Major Depressive Disorder (DSM-IV-TR #296.2–296.3)

Major depressive disorder, or as it is often called, "major depression," is characterized by the presence of one or more depressive episodes during the patient's lifetime. Typically, a depressive episode lasts anywhere from months to years, after which most patients are generally left again in their normal state of health. Although some patients may have only one episode during their lifetime, the majority have two or more. Thus major depression is a periodic, or cyclic, illness with the patient "cycling" down into, and then up out of periods of depression. Exceptions, however, do occur. For example, in a minority of cases the depressive episode may be chronic, and an episode once begun may persist throughout the patient's life.

Synonyms for this disorder include unipolar affective disorder; melancholia; and manic-depressive illness, depressed type. "Unipolar" highlights the critical difference between major depression and bipolar disorder, namely the fact that the patient with major depression cycles in only one direction, toward the depressive "pole," in contrast to the patient with bipolar disorder, who cycles at times not only to the depressive pole but also at other times to the manic pole. "Melancholia" is the most ancient term for this disorder, coming to us from the Greek, meaning black bile. However, over the centuries its meaning has changed, and hence it remains open to misinterpretation. "Manic-depressive illness, depressed type," is perhaps the least satisfactory of these synonyms. Kraepelin, as best as can be made out, felt that patients with only recurrent depression and those with both episodes of depression and episodes of mania had in fact the same illness, which he called "manic-depressive insanity." Later clinicians, recognizing that this was probably not the case, separated the "depressed" type of "manic-depressive illness" from the "circular" type; however, this continued to cloud the fundamental distinction between these two groups of patients. Currently, at least in the United States, when one speaks of manic-depressive illness, most often one is referring to bipolar disorder, and, at least for now, this developing convention should probably be honored, and the term "manic-depressive illness, depressed type," should probably be left in the history books.

Major depression is a common disorder. Prevalence figures vary according to methodology, but at least 5% of the general adult population has this disorder. Given, however, the relapsing and remitting nature of the depressive episodes, a lower percentage of the population is actually in the midst of a depressive episode at any given time. Again, estimates vary, with point prevalence figures ranging anywhere from 2 to 5%.

Amongst adults, major depression is seen twice as frequently among women as men; however, among children the sex ratio is equal.

ONSET

Although the first depressive episode generally occurs in the mid-twenties, not uncommonly the first episode is seen in adolescence or, on the other extreme, in old age. Indeed in rare instances the onset may be seen in early childhood or as late as the ninth decade.

Most depressive episodes appear gradually and insidiously. Typically, a long prodrome occurs, sometimes lasting months or in rare instances years, characterized by indefinite and at times fleeting symptoms such as moodiness, anxiety, or fatigue. Furthermore, when depressive symptoms finally do settle in, their several severities accrue and worsen often haltingly or imperceptibly, and it is the rare patient who can date the onset with any precision. This is not to say that acute onsets are never seen. To the contrary, they do occur, and some patients describe a rapid fall from emotional well-being into a depressive episode in as little as a few weeks. Such acute onsets of depressive episodes, however, are the exception rather than the rule for major depression.

In major depression a stressful life event, typically a serious loss, not uncommonly precedes and apparently triggers a depressive episode. Examples include the death of a loved one, divorce, the loss of a job, and the like. At times, however, close inquiry may reveal that the stressful life event, rather than actually precipitating the depressive episode, was to the contrary itself caused by the depressive episode. For example, a married patient in the midst of a prodrome may be sufficiently irritable to cause the spouse to leave. Here the patient may blame the depression on the separation; however, it appears that the depression itself led to the separation. In that group of patients where an independent precipitating stress occurs, subsequent episodes tend to become independent and autonomous and occur whether there is a stressor or not.

