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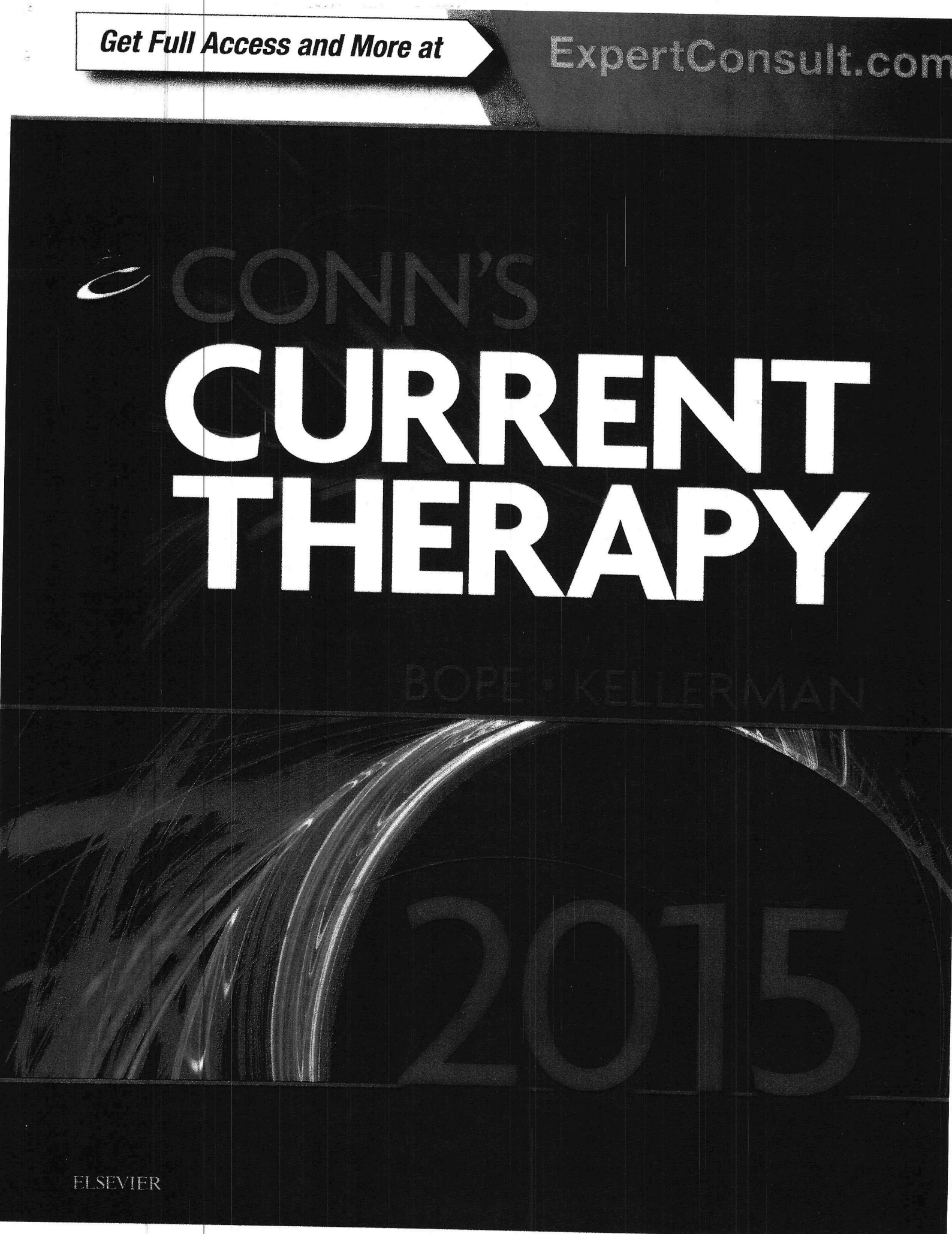

history, psychiatric symptoms, development, and underlying medical causes must be ruled out before making a diagnosis.

Individuals with ARFID often exhibit selective eating, food neophobia, and hypersensitivity to sensory features of food (texture, taste, temperature, appearance). Similar clinical presentations may have varying etiology, requiring individualized treatment plans. In some, development of food avoidance can be traced to a specific aversive event, trauma, or related gastrointestinal problem, or may arise out of a choking, swallowing, or vomiting phobia. Individuals may also have a lack of drive or interest in eating or heightened textural sensitivity, which is common in autism spectrum disorders.

Epidemiology

No data exist on prevalence, course, and outcome of this disorder. Surveillance studies are underway in the UK and Canada for related "food avoidance emotional disorder," with overlap in clinical features. ARFID appears to arise most commonly in infancy and early childhood, but can occur at any age and last into adulthood. Preliminary data suggest ARFID occurs at equal rates in males and females. There is no evidence to guide for whom clinical intervention is warranted versus those whose symptoms resolve over time.

Treatment

There are no systematically studied treatments to date for ARFID; however, behavioral interventions with contingency management have been successfully utilized among children who have food neophobia in the context of a developmental disability. Given limited data, individualized treatment plans are best derived through assessment of medical history, temperament, psychiatric symptoms, and development. Food avoidance may be treated through use of behavioral strategies (e.g., shaping, chaining, contingency management, extinction) that systematically desensitize individuals to a wider range of foods. Related anxiety management techniques (relaxation training, visualization for mastery), and cognitive strategies derived from CBT may address maintaining psychiatric features. CBT was successfully applied in a case study of young adults with food neophobia. In most severe cases of malnutrition, hospitalization may be needed before outpatient therapy.

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MOOD DISORDERS: DEPRESSION, BIPOLAR DISEASE, AND MOOD DYSREGULATION

Method of
Andrei Novac, MD

CURRENT DIAGNOSIS

- Clinical evaluation of mood disorders starts with a thorough psychosocial and medical history.
- Identify symptoms and patterns of the appearance of mood changes.
- Differentiate between unipolar and bipolar symptom patterns.
- Use collateral history, if possible.
- For recent-onset disorder, rule out new medical disorders. Always check thyroid function.

CURRENT THERAPY

- Any underlying medical conditions must be treated simultaneously.
- The mainstay of treatment for all mood disorders remains the combination of pharmacology and psychotherapy.
- Monitor frequently for suicidality.
- Allow for at least 2 to 4 weeks for response before a medication switch.
- Switch medication early in cases of intense side effects.
- Monitor for hypomanic switch on medications in undiagnosed bipolarity.

