (autonomic) excess
N	Neuromuscular hyperactivity
A	Altered mental status
G	Gastrointestinal irritation
G	Gait disturbance (and Go check the Hunter Criteria)
L	Neuromuscular symptoms more prominent in the lower extremities
E	

High-Risk Factors for Suicide
• Highly lethal attempt mechanism • Previous suicide attempts • Plan for future attempt • Access to lethal means • Mental disorders, including depression and other mood disorders • Male > female • Age < 19 years or > 45 years • Single, divorced, or widowed • History of alcohol or other substance use disorder • Lack of social supports • Chronic medical conditions • Family history of suicide, or history of suicide by a friend or acquaintance
Source: DeSelm TM. Mood and anxiety disorders. In: Tintinalli J, Stapczynski J, Ma O, et al, eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*. 8th ed. New York: McGraw-Hill; 2016:1963.

Supplement to *Emergency Medicine Reports*, January 15, 2019: "Code Melancholia: A Review of Depression for Emergency Physicians." Author: Frank J. Edwards, MD, FACEP, Program Director, Emergency Medicine Residency Program, Arnot Ogden Medical Center, Elmira, NY.