CLINICAL FEATURES

From a clinical point of view the core symptoms of a depressive episode include the following: depressed mood; loss of energy; difficulty with concentration and short-term memory and decision making; loss of interest in heretofore pleasurable activities; insomnia or, less commonly, hypersomnia; anorexia and weight loss or, less

commonly, hyperphagia and weight gain; psychomotor agitation or, less commonly, retardation; and, finally, a pessimistic outlook that is often accompanied by suicidal ideation. Not uncommonly, patients also describe a diurnal variation in their symptoms: they feel markedly worse in the morning and experience some degree of relief as the afternoon or evening comes on. In the following paragraphs each of these symptoms is discussed in some detail.

Mood is depressed or sometimes irritable. Some patients may complain of anxiety, and irascibility may occur. Some, however, despite a dejected facial expression, may deny

feeling depressed at all. Rather they may speak of a sense of discouragement, or complain of a sense of lassitude or heaviness, of being weighted down. The patients' affect generally reflects their mood. The facial musculature may sag lifelessly; they may have copious tears. At other times, particularly in anxious patients, a "pained" facial expression is evident, and occasionally one may see the classic "omega sign" of depression wherein the brow is so peculiarly furrowed and pinched as to create the Greek letter omega on the forehead, arising up from between the eyes. Some patients may attempt to hide their mood by feigning a cheerful affect, thus presenting the so-called smiling depression.

Energy is lacking. Patients complain of feeling tired, fatigued, lifeless, or drained. The exhaustion may at times be so extreme that patients are unable to complete their chores or even dress themselves. Occasionally a patient may complain of too much energy; however, on close questioning, a "nervous energy," akin to agitation, is apparent. This energy is useless to the patient and is always shadowed by a sense of imminent and impending exhaustion.

Thinking becomes difficult; patients complain of difficulty concentrating, remembering, or in making decisions. A dull, heavy-headedness, "like a fog," impairs the patient's ability to concentrate. Memory fails, and patients are unable to recall where they put things or what was said earlier in the day. Attempts to read or watch television may end in miserable failure. The same paragraph may be read again and again, without the patient being able to grasp its meaning or recall what had just preceded. Making decisions, even simple ones, may become an insuperable task. Everything appears too complicated to the patient, with too many options and possibilities. In severe cases patients may be unable to decide what shirt to wear and may remain in front of their closet until someone else makes the decision for them.

Patients lose interest in former things and have no curiosity for what is new in life. They take no pleasure in their activities; nothing arouses them. Libido is diminished. They must force themselves to do what they formerly enjoyed doing, and they go about their day lifeless and desolate.

Insomnia is common, and may be a particular torment to the patient. Although many complain of what is technically known as initial insomnia, or trouble falling asleep, the most characteristic kind of insomnia comes later in the night as either middle insomnia or early-morning awakening. In middle insomnia the patient awakens for no apparent reason and then has difficulty falling back asleep, lying awake for an hour or more until sleep finally returns. Early-morning awakening comes later in the night; here the patient awakens well before the customary hour and then cannot fall back asleep at all. Many, as they lie awake, experience ruminations or racing, restless thoughts. Finally, when morning comes, patients arise unrefreshed, exhausted, as if they had not slept at all. Rarely, patients with major depression complain of hypersomnia; however, as is noted in the section on differential diagnosis, this symptom should always raise the possibility of bipolar disorder.

Appetite is routinely lost, and many patients lose weight, sometimes in substantial amounts. Food may lose its taste or become unpalatable. Patients may complain it tastes like cardboard or that it leaves them nauseated. Some force themselves to eat; however, others do not and may lose 10 to 30 or more pounds. Uncommonly, some patients complain of increased appetite and weight gain, at times of substantial degree. As with hypersomnia, however, this is somewhat more common in bipolar disorder.

Constipation is common. Patients may also complain of headaches and myalgia. In severe cases the body temperature may fall, and menstruation may cease. The patient may appear to have aged precipitously: the skin appears dry, roughened, and wrinkled; the hair loses its luster, and the eyes appear dull. The overall effect may be shocking to an acquaintance who has not seen the patient since before the onset of the depressive episode.