Mood disorders and mood dysregulation encompass a broad range of human experiences. They can be divided into three types of manifestations: (1) psychiatric disorders, which make up a major chapter in medical texts; (2) a variety of mood syndromes, often comorbid, less well classified, that coexist with medical and psychiatric disorders alike; (3) an aggregate of reactive transient behavioral manifestations outside the pathologic realm, inherent to human nature. Only the first two areas will be the focus of this chapter. Mood disorders and mood dysregulation are among the most common manifestations of human suffering. They are not mutually exclusive; dysregulation of mood may be present both as an independent symptom and as part of a mood disorder. They all deserve particular attention because they can gravely impact the level of functioning, compliance, treatment outcome, and quality of life.

Mood Disorders*

Both the *Diagnostic and Statistical Manual*, 5th ed. (DSM-5) (2013), and the ICD-10 classify mood disorders into similar types. These include: major depressive disorders (unipolar, single episodes, and recurrent), persistent depressive disorder (dysthymia), bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to medical conditions, substance-induced mood disorders, and the "unspecified" unipolar and bipolar disorders. In addition, the DSM-5 has included new clinical entries, such as disruptive mood dysregulation disorder, persistent depressive disorder (dysthymia) with intermittent major depressive disorders and premenstrual dysphoric disorder. The previously entitled "not otherwise specified" syndromes are now called "unspecified mood disorders." New to the DSM-5 are the following *specifiers* that apply to *both* bipolar and unipolar disorders: (a) with anxious distress (a mixture of mood disorder and anxiety disorder); (b) with mixed features; (c) with melancholic features; (d) with atypical features; (e) with psychotic features; (f) with catatonia; (g) with peripartum onset; and (h) with seasonal pattern.

Epidemiology

Most recent data regarding prevalence comes from the National Comorbidity Survey, which has exposed in detail the rates of subtypes of mood disorders: unipolar, bipolar, and the subthreshold disorders. The lifetime prevalence of any mood disorder was found to be 21.4% (female 24.9%, male 17.5%), with major depression occurring at a lifetime prevalence of 16.9% (female 20.2%, male

*In this chapter, no DSM-5 or ICD-10 diagnostic codes are included. The clinician is advised to consult the DSM-5 for specific diagnostic codes.

13.2%) and 12-month prevalence of 6.8%. Persistent depressive disorder (dysthymia) occurs at a lifetime prevalence of 2.5% (female 3.1%, male 1.8%) and 12-month prevalence of 1.5%. The DSM-5 specifies the prevalence for dysthymia as being approximately 0.5% and for the chronic form of major depressive disorder, 1.5%. Bipolar disorders present with a lifetime prevalence of 4.4% (female 4.5%, male 4.3%). If broken down, bipolar I disorder occurs at a lifetime prevalence of 1.0%, and 0.6% of new cases over 12 months. Bipolar II disorder occurs at the prevalence of 1.1% and 0.8%, respectively. Subthreshold bipolar disorder is twice as common at 2.4% lifetime and 1.4% new cases over 12 months.

Risk Factors

For unipolar major depressive disorders, risk factors include: gender (women at greater risk), age (18–44 years of age at greater risk), marital status (separated and divorced at greater risk), family history (relatives with depression), early parental death, life events (negative stressful events, chronic exposure to stress), low confidence, and urban environments. For bipolar disorder, risk factors are similar. In addition, for bipolar disorder, higher rather than lower socioeconomic status and suburban environments have been cited as risk factors.

Individuals with anxiety disorder, chronic exposure to stress and trauma, substance abuse, psychotic disorders, and chronic medical conditions are all known to be at risk for mood disorders.

Depressive Disorder (Unipolar Mood Disorder)

Major Depression

The mainstay of major depressive disorder is a major depressive episode. The DSM-5 provides criteria according to a threshold of symptoms, yet all mood disorders have to be understood as lying on a continuum. Therefore, even individuals who do not meet all criteria have to be carefully followed, and in many cases preventive treatment is warranted.

At least five or more of the following symptoms during the same 2-week period are required: (1) depressed mood most of the day, nearly every day (sadness, feelings of emptiness, tearfulness); (2) marked diminished interest or pleasure in almost all activities; (3) significant weight loss or weight gain or fluctuations in appetite; (4) insomnia or hypersomnia; (5) psychomotor retardation or agitation nearly every day; (6) fatigue or loss of energy; (7) feelings of worthlessness and/or inappropriate guilt; (8) inability to concentrate, think, and make decisions; and (9) recurrent thoughts of death and/or suicidal ideations. These symptoms: (1) cause significant distress or impairment in social, occupational, and/or personal functions; and (2) are not due to a general medical condition. In the DSM-5, contrary to previous classifications, the bereavement and depression are not mutually exclusive. In fact, bereaved individuals can also develop major depression, which would warrant additional medical treatment (see Table 3.)

Following are some forms of manifestations:

- Major depressive disorder, single episode: Episodes may occur only one time in life or may occur again years later, usually triggered by major stressful events.
- Major depressive disorder, recurrent type: Episodes reoccur at shorter intervals. Often the distance between episodes shortens with advancement in age. The first few episodes are more likely to be triggered by stressful life events, while in time the condition becomes self-maintained and self-triggered.
- Depressive disorder with catatonic features (motoric immobility, catalepsy, stupor, extreme opposition, posturing, echolalia).
- Major depression occurring after giving birth may predict further depressive episodes years later. Postpartum depression has also been associated with bipolar disorder.

Depressive disorder can also take a chronic course. Some patients present with *melancholic features* (profound loss of pleasure, depression worse in the morning, early morning awakening, severe psychomotor retardation, severe anorexia and weight loss). Melancholia may be a predictor of relatively good response to medications. *Atypical depression* features are characterized by inverted functional shift (weight gain and increased appetite, craving for sweets, hypersomnia, leaden paralysis, long-standing interpersonal rejection sensitivity). Table 1 presents the subtypes (specifiers) of mood disorders according to the DSM-5. These subtypes are encountered both in unipolar and bipolar mood disorders. Under these new DSM-V classifications, conditions such as catatonia, seasonal affective disorders, and atypical depression may occur both in individuals with unipolar and bipolar disorders.