Psychomotor agitation or, less commonly, retardation may be seen. Agitation, when slight, may be confined to a certain inner restlessness. When more severe, hand-wringing and nervous pacing about may occur. Patients complain of being unable to keep still; they may lament their fate out loud, and some may give way to wailing and repetitive pleas for help. The tension of these patients may be extreme, almost palpable, and yet, despite their pitiful pleas for help, they cannot be comforted, no matter what is done for them. Some may loudly berate themselves over and over again, confessing and accusing themselves of the worst sins and derelictions. Some may beg to be put out of their misery.

If psychomotor retardation occurs, the patient, drained of all vigor, may slip into a torpor. Speech, when it occurs, is slow and halting, and in some cases may cease altogether as if the effort to go on were simply too great. Some patients may sit immobile for hours; efforts to take them to the bathroom or to meals may be met with reluctance, even irritation. Left undisturbed, they may neither bathe nor change clothes, even though they may have defecated or urinated on themselves.

The attitude and outlook of these patients may become profoundly negative and pessimistic. They have no hope for themselves or for the future. They see no way out. Self-esteem sinks, and the workings of conscience become prominent. Patients see themselves as worthless, as having never done anything of value. Rather they see their sins multiply before them. Indeed, in reviewing their past they seem blind to their accomplishments and fix only on their misdeeds or shortcomings, which, as they recall them, become magnified at times to heinous proportions. Some may begin to ruminate: failings, defects, and gloomy predictions of the future may repeat themselves again and again in an implacable litany.

Thoughts of suicide are almost always present. At times these may be passive, and patients may wish aloud that they might die of some disease or accident. Conversely, they may be active, and patients consider hanging or shooting themselves, jumping from tall buildings, or overdosing on dangerous medicines. Often the risk of a suicide attempt is greatest as patients begin to recover. Still seeing themselves as worthless and hopeless sinners, these patients, now rising from their fatigue, may have enough energy to carry out the plan. Tragically, some also take their families with them. In their profound pessimism, they may see family members as equally hopeless, and take their lives to spare them their misery.

In addition to these core symptoms of depression some patients have panic attacks. Others may experience obsessions or compulsions. A particularly common

compulsion is the "horrific temptation" to use a knife or gun to kill a loved one, and a consequent overwhelming necessity to rid the house of such objects and to avoid coming into contact with them outside the house.

A minority, perhaps 15%, of depressive episodes are characterized by delusions or hallucinations. Typically, these episodes are severe, with prominent psychomotor change. Those inclined to agitation may wail ceaselessly, pacing agitatedly about their room, begging for deliverance. Those who develop psychomotor retardation may fall into a profound stupor. They may lie immobile for hours or days, mute, at times incontinent, seemingly lifeless. Consciousness is clouded, and upon recovery some patients may not be able to recall their experiences during this time.

The delusions are mood congruent in that they are in some fantastic, extreme way appropriate to the patients' mood and to their view of themselves. Guilt becomes extreme, and patients may confess to unspeakable, impossible sins. They have poisoned their children; family and friends are imprisoned for some crime the patient committed. They believe they are condemned to hell; they have only hours to live; death is deserved and is near. Persecutory delusions are also common and have a peculiar twist to them. Here patients fully believe that they deserve such persecution for their miserable sins and shortcomings. Neighbors whisper about them as they leave the house; the police have been alerted; a warrant is drawn up; the electric chair is readied; a trial is not necessary, for their guilt is self-evident.

Delusions of poverty and nihilistic delusions may occur and are consonant with patients' view of themselves as worthless and hopeless. They are without funds; bills cannot be paid, and the family will be destitute. Having them look at a favorable bank statement is to no avail; they know more bills are due, that it is a fraud. Allied with these delusions of poverty are nihilistic delusions. Patients believe themselves either dead or near death; their insides have turned to dust or concrete; their brains have shriveled; the heart has dried up for lack of blood. In extreme cases patients may assert that they are in fact dead. In other cases they may insist that everyone about them is dead. Death has covered the world leaving only robots or automatons.

Auditory hallucinations may occur and generally reflect the patients' delusions. Voices may accuse them or announce their execution. They may hear the hum of the electric chair as it is readied for their execution. Visual hallucinations, though less common, also occur. Beheaded corpses may appear. Olfactory, gustatory, and tactile hallucinations are rare. Some may smell rotting flesh.

All the foregoing descriptions apply most particularly to adults. The presentation of a depressive episode in childhood years or later years or in those with mental retardation may be somewhat different. In prepubertal children one of the first indicators of depression may be a lack of weight gain. One may also see irritability. Some children may also develop severe anxiety over the prospect of being separated from their parents, and they may have numerous complaints of headaches, stomachaches, and general malaise. Among adolescents serious misconduct may appear. Rebelliousness and irritability may be seen. Grades fall as concentration is impaired, and patients may fall in with others who have a conduct disorder and adopt their attitudes and behavior. Among the elderly, agitation and hypochondriacal concerns

are common, and indeed the patient may deny feeling depressed at all. Memory and concentration may be so impaired in the elderly that a dementia occurs. In the past this has been called a "pseudodementia," presumably to distinguish it from other kinds of dementia. However, a better, more recent term is "dementia syndrome of depression." Mentally retarded patients may be unable to describe their mood or how they view themselves. Hence the presentation may be with unexplained weight loss, insomnia, agitation, and other signs.

Recently, much attention has been focused on patients whose affective episodes seem entrained to the changing seasons. Patients with major depression who exhibit this seasonal pattern tend to have their depressive episodes in fall or winter and seem more likely to have hyperphagia and hypersomnia. It must be kept in mind that, although a major depression may exhibit a seasonal pattern, such a seasonal pattern is more commonly found in bipolar disorder.

COURSE

Major depression is a relapsing and remitting illness, characterized in most patients by the recurrence of depressive episodes throughout life, in between which the patient remains more or less in a normal state of health.

In perhaps one-half of cases, the depressive episode gradually undergoes a full remission within 6 to 12 months; in the remainder one sees either a partial remission or a persistence of the full syndrome. Overall, however, the long-term outlook for a given episode of depression is good, with less than one-tenth of episodes persisting in full form past two years.

After the first episode of depression has remitted, it is difficult to predict when the next is destined to occur: in some patients, it may appear in less than a year whereas, on the other extreme, in some patients the next episode may not be destined to occur until after the patient dies of some unrelated cause, thus perhaps accounting for those cases wherein only one depressive episode is seen in the patient's entire life. Despite this wide variability, it does appear that, on average, the interval between episodes is about five years. Over time, however, and with repeated occurrences of episodes, this interval becomes shorter, and the duration of the episode longer, until, in some cases, after many years, the episodes "merge" to create a chronic depression.

COMPLICATIONS

Work performance typically declines. Fatigue and lack of interest leave patients falling behind, and difficulty with memory, concentration, and decision making impair their ability to complete any task they may attempt. Patients may miss promotions, be put on notice, or even be fired. Children and adolescents do poorly in school for similar reasons and, as noted earlier, become at risk for drifting down toward those whose misconduct may then become a compelling pattern for the patient.

Relations with family and friends typically suffer. Parents may be unable to care for children. Marital discord is common, and separation or divorce may occur.

"Self-medication," typically with alcohol or benzodiazepines, is relatively common, and in those so predisposed may occasion a pattern of abusive use or may result in substance dependence.

Faulty, regrettable decisions are not uncommon. Convinced of their pessimistic outlook patients may decide against taking offered opportunities, or may withdraw from a current enterprise that to them now seems doomed.

Those with other illnesses may lose hope in recovery from those illnesses and stop their medicines or withdraw from treatment, thus occasioning further suffering.

The overall suicide rate in major depression is about 4%; among hospitalized patients, however, the risk rises to 9%.

ETIOLOGY

Major depression appears in part to be inherited. Among the first-degree relatives of patients with major depression, the prevalence of major depression is some two to three times higher than among the first-degree relatives of normal controls. Furthermore, whereas the concordance rate for dizygotic twins is about 20%, the rate for monozygotic twins rises to about 50%. Adoption studies further support a role for heredity in major depression. Despite these findings, however, genetic studies have not as yet identified any loci or genes which can be confidently associated with this illness, indicating that in all likelihood major depression is genetically complex, involving not only multiple genes, but also possibly multiple modes of inheritance.