Persistent Depressive Disorder (Dysthymia)

Persistent depressive disorder, the new designation for dysthymic disorder, is a chronic form of depression in which the depressed mood has persisted for at least 2 years (in children for at least

TABLE 1 Subtypes of Mood Disorders (Specifiers) Common to Both Unipolar and Bipolar Mood Disorders

SUBTYPE WITH	PRESENTATION	FEATURES
Anxious distress (with elements of mood disorder and anxiety disorder)	During the majority of days of depressive, manic or hypomanic episode	Feeling keyed-up or tense, feeling restless, unable to concentrate, fear that something awful may happen, etc.
Mixed features	Meets criteria for either mania, hypomania, or depression	With mixed symptoms (if manic, there is associated dysphoria and depression), observable by others
Melancholic features	During the most severe period	Severe anhedonia, worse in the morning, early morning awakening, psychomotor retardation or agitation, weight loss or gain
Typical features	During majority of days of a major depressive episode	Inverted functional shift (hypersomnia, hyperphasia, weight gain), leaden paralysis, long-standing pattern of interpersonal rejection sensitivity
Psychotic features	The presence of delusions and/or hallucinations	• Mood-congruent psychosis (delusion/hallucinations include themes consistent with the type of mood [manic or depressed]) • (b) Mood-incongruent psychosis
Catatonia	The presence of catatonia	Catatonic features are present during most of depressive or manic episodes
Peripartum onset	Mania, hypomania, major depression in bipolar I or II disorders	During pregnancy or in the 4 weeks following delivery
Seasonal pattern	At least one type of episode (mania, hypomania or depression) within a seasonal pattern	Temporal relationship between an episode and a particular time of the year (fall or winter, in bipolar I or II)

1 year), as manifested by at least two of the following symptoms: (1) poor appetite or overeating; (2) insomnia or hypersomnia; (3) low energy or fatigue; (4) low self-esteem; (5) poor concentration or difficulty making decisions; (6) feelings of hopelessness. These manifestations are distinct from any major depressive episode, there have been no manic symptoms, and there is significant distress or impairment in social, occupational, or personal functioning. Dysthymia can occur in any age and can co-occur with major depressive disorder.

The following clinical forms have been identified: (1) with pure dysthymic syndrome: no full criteria of major depression have been met in the past 2 years; (2) with persistent major depressive episode: full criteria of a major depressive episode have been present in the past 2 years; (3) with intermittent major depressive episodes, with current episode: full criteria for major depressive episodes are currently met but there have been periods of at least 8 weeks in the last 2 years when major depression criteria have not been met; (4) with intermittent major depressive episodes, without current episode: no current major depression is identified (only symptoms of dysthymia) but there has been one or more major depressive episode in the past 2 years. Persistent depressive disorder may also qualify for any of the specifiers described in Table 1. (Note: Table 1 specifiers can apply to any of the unipolar and bipolar form of mood disorders.)

Disruptive Mood Dysregulation Disorder

This condition occurs in childhood or adolescence between the ages of 6 and 18. It is characterized by (1) severe recurrent temper outbursts manifested verbally (verbal rages) and/or behaviorally (physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation; (2) temper outbursts that are inconsistent with developmental level; (3) temper outbursts that occur on average three or more times per week; (4) a mood between temper outbursts that is persistently irritable or angry most of the day, nearly every day, and is observable by others; (5) the above criteria, which have been present for 12 or more months (with no lapse in symptoms for a duration of 3 or more months); (6) an age of onset that is before 10. Diagnosis should not be made before age 6 or after 18.

Pre-menstrual Dysphoric Disorder

- The condition is characterized by the majority of menstrual cycles that include five symptoms. The following symptoms occur in the final week before the onset of menses and begin to improve within a few days after the onset of menses.
- One or more of the following symptoms must be present: (1) marked affective lability (mood swings; feeling suddenly sad or tearful; increased sensitivity to rejection); (2) marked irritability or anger or increased interpersonal conflict; (3) marked depressed mood, feelings of hopelessness or self-deprecating thoughts; (4) marked anxiety, tension, and/or feelings of being keyed-up or on edge.
- One or more of the following symptoms must be present to reach a total of five symptoms: decreased interest in usual activities; subjective difficulty in concentration; lethargy; easily fatigued; marked changes in appetite, overeating, specific food cravings; hypersomnia or insomnia; a sense of being overwhelmed or out of control; physical symptoms such as breast tenderness or swelling, joint or muscle pain, bloating or weight gain.

Substance/Medication Induced Depressive Disorder

This diagnosis is used when persistent disturbance in mood predominates the clinical picture and is characterized by depression and diminished interest or pleasure in activities. These symptoms occur during or soon after substance intoxication or withdrawal or after exposure to a medication. The substance in question has to be known to cause symptoms of depression.

Depressive Disorder Due to Another Medical Condition

This diagnosis is used when a depressive disorder is triggered by a medical condition (diagnosed by physical examination and laboratory findings) known to cause symptoms of depression. These may include disorder of the CNS, systemic disorders (Lupus, cancer), etc.

Other Specified Depressive Disorders

These are depressions that do not fully meet criteria of the above-described conditions. However, they may appear in one of the following forms:

- recurrent brief depression (symptoms of depression lasting from 2–13 days at least once per month) not associated with menstrual cycles;
- short duration depressive episode (lasting from 4–13 days), with at least four symptoms of major depressive episode associated with clinical distress and impaired functioning that persist but never meets criteria of major depression;
- depressive episode with insufficient symptoms (at least one of the symptoms of major depression associated with distress and impairment persisting for at least 2 weeks with no prior history of major depression).

These "other specified depressive disorders" are helpful to clinicians in refining the description of a clinical pattern exhibited by a particular patient.

Unspecified Depressive Disorder

Finally, the previously used designation of "not otherwise specified" now reads "unspecified depressive disorder" (when none of the criteria are fully met, yet the patient is suffering from a mood disorder).

Bipolar Mood Disorders

Manic Episode

A manic episode is characterized by a period of at least 1 week with abnormal and persistently elevated, expansive, or irritable mood. At least three of the following should be also present: (1) inflated self-esteem or grandiosity; (2) decreased need for sleep (yet still feeling rested); (3) more talkative than usual or inability to stop talking; (4) flight of ideas or racing thoughts; (5) distractibility; (6) increase in goal-oriented activities (socially, sexually) or psychomotor agitation; (7) excessive involvement in pleasurable activities with little regard for consequences (e.g., sexual indiscretions, unwise investments). These symptoms (1) result in marked impairment in most areas of life, and (2) are not due to substance abuse or general medical conditions.

Hypomania

A hypomanic episode is similar to, but less intense, than a manic episode. At least three symptoms from the same symptom cluster (inflated self-esteem, decreased need for sleep, excessive talking, racing thoughts, hyperactivity, increased involvement in pleasurable activities) are required, but the condition is not severe enough to cause marked impairment in social, occupational, and personal functioning, and it does not necessitate hospitalization. However, functional impairment is noticeable over time.