Abnormalities in the hypothalamic-pituitary axis are clearly present in major depression, and the great majority of patients will demonstrate non-suppression on the dexamethasone suppression test, blunting of the TSH response to TRH or blunting of the growth hormone response to clonidine. DST non-suppression has been most extensively studied, and it is clear that this is related to hypothalamic changes: the concentration of corticotrophin releasing factor (CRF) in the hypothalamic paraventricular and supraoptic nuclei is elevated, and the response of ACTH to exogenous CRF is blunted, as would be expected with chronic over-stimulation of the pituitary by endogenous CRF. In a similar vein, it appears that the blunted TSH response to TRH is also likely related to hypothalamic changes, as the CSF concentration of TRH is elevated in depressed patients.

Abnormalities of sleep architecture, as might be expected, are also present, and of these the most interesting is a shortened REM latency. REM sleep, in normals, may be induced by the infusion of cholinergic agents, and patients with major depression exhibit an enhanced sensitivity to two cholinergic agents, arecoline and donepezil, with a prompter onset of REM sleep after infusion.

Neuroanatomic abnormalities may or may not be present in major depression: as yet MRI studies have not yielded conclusive results. PET studies have generally indicated bilateral hypofrontality, which, in some studies, has been more pronounced on the left side.

The undoubtable success of various antidepressants has focused attention on the biogenic amines: given that all antidepressants have effects on either noradrenergic or serotoninergic functioning, it appears reasonable to assume that there is a complementary disturbance in these amines in patients with major depression. Despite enormous research effort, consistent findings implicating these amines have been difficult to obtain. One exception is the finding that, in patients with major depression currently in an SSRI-induced remission, a depletion of tryptophan, the dietary precursor of serotonin, is generally followed by a rapid relapse of depressive symptoms.

Inheritance, though of great importance in major depression, cannot account for all cases, and environmental factors are clearly important. Among the various factors postulated, it appears that early childhood loss may be the most important. Significant loss, as for example through death or divorce, also appears important as a precipitant for episodes in adult life. The importance of precipitants, however, tends to wane with successive episodes, such that after repeated episodes, little or nothing by way of a precipitant may be required for the next episode to make its appearance.

Integrating the foregoing etiologic factors into a coherent theory is problematic, and typically involves some speculation. With this caveat in mind, however, it appears reasonable to say that major depression is characterized by an inherited abnormality of noradrenergic, serotoninergic or cholinergic functioning, of variable degree, in the hypothalamus (or related limbic structures) and certain brainstem structures (such as the noradrenergic locus ceruleus, the serotoninergic dorsal raphe nucleus and the cholinergic pedunculopontine nucleus), which, though spontaneously reversible early on, eventually becomes permanent with repeated episodes. It also appears plausible to say that the experience of loss in childhood or adult years may exacerbate this inherited abnormality, or even possibly, in some cases, cause it, but that once these abnormalities appear, that they persist.

DIFFERENTIAL DIAGNOSIS

In the normal course of life, adverse events, especially losses, are followed by depressive symptoms. A common example is bereavement following upon the death of a loved one. At times, however, especially when these symptoms are severe or long lasting, the clinician is asked to decide whether the patient is still in the midst of a "reactive" depression, that is to say a "normal" reaction to the event, or whether the event has precipitated a depressive episode that would perpetuate symptoms long after the patient would "normally" have recovered and "gotten over it." Four differential points aid in this distinction. First, consider whether the severity of the symptoms is out of proportion to the event. Severe symptoms are to be expected after the death of a child, but not after failing to win a promotion. Second, consider the duration of symptoms. Assuming that the adverse event is not ongoing, a duration beyond 6 months and certainly beyond a year is highly suggestive that another process has supervened. Third, be alert to symptoms that, though not uncommon in a depressive episode, are unusual for a "normal" or "reactive" depression, such as severe and unremitting guilt and self-deprecation; profound and prolonged psychomotor change; middle insomnia or early-morning awakening; and, most assuredly, delusions or hallucinations of any sort. Fourth, and finally, consider whether a personal or family history of major depression exists, as this increases the likelihood that a depressive episode may have supervened. In general, one is looking to see whether the patient's symptoms in some way

or other have become "autonomous" and have achieved a life of their own, independent of whatever event may have triggered them.

Dysthymia is characterized by chronic, yet generally mild, depressive symptoms. At times when mild depressive symptoms arise de novo from euthymic functioning, the diagnostician may wonder whether this is a dysthymia or perhaps only a long prodrome to a depressive episode. Certainly, if the patient has had previous depressive episodes, one would lean toward the diagnosis of a prodrome; if the patient lacks this history, however, one may have to diagnose a dysthymia, but remain alert to the occurrence of an episode that would prompt a diagnostic revision.

The distinction between a depressive episode occurring as part of a major depression and a depressive episode occurring as part of a bipolar disorder is critical and at times very difficult. Certainly, with a history of mania, a diagnosis of major depression is definitely ruled out. Obtaining this history, however, may be very difficult. Depressed patients suffused with pessimism and hopelessness may simply be unable to recall having been manic. The experience of euphoria or increased energy may simply be so far from their current existence that it does not come to mind. Here careful questioning of relatives and friends is very important. Furthermore, even if one can say with certainty that no history of mania exists, then the question still arises as to whether or not a manic episode might occur in the years to come. The majority of patients with bipolar disorder begin their illness with a depressive episode, and they may have more than one before the first manic episode occurs. Four ways are used to assess the risk of a future manic episode. First, determine both the number of previous depressive episodes, if any, and the length of time from the first one to the current one. A history of five or more prior depressive episodes, or a duration of 10 or more years from the first to the current depressive episode, makes the likelihood of a future manic episode very low. Second, determine whether an episode of major depression occurred in childhood or early adolescence: patients with depressive episodes of such early onset are far more likely to have a manic one in their lifetimes than are patients whose first depressive episode did not occur until adult years. Third, inquire as to a family history of mania. Although this may be found among the relatives of patients with a major depression, it is far more common among relatives of those with a bipolar disorder. Fourth, examine closely the onset and symptomatology of the current episode itself for features that, though certainly possible in a depressive episode of a major depression, are nonetheless more commonly seen in a bipolar depression. Bipolar depressions tend to be of acute onset, in contrast to those in major depression, which are generally gradual. In terms of symptoms, bipolar depression tends to be characterized by psychomotor retardation, hyperphagia, and hypersomnia, whereas in major depression one tends to see agitation, insomnia, and anorexia with weight loss; furthermore, although psychotic symptoms may occur in major depression, they are far more common in bipolar depression. Another important point to keep in mind when evaluating depressive symptomatology is that "a hint of mania" means that, rather than a depressive episode, one is actually seeing a "mixed-manic" episode with a heavy preponderance of depressive symptoms. Examples include the following: "racing thoughts" or "flight of thought" that may be confused with incessant ruminations occurring in major depression, prominent mood lability, and a certain tense inner excitement that may be confused with agitation of major depression. Certainly, if the depressed patient appears

wearing a garland in her hair, or a gay boutonniere in his jacket, even if only for a few moments, one would begin to doubt this is a "pure" depressive episode.

Atypical depression is a controversial entity: earlier authorities believed it to be a disorder separate from major depression, whereas current thinking holds it to be a variant. In this book, it is treated separately in Chapter 76 . Whether one considers it to be a separate disorder or a variant, there is general agreement on what constitute atypical features, namely mood reactivity, rejection sensitivity, leaden fatigue, hypersomnia and hyperphagia.

Postpartum depression, as discussed in that chapter, is generally diagnosed only when the depressive episodes are "entrained" exclusively to the immediate postpartum period and do not occur at other times.

Premenstrual dysphoric disorder, as discussed in that chapter, is distinguished by the prompt remission of symptoms with the onset of menstrual flow.