"Bipolar I" disorder requires only one full manic episode for the diagnosis. Usually, individuals with bipolar I disorder also have both manic and depressive episodes, but the depressions can range from severe and disabling to very brief and unnoticed. Therefore, a history of a depressive episode is not required for the diagnosis.

"Bipolar II" disorder is characterized by long periods of hypomania, with occasional major depressive episodes. Such individuals are usually not hospitalized for their hypomania and tend to function relatively well between depressive episodes. Hypomanic states are episodic and exhibit an unequivocal change in functioning that is uncharacteristic for the individual when not symptomatic. These changes are observable by others. Depressions tend to be severe and disabling. Bipolar II disorders do not include full manic episodes.

Mixed States and Rapid Cycling

The particular specifiers for bipolar disorder are mixed states and rapid cycling. "Mixed states" refers to manic or hypomanic episodes with at least three of the following depressive symptoms: prominent dysphoria or depressed mood, diminished interest in activities, psychomotor retardation, fatigue or loss of energy, feelings of worthlessness, recurrent thoughts of death. Often there is a rapid alternation between mania and depression (rapid cycling). Contingent upon severity, mixed states are usually accompanied by severe impairment. "Rapid cycling" refers to bipolar disorder that includes at least four episodes of illness per year. In addition, bipolar disorders may include any of the specifiers described in Table 1, under the section titled unipolar depression.

Cyclothymic Disorder

Cyclothymic disorder is a cycling mood disorder lasting for 2 years or more and is characterized by numerous periods with hypomanic symptoms and depressive symptoms that do not meet criteria for bipolar disorder or major depression. During a 2-year period (1 year in children and adolescents), hypomanic and depressive periods have been present for at least half the time, and the individual has not been without symptoms for more than 2 months at a time. Criteria for major depression, mania, or hypomanic episodes have never been met. However, in the long run, some patients may develop symptoms of bipolar affective disorder. These symptoms should not be attributable to the effect of a substance (drug abuse, medication) or another medical condition (hyperthyroidism, Cushing's disease, etc.). The condition is significantly impairing and includes psychological distress. Cyclothymia has the specifier (subtype) "cyclothymia with anxious distress." This condition comprises cyclothymia and features of anxious distress as outlined in Table 1. A variety of subclinical forms of *subthreshold cyclothymia* may be encountered in clinical practice. Such patients tend to develop overt symptoms of cyclothymia, or even bipolar disorder, when exposed to a variety of psychosocial stressors, substance abuse, and/or a variety of medications. Finally, Table 2 presents subtypes of bipolar disorder currently listed in the DSM-5 as: "Other specified bipolar and related disorders" and "unspecified bipolar and related disorder."

Specifiers for Bipolar and Related Disorders

Please refer to Table 1 for specifiers of depressive disorders that apply to bipolar disorders as well.

Diagnosis

When faced with symptoms of mood disorder, a clinician has to decide whether these are transient manifestations related to life circumstances or symptoms of treatable psychopathology. The clinical evaluation of patients with mood disorders starts with a thorough history of the present illness. A thorough medical history is paramount given the numerous medical disorders that present with depression or mania. Mood disorders are, in general, recurrent conditions. Past history will provide not only a suspicion toward a diagnosis, but also clues toward clinical manifestations, which, in the cases of depression and mania, are often similar to previous episodes. An early history of childhood behavioral problems can constitute a precursor of mood disorders. The Mental Status Examination provides further clues to the diagnosis. For depressive states, patients often exhibit psychomotor retardation; slow speech; constricted affect; and slow, observable mental activity. For mania and hypomania, the opposite can be observed. Patients show increased psychomotor activity, pressured speech, full or labile affect, and elevated mood. Often, they will appear unrealistically optimistic. In general, the diagnosis of mood disorder is aided significantly by obtaining a collateral history from friends or family members. The value of the Mental Status Examination is enhanced if the clinician knows the patient from before the mood disorder episode. A variety of psychological tests and depression rating scales exist, including the Beck Depression Inventory, the Hamilton Depression Rating Scale, and the Profile of Mood States (POMS) Depression Scale. While extremely useful in quantifying symptoms of depression, psychological testing is time-consuming and not necessary for the initial diagnosis of a mood disorder.

A thorough account of all symptoms present in a patient can point to treatment choice and outcome. Depression symptoms can be classified into at least three major groups:

- Emotional symptoms: sadness, dysphoria, emotional numbness
- Physical symptoms: low energy, sluggishness with difficulties in initiating activities, difficulties concentrating, sleep and appetite problems
- Cognitive (mental) symptoms: pessimism, loss of enthusiasm, hopelessness, thoughts of death

Not all three groups of symptoms are present from the beginning. In many individuals, the presence of cognitive symptoms may be a sign of chronicity. At other times, it may have been a premorbid feature or a constant presence between episodes. Cognitive symptoms tend to respond both to medication and psychotherapy (cognitive-behavioral techniques), and their monitoring is paramount to suicide prevention. If a mood disorder is secondary to a medical condition, the diagnosis will be made both by monitoring for mood symptoms and pathognomonic medical findings.

TABLE 2 Other Specified and Unspecified Bipolar Disorders

SUBTYPE	PRESENTATION	FEATURES
Substance/medication-induced bipolar and related disorder	Persistent disturbance of mood characterized by manic, hypomanic, with or without depressed mood, which occurs soon after substance intoxication or withdrawal or after administration of a medication	• Substance involved is capable of producing described mood symptoms • Does not occur in the course of delirium • There is significant stress or impairment
Bipolar and related disorder due to another medical condition	• Persistent period of abnormally elevated expansive or irritable mood • Evidence from history, physical examination, laboratory findings that disturbance is a direct pathophysiologic consequence of another medical condition	• With manic features • With manic or hypomanic-like episode • With mixed features (depression is also present)
Other specified bipolar and related disorder	Symptoms of bipolar disorder, but do not meet full criteria	• Short duration hypomanic episodes (2–3 days) and major depressive episodes • Hypomanic episodes with insufficient symptoms and major depressive episodes • Hypomanic episode without prior major depressive episode • Short duration cyclothymia (less than 24 mo)
Unspecified bipolar and related disorders	Patients with bipolar symptoms and clinical distress and impairment; however, the clinician chooses not to specify the reason that the criteria are not met	

Differential Diagnosis

Given the multitude of clinical manifestations, both a differential diagnosis between subtypes of mood disorders and mood and other psychiatric disorders is necessary. Table 3 presents comparisons and differences between subtypes of mood disorders and guidelines to the differential diagnoses.