Obsessive-compulsive disorder is often accompanied by depressive symptoms, yet here the obsessions and compulsions long precede the depressive symptoms. By contrast the occasional isolated obsessions or compulsions that sometimes complicate a depressive episode are preceded by prominent depressive symptoms. Posttraumatic stress disorder, Briquet's syndrome, and hypochondriasis may all be complicated by depressive symptoms. Yet here, as in obsessive-compulsive disorder, the depressive symptoms occur within the context of the other symptoms of these illnesses.

Schizoaffective disorder, depressed type, is distinguished from major depression by the persistence of psychotic symptoms throughout the intervals between depressive episodes.

Severe generalized anxiety disorder is distinguished from an agitated depressive episode by the relative absence of such symptoms as fatigue, loss of interest, guilt, and middle insomnia or early-morning awakening.

Secondary depression, such as may occur in Cushing's syndrome, hypothyroidism, and so forth, is discussed in that chapter.

Active alcoholism, alcohol withdrawal, and withdrawal from cocaine or stimulants are all typically complicated by depressive symptoms, which may be severe. Here, however, within 3 or 4 weeks of abstinence, symptoms begin to clear spontaneously.

In anorexia nervosa significant weight loss is generally accompanied by depressive symptoms. However, the depressive symptoms clear fairly promptly with weight restoration.

In the elderly a depression often manifests with prominent loss of memory and concentration, with other symptoms being at times relatively insignificant. This "dementia syndrome of depression" may be suspected when there is a history of prior episodes of depression or when the incorrect answers on the mental status examination seem to stem from

an inability to put forth the effort to answer them. The possibility of a concurrence of both a dementia syndrome of depression and another dementing disease, such as Alzheimer's disease, must also be kept in mind.

TREATMENT

The overall treatment of major depression is conveniently divided into three phases: "acute" treatment directed at the current depressive episode, "continuation" treatment directed at preventing a relapse into the current episode, and, "prophylactic," or "maintenance," treatment directed at the prevention of future episodes.

Regarding acute treatment for a depressive episode, one may, in addition to routine supportive psychotherapy, use either antidepressant medications or a specific psychotherapeutic method, such as cognitive therapy, or at times a combination of these two approaches. Since cognitive therapy (and an allied approach, interpersonal psychotherapy) has been demonstrated to be effective only in patients with mild to moderately severe depressive episodes, it is not the first choice for patients who are severely depressed or in those with psychotic symptoms, such as hallucinations or delusions. Antidepressants, however, are effective regardless of severity, and the following scheme for their use is now presented.

The initial step in this scheme is to select an antidepressant from the various available groups of antidepressants, each of which is discussed in detail in its respective chapter in the section on Psychopharmacology. These groups include the SSRIs (e.g., citalopram), the tricyclics (e.g., nortriptyline), the MAOIs (e.g., phenelzine) and a miscellaneous group including venlafaxine, mirtazapine, bupropion, nefazodone and trazodone. Several considerations come into play when making this selection, including: first, overall effectiveness; second, a personal or family history of antidepressant treatment with special attention to effectiveness and tolerability; third, anticipated side effects; fourth, potential drug-drug interactions; and, fifth, lethality in overdose.

First, overall, it appears that the various antidepressants are, by and large, of equal effectiveness in relieving depression. There may,

however, be certain exceptions to this rule. There is some evidence for superior effectiveness of venlafaxine and tricyclics over other agents. In addition, it appears that trazodone may be somewhat less effective than the others. These possible differences in effectiveness, however, are of no more than modest degree.

Second, inquire closely as to a personal or family history of treatment with an antidepressant, with particular reference not only to effectiveness but also the occurrence of side effects. History tends to repeat itself and if a patient responded well to a certain agent in the past, with no or modest side effects, then it makes sense to strongly consider using this agent again. Family history is less strong as a predictor, but still has some effect.