Given the frequent overlap of anxiety and mood disorders, it is useful to inquire about the presence of anxiety disorder in a systematic manner. Anxiety disorder symptoms can also be classified into at least three major groups:

- Emotional symptoms: anxiety and/or fear, either fluctuating or in form of attacks
- Physical symptoms: palpitations, tachycardia, diaphoresis, sweaty palms, sensation of a knot in the throat, muscle tension, shortness of breath, GI symptoms, insomnia, etc.
- Cognitive symptoms: (a) intrusive thoughts (such as, "What if...," "I should have...," other specific exaggerated worries); (b) racing thoughts; (c) ruminative thoughts, etc.

Because of the long-term, chronic, egosyntonic nature of these symptoms, they are often not readily volunteered by the patient unless specifically asked about. Between mood disorders and anxiety disorders, there is a comorbidity of over 50% with generalized anxiety, panic disorders, and posttraumatic stress disorders constituting both a risk factor for and a possible complication of mood disorders. Please note that the DSM-5 allows for a specifier "with anxious distress" that can be applied to both unipolar and bipolar mood disorders. Depending on the primary diagnosis, the clinician may choose between adding this specifier or the comorbid separate diagnosis of "anxiety disorder" in addition to mood disorder.

Treatment

As a general rule, the treatment approach to mood disorders relies on the combination of psychopharmacology and psychotherapy. An accurate initial diagnosis directs the first choice of treatment. Close monitoring of treatment with frequent visits usually predicts better outcome. In general, response is considered to be a 50% reduction of symptoms, while remission refers usually to the absence or only minimal symptoms for 6 months or more. By Tohen and colleagues' opinion, relapse is considered a return of symptoms within 6 months, while recurrence is after 6 months of remission.

Treatment of Unipolar Depression (Major Depression and Dysthymia)

Given the fact that many depressive disorders occur along a spectrum, the treatment of major depression and dysthymia will be covered together.**

Psychopharmacology

First, a thorough medical work-up should be performed in any new case of mood disorder. The NIH-sponsored STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) recommends the initial choice of an SSRI (citalopram [Celexa]). In the study, nonresponders were then switched to sertraline (Zoloft) and/or venlafaxine XR (Effexor XR). In clinical practice, other factors have to be weighed when choosing the first antidepressant. Prior response history to a specific antidepressant or to an overall treatment modality should take precedence in the first choice of treatment. If such a history is unavailable, any family history of response to a specific treatment should be considered. Response to treatment seems to be similar among blood relatives. Table 4 includes a list of the more common medications used in clinical practice for the treatment of unipolar and bipolar disorder. Given the possibility of manic switch with antidepressants, it is recommended that in bipolar depression, mood stabilizers be started concomitantly with antidepressants.

Although a myriad of side effects are known to exist for each medication, all selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are generally well tolerated. Any trial of medications should be continued for 4 to 6 weeks before failure is declared. However, clinical judgment in assessing each circumstance, especially regarding suicide risk, is crucial. Often in the initial phase of response, the physical symptom of low energy remits first while cognitive symptoms of depression (persistent thoughts of death) persist. The coexistence of higher energy and thoughts of death may constitute a temporary suicide risk in the initial phase of antidepressant treatment. Currently, biological markers for the prediction of treatment response and side effects are being considered. Reference EEG (rEEG), renamed Psychiatric EEG Evaluation Registry (PEER), compares variations of normal awake EEG readings with a large database of medication responders. Results are available for antidepressants, mood stabilizers, stimulants, second-generation antipsychotics, etc. The AmpliChip CYP450 Test is a method that predicts side effects by measuring the activity of genes that control the P450 hepatic enzyme system and implicitly the ability to metabolize a specific drug. Both methods are promising, but high cost has so far prevented general use.

Given the risk of suicide, close monitoring during treatment of major depression is required. The choice of medication and adjustment has to be tailored according to the most dominant initial presentation. For patients with severe insomnia, an SSRI is indicated. If the initial choice (e.g., citalopram [Celexa], escitalopram [Lexapro], or sertraline [Zoloft]) shows little impact in improving sleep, the temporary addition of a sleep aid is a reasonable choice. Alternatively, some clinicians prefer to avoid hypnotics, which may allow close monitoring of the natural improvement in sleep during the first 2 weeks of SSRI treatment. This in turn may predict a good response. For many years, in patients with hypersomnia and hyperphagia—a variant known as "atypical depression"—the first choice was a monoamine oxidase inhibitor (MAOI). Currently, for atypical depression, clinicians prefer as a first choice a norepinephrine/serotonin reuptake inhibitor (venlafaxine [Effexor], desvenlafaxine [Pristiq]), or a norepinephrine/dopamine active medication (bupropion [Wellbutrin]). Response to medications is often difficult to predict. Again, early in treatment, a thorough medical work-up, which should always include a thyroid panel, should be the norm. Sometimes switches to other classes of antidepressants (dopamine enhancers, tricyclics) are necessary before a result is obtained. Pharmacologic augmentation with mood stabilizers, neuroleptics, and thyroid hormone has been used in cases of treatment-resistant depression. In cases where severe anxiety, insomnia, and poor appetite dominate the picture, the early addition of a second-generation neuroleptic (olanzapine [Zyprexa], quetiapine [Seroquel], risperidone [Risperdal],[1] and aripiprazole [Abilify]) is recommended. Medication resistance (after several failed trials) dictates the reassessment of diagnosis to further rule out psychiatric and medical comorbidity. For medication-resistant mood disorders, Table 5 presents a list of further biological treatments. Some of these treatments are promising, but have yet to be included as routine choices in some of the most difficult-to-treat patients.

Psychotherapy

For mood disorders, cognitive-behavioral and interpersonal psychotherapy have been considered therapies of choice. The former directly addresses the negative, pessimistic bias of the depressive thinking, which is a maintenance factor of depressed mood. The latter addresses social and interpersonal functioning by enhancing coping abilities. Their popularity has been increasing; however, they require special training and supervision. In clinical practice, though, the most readily available therapies remain supportive and insight-

**The newly introduced DSM-5 diagnosis, Disruptive Mood Dysregulation Disorder, is a condition of childhood and adolescence. Prior to the publication of the DSM-5, many of these patients were diagnosed as bipolar. Many clinicians prefer to initiate treatment with psychotherapy, which includes addressing a variety of family issues, before initiating psychopharmacological intervention. Premenstrual Dysphoric Disorder, also newly introduced in the DSM-5, is treated, depending upon the intensity of symptoms, by using protocols similar to those utilized in the treatment of dysthymic and/or cyclothymic disorders.

[1]Not FDA approved for this indication.

TABLE 3 Guidelines to the Differential Diagnoses

DIAGNOSIS	SIMILARITIES	DIFFERENTIATING DETAILS	CLINICAL CLUES	TREATMENT RESPONSE
Major depression (MDD) versus persistent depressive disorder (dysthymia) (PDD)	Depressed mood; depressive cognition (pessimism); vegetative symptoms (physical)	MDD: Acute or subacute onset; possible recent life stressors; often more numerous symptoms PDD: May overlap with MDD; chronic, fluctuating course	MDD: Usually a marked drop in functionality PDD: Significant chronic impairment; often symptoms are ego-syntonic; "personality disorder" flavor	MDD: Antidepressants and/or initial antianxiety medications; consider psychotherapy PDD: Cognitive- behavioral psychotherapy; antidepressants (often long term); sometimes enhancement pharmacology
Mixed mania versus agitated depression	Psychomotor agitation; dysphoria; mood swings	Mixed mania: Labile affect; often rapid switch with brief euphoric states Agitated depression: No euphoric states; severe anxiety, including sympathetic symptoms	Mixed mania: Personal and family history Agitated depression: Anxiety symptoms, often subtle, precede depressive symptoms	Mixed mania: Mood stabilizers; caution regarding antidepressants: can cause worsening Agitated depression: Antidepressants and sedating mood stabilizers; avoid long-term tranquilizers
Mania versus cyclothymia	Intermittent states of high energy and euphoria with or without recurrent depression	Mania: Distinct states of high energy; depression is sometimes unnoticed Cyclothymia: Distinct cycling from depression to hypomania	Mania: More often severe insomnia without fatigue; severity of mania and insomnia directly related Cyclothymia: May take unpredictable forms; fluctuation of mood and sleep	Mania: Mood stabilizers; caution about antidepressants; atypical antipsychotics if needed Cyclothymia: Same as above, according to clinical judgment
Substance abuse disorder versus cyclothymia	Intermittent use of stimulant abuse may mimic cycling mood disorder; may coexist	Substance abuse: Substance abuse tends to escalate Cyclothymia: Cyclothymia may remain constant for years (even lifelong)	Substance abuse: Look for specific syndromes; drug screen Cyclothymia: Negative drug screens; no withdrawals; no drug culture history	Substance abuse: Rehabilitation; treat underlying psychiatric symptoms Cyclothymia: Mood stabilizers and/or antidepressants and/or atypical antipsychotics
Personality disorder versus mood disorder	More often overlap; requires concomitant treatment	Personality disorder: Long-term pervasive history since adolescence Mood disorder: More often episodic	Personality disorder: Borderline personality disorder includes mood lability/depressive episodes; often narcissistic personality, includes grandiose/ hypomanic states Mood disorder: More often symptoms are egodystonic	Personality disorder: Acute decompensation; long-term psychotherapy; mood stabilizers; atypical antipsychotics Mood disorder: See treatment of mood disorders
Bereavement versus MDD	May overlap; attention to recent major loss; sometimes similar picture; bereavement and MDD may co-occur	Bereavement: Tends to improve over time MDD: Tends to worsen over time	Bereavement: Preoccupation with loss persists MDD: Duration of average major depressive episode is 9 mo	Bereavement: Social support; grief counseling; psychotherapy; if MDD present, treat as MDD MDD: See treatment of MDD
Primary mood disorder versus mood disorder arising from medical condition	Clinical picture may be identical	Primary mood disorder: May be triggered by external stressful events Medical condition: Often onset is insidious; sometimes precedes medical condition	Neurological, endocrine, infectious, systemic, and blood disorders*	Treat both primary medical condition and mood disorder; treatment same as for primary mood disorder

*Medical conditions complicated by mood disorders: Addison's disease, AIDS, anemia, brain tumors, chronic pain, complex partial seizures, Cushing's disease, CVA, dementia, diabetes mellitus, encephalitis, head trauma, hepatitis, hyperparathyroidism, hyperthyroidism, hypopituitarism, hypothyroidism, infectious mononucleosis, influenza, lupus erythematosus disseminatus, meningitis, multiple sclerosis, pneumonia, porphyria, rheumatoid arthritis, scleroderma, sleep apnea, toxoplasmosis, and others.

TABLE 4 Medications Used for the Treatment of Unipolar and Bipolar Depression

MEDICATION GROUP	MEDICATION	USUAL DAILY DOSE	CAUTIONS
SSRI	Fluoxetine (Prozac)	10–80 mg	All can cause sedation, agitation, insomnia, GI side effects, sexual dysfunction
	Sertraline (Zoloft)	25–200 mg	
	Paroxetine (Paxil)	5–60 mg	
	Citalopram (Celexa)	10–40 mg	
	Escitalopram (Lexapro)	5–20 mg	
	Fluvoxamine (Luvox)[1]	100–300 mg	
SSRIs with combined action	Vilazodone (Viibryd) Functions of SSRI and a 5-HT_{1A} Receptor Agonist	10–40 mg 5–20 mg	Same as above
	Vortioxetine (Brintellix) Functions of SSRI and multiple Serotonin Receptor Agonists and Antagonist		
NSRI	Venlafaxine XR (Effexor XR)	37.5–225 mg	Insomnia, sedation, possible HTN Mydrasis, urinary hesitation
	Desvenlafaxine (Pristiq)	50–100 mg	
	Levomilnacipran ER (Fetzima)	40–120 mg	
Dopamine/norepinephrine agonist	Bupropion SR, XL (Wellbutrin SR, XL)	100–450 mg	Agitation, GI side effects, possible HTN
Stimulants (usually used to enhance effects of other antidepressants)	Methylphenidate (Ritalin)[1]	10–60 mg	Agitation, insomnia, psychosis, HTN, seizures
	Dextroamphetamine (Dexedrine)[1]	5–60 mg	
	Amphetamine/dextroamphetamine mixed (Adderall)[1]	5–60 mg	
Second-generation neuroleptics	Olanzapine (Zyprexa)	2.5–20 mg (in unipolar depression, olanzapine 5 mg, plus fluoxetine 20 mg [Symbyax])	Metabolic syndrome, sedation
	Quetiapine (Seroquel)	50–300 mg (up to 800 mg in bipolar disorder)	Over-sedation, metabolic syndrome, cardiovascular complications in elderly
	Aripiprazole (Abilify)	2–30 mg	Oversedation, metabolic syndrome, hyperprolactinemia
	Risperidone (Risperdal)[1]	0.5–6 mg	
Tricyclic antidepressants	Amitriptyline (Elavil)	50–300 mg	All can cause anticholinergic effects, sedation; occasional agitation, weight gain
	Imipramine (Tofranil)	50–300 mg	
	Doxepin (Sinequan)	50–300 mg	
	Desipramine (Norpramin)	50–300 mg	
	Nortriptyline (Pamelor)	20–200 mg[3]	
	Maprotiline (Ludiomil)	100–225 mg	
	Protriptyline (Vivactil)	20–60 mg	
Mixed action (presynaptic and postsynaptic, multiple neurotransmitter action)	Mirtazapine (Remeron)	15–30 mg	Sedation, weight gain
	Trazodone (Desyrel)	150–600 mg	
	Clomipramine (Anafranil)[1]	50–300 mg[3]	
MAOI (Dietary restrictions are obligatory)	Phenelzine (Nardil)	15–90 mg	Hypertensive crisis, occasional sedation/activation
	Tranylcypromine (Parnate)	30–60 mg	
Mood stabilizers	Lithium Carbonate/Citrate/ER[1]	600–1800 mg (attaining blood level from 0.6–1.2 mEq/L)	Signs of toxicity: tremor, nausea, vomiting, staggering gait; monitor kidney and thyroid function
	Valproate (Valproic Acid, Depakote ER)[1]	250–1500 mg (attaining blood level from 50–100 mcg/ml)	Oversedation, GI side effects, may affect blood levels of other medications, weight gain
	Lamotrigine (Lamictal)/ER[1]	50–300 mg	A variety of severe skin rashes, Stevens-Johnson syndrome
	Carbamazepine (Tegretol)[1]	200–1000 mg (attaining blood level from 5–12 mdg/mL)	Monitor blood count for aplastic anemia/agranulocytosis, possible Stevens-Johnson syndrome, sedation

[1]Not FDA approved for this indication.
[3]Exceeds dosage recommended by the manufacturer.
Abbreviations: ER = extended release; GI = gastrointestinal; HTN = hypertension; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor.

TABLE 5 Biological Treatments for Medication-Resistant Mood Disorders

TYPE OF INTERVENTION	REPORTED RESPONSE	CURRENT AVAILABILITY
Electroconvulsive therapy (ECT)	50.9%–53.2% remission rate	Common
Transcranial magnetic stimulation (TMS)	41.5%–56.4% response rate, 26.5%–28.7% remission rate	Rare
Vagal nerve stimulation (VNS)	53% response rate, 33% remission after 1 year	Rare (neurosurgical)
Deep brain stimulation (DBS)	29% response rate at 1 year	Rare (neurosurgical)
Ketamine (Ketalar) infusion[1]	79% response rate	Very rare (only in selective institutions)
Anterior cingulotomy	33.3% response rate, after 30 mo	Very rare (only in selective institutions, neurosurgical)

[1]Not FDA approved for this indication.

oriented psychotherapy. They too complement the effect of pharmacology. Brain imaging studies have revealed that the activity of the subgenual anterior cingulate cortex (Brodmann area 25) predicts the outcome of response to cognitive-behavioral psychotherapy in depression. As a general rule, therapies should have specific goals that need to be discussed with patients at onset of treatment. This needs to be part of an overall "informed consent" approach to treatment. Given the availability of a variety of clinicians with different levels of expertise that provide psychotherapy, it is important to monitor results and coordinate care. If "split" treatment (pharmacology and psychotherapy provided by different clinicians) is chosen, communication between parties of the treatment team remains a crucial requirement for rapid response and recovery. Other therapeutic measures, such as an increase in physical activity, normalization of sleep, and improvement of social support, are particularly important in promoting recovery.

Treatment of Bipolar Disorders (Bipolar Type-I, Type-II, Mixed Type, and Cyclothymia)

The treatment of bipolar disorder has been well refined over the years by a large body of literature. For acute mania, the treatment with mood stabilizers and/or antipsychotics has remained the main approach for the past several decades. Severe forms of mania and psychosis usually require hospitalization. Table 6 indicates intervention options for different phases of bipolar disorder.

As indicated in the table, some of the medication choices overlap between different clinical presentations. For chronic forms of bipolarity, such as mixed bipolar and cyclothymic disorder, a variety of new approaches has been developed, including social rhythm therapy. The latter includes monitoring and optimization of social interactions, sleep, and circadian rhythms that seem to benefit bipolar patients. Chronic bipolarity, with its significant impairment and suicide risk, remains a major problem, often requiring multidisciplinary consultations and referral to a tertiary institution. In treatment-resistant cases, employment of electroconvulsive therapy and other novel biological approaches can be lifesaving. Even with partial treatment response, maintenance is paramount. Lifelong maintenance treatment is likely to prevent suicide and further functional deterioration. More recently, suicide prevention both in chronic mood disorders and/or personality disorders has been reported with maintenance treatment of lithium carbonate and clozapine (Clozaril).[1]

TABLE 6 Intervention Options for Phases of Bipolar Disorder

PHASE OF DISORDER	INTERVENTIONS
Acute	Hospitalization if necessary Antipsychotics, tranquilization, start mood stabilizers
Subacute	Antipsychotics/neuroleptics, mood stabilizers If already medicated, adjust dose
Rapid cycling/mixed	As in acute phase; check thyroid; medical work-up Rule out substance abuse May require treatment indefinitely
Cyclothymia	Mood stabilizers, long-term, with or without antidepressants based on history Close initial monitoring May need treatment indefinitely

Mood Dysregulation

Mood dysregulation is a broad phenomenon encountered both in clinical and nonclinical settings. For clinicians, a variety of difficult-to-classify syndromes remain relevant (referred to here as "mood syndrome variants"). These mood syndrome variants present anecdotal but clinically pertinent manifestations collected from the medical literature of the past century. Psychiatric and medical disorders often coexist with different degrees of mood dysregulation. A more detailed description of each clinical entity in Table 7 is beyond the scope of this chapter. As seen from the table, different forms of mood dysregulation can occur both within and outside DSM diagnoses. For instance, atypical depression has been included in the DSM whereas other syndromes, such as neurasthenia, remain unclassified. When encountered, any of the listed syndromes should raise suspicion of an underlying mood disorder. A diagnosis of "unspecified depressive disorder" (311) can be made, and the entire mood disorder treatment armamentarium should be considered.

Clinical Course and Prognosis of Mood Disorders

Given the heterogeneity of mood disorders, there is great variation in clinical outcome. Clinical course and outcome depend on whether treatment was available, whether an individual is sensitive or resistant to the treatment, and the degree of compliance. Many individuals with mild and subsyndromal disorders remain undiagnosed, whereas others with severe forms of mood disorders refuse treatment. As a general rule, most untreated mood disorders tend to become chronic. Episodic disorders, such as bipolar I and II and depression, recurrent type, may show more frequent recurrences with advancement in age. Other patients with hyposymptomatic presentations and infrequent episodes may show long-term remissions. Such remissions are favored by stable, low-stress lifestyles. Table 8 demonstrates the severe impact on life expectancy

[1]Not FDA approved for this indication.

TABLE 7 Examples of Mood Syndrome Variants (MSV) with Different Degrees of Mood Dysregulation as Encountered in the Literature over the Past Century

I MSV WITH MANIFESTATIONS OF OTHER PSYCHIATRIC DISORDERS	II MSV WITH UNUSUAL SYMPTOMS (MASKED DEPRESSION)	III MSV AS PART OF OTHER CONDITIONS
Atypical depression	Mood dysregulation and thrill-seeking behavior (gambling, racing, substance abuse, hypersexuality)	Postpartum depression
Subaffective dysthymia	Reactive overeating	Depression secondary to chronic pain
Hysteroid dysphoria	Isolated sleep disturbance and mood dysregulation	Substance- and medication-induced mood dysregulation*
Pseudodementia	Atypical facial pain	"Organic" mood disorders (due to CNS disorders)
Pseudoborderline	Dysphagia	Vicarious traumatization†
Somatic depression	Monosymptomatic hypochrondriasis	
Underground depression	Monosymptomatic delusions	
Neurasthenia		
Mood syndrome as part of personality disorders		
Mood syndromes and depression in schizophrenia		

Source: Novac and Djenderedjian, unpublished data.
*Medications more often associated with depression are, among others are: Reserpine, alpha-methyldopa (Aldomet), some alpha- and beta-blockers, sedative hypnotics, cimetidine (Tagamet), indomethacin (Indocin), anticancer medications, oral contraceptives, and corticosteroids.
†It has been described as a form of secondary trauma in mental health professionals who treat victims of trauma.

TABLE 8 Causes of Mortality in Patients with Bipolar Disease: Index Group Compared to the General Population

CAUSE OF DEATH	OBSERVED DEATHS (% STUDY GROUP)	EXPECTED DEATHS (% REGISTRAR GENERAL'S* FIGURES)	MORTALITY RATIO (ACTUAL STUDY)
Suicide	15.7	0.67	23.4
Cardiovascular system	42.1	14	3.0
Respiratory system	33.3	1.08	30.8

Data from Sharma and Markar (1994).
*Edinburgh Registrar General's Office.

of bipolar disorder. Mortality comes from suicide, cardiovascular disease, and respiratory disorders. However, treatment can at least partially reverse these trends.

Prevention

Primary prevention of mood disorders requires a concerted effort to educate the public and policymakers for funding of prevention. "Depression Awareness Week" and other community efforts enhance awareness and decrease stigma. Primary prevention may also include the promotion of general health and healthy work environments and addressing of major social problems, including the avoidance of early trauma and family problems as well as prevention of excessive stress and trauma in adults. These are all known to be associated with mental illness. Populations at risk need to be identified in primary care settings. Secondary prevention requires availability of mental health services, including early detection, education about the need for adequate treatment, and continuity of care to prevent impairment. Tertiary prevention would include continuation of treatment to prevent comorbidity of other psychiatric disorders and catastrophic complications, including suicide. Finally, in the case of mood disorders, quaternary prevention would include long-term follow-up, monitoring of recurrences, and medical comorbidity (accidents, cardiovascular, respiratory, and other medical conditions), to avoid the overburdening of the health system.

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PANIC DISORDER

Method of
Cheryl Wehler, MD

CURRENT DIAGNOSIS

- Panic disorder (PD) is characterized by the presence of multiple untriggered panic attacks.
- These unexpected panic attacks are associated with significant anticipatory anxiety and/or changes in behavior to minimize the consequences or avoid another panic attack.
  - Patients worry about being negatively judged due to visible panic symptoms.
  - Patients worry about dying or "going crazy."
- The panic attacks are not attributable to another medical condition or to the effects of a substance (medication or drug of abuse).
- The panic attacks are not better explained by another mental disorder.
- Patients frequently present with concern about somatic symptoms (e.g., fear of heart attack because of shortness of breath and chest discomfort).
- Assess patients for suicidality, as suicide risk increases with panic attacks or recent diagnosis of panic disorder.

CURRENT THERAPY

- Pharmacology and psychotherapy are effective treatments for PD.
- Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and benzodiazepines have demonstrated efficacy for the treatment of PD.
- The favorable safety profile of SSRIs and SNRIs make them first-line monotherapy agents.
- While TCAs are effective, their side effects and greater toxicity in overdose limit their clinical utility.
- Monoamine oxidase inhibitors (MAOIs) also appear effective but are reserved for patients who are nonresponders to multiple first-line treatments because of their safety profile limitations.
- Benzodiazepines are not first-line monotherapy but are useful adjuncts to antidepressants if residual anxiety requires additional treatment.
- While the more rapid response of benzodiazepines (compared with SSRIs/SNRIs) make them attractive, the inevitable physiological dependence make them less so.
- Patients with PD can be sensitive to medication side effects; therefore, the adage "start low and go slow" is applicable to dosing.
- Cognitive behavioral therapy (CBT) or CBT with medications are first-line treatments for children and adults with PD.

Epidemiology

The 12-month prevalence estimate for panic disorder (PD) in the general population of the United States and Europe is approximately 2% to 3% in adults and adolescents. Non-Latino Caucasians and Native Americans have significantly higher rates than Latinos, African Americans, and Asian Americans. Adolescent and adult females are approximately twice as likely as males to be affected (although the clinical features of PD do not differ between males and females). The prevalence is highest in adult females. Prevalence rates decline in older individuals. The overall prevalence of PD is low in children (<14 years). PD is associated with the highest number of medical visits among all anxiety disorders.