Third, consider the burden of anticipated side effects. Weight gain can be a significant factor over the long haul, and in this regard an SSRI is probably preferable to a tricyclic or mirtazapine. Sexual side effects (e.g., erectile dysfunction,

decreased lubrication, delayed orgasm) are common with most antidepressants, with the notable exceptions of mirtazapine, bupropion and nefazodone. Orthostatic hypotension, with possible falls or "watershed" cerebral infarctions in the elderly, is unlikely with SSRIs, venlafaxine, bupropion and mirtazapine, but not uncommon with tricyclics. Cardiac arrhythmias may be induced or exacerbated by tricyclics, but SSRIs carry little risk in this regard. The seizure threshold is reduced by tricyclics (especially maprotiline and clomipramine), bupropion and venlafaxine, and this consideration is especially important in those with a history of seizures or, in the case of bupropion, in patients with a history of bulimia, as such patients, for unclear reasons, may be especially prone to seize if treated with bupropion. Another side effect to consider is sedation, which tends to be more prominent with tricyclics (with the exception of nortriptyline, protriptyline and desipramine), mirtazapine, nefazodone and trazodone than with other agents, such as SSRIs. In the past, it was felt that this side effect could be put to good use in agitated patients, as it was believed that agitation responded better to a sedating drug, such as a tricyclic, than to other agents, such as an SSRI: as it turns out, however, tricyclics are no better in treated "agitated" depressions than are SSRIs.

Fourth, consider possible drug-drug interactions with other medications the patient is taking, or is likely to. In this regard, the "cleanest" agents are the SSRIs citalopram and escitalopram, and by far the most problematic are the MAOIs. Indeed the list of medications (and foods) that must be avoided when taking one of the currently available MAOIs is of such length that these agents are generally a last choice in the treatment of major depression.

Fifth, and finally, consider the potential lethality of these agents in the case of overdose. In this regard, the SSRIs are unquestionably the safest agents, followed by venlafaxine, mirtazapine, and nefazodone: the tricyclics and MAOIs are by far the most dangerous.

Clearly, given the large number of antidepressants available, and the multiple considerations involved in choosing among them, arriving at the best first choice for any given patient is a complex task that must be individualized. All other things being equal, however, several good choices stand out, including the SSRI escitalopram, the tricyclic nortriptyline, and, from the miscellaneous group, bupropion, mirtazapine or venlafaxine.

Once an agent is chosen, it must be given an "adequate trial," assuming of course that no unacceptable side effects are seen. An "adequate trial" means treatment with an "adequate" dose for an "adequate" period of time. In general, one increases the dose as tolerated up to the "average" dose for that agent, as described in their respective chapters, always keeping in mind that reduced doses are indicated for the elderly, the debilitated, and those with significant hepatic disease. At this point blood levels are not required, with the exception of nortriptyline, which probably has a "therapeutic window." In general one should not expect to see much improvement for the first 1 or 2 weeks after reaching an "average" dose; if none is seen by the end of the third week, then one may assume that, at least at the current dose, the medicine probably will not be that helpful. In cases, however, where improvement is seen by 3 weeks, one must tell a patient that it may take up to 3 months to see the full effect.

If, after approximately 3 weeks, there is minimal or no improvement, one should, if not already done, check thyroxine and TSH levels. Hypothyroidism, even if only "chemical," perhaps being manifest only by an elevated TSH level, will blunt the response to antidepressants and must be corrected. Presuming that both thyroxine and TSH levels are normal, one may, if side effects are tolerable, consider increasing the dose of the antidepressant. With the exception of nortriptyline, which, as noted earlier, has a "therapeutic window," it appears that for most other antidepressants the dose-response curve is generally linear, and thus one may gradually increase the dose up to the maximum described for each agent in its respective chapter.

If the patient does not respond to high dose treatment and the thyroid status is normal, or if side-effects preclude a significant dose increase, then one may consider either switching to another antidepressant or trying a combination. Switching antidepressants is a viable option, but in so doing one should probably switch to an antidepressant from a different group. In some cases, one must be careful of potential drug-drug interactions in making a transition: for example, given the long half-life of some SSRIs and their ability to inhibit the metabolism of tricyclics, one should generally, if switching from an SSRI to a tricyclic, phase in the tricyclic relatively slowly after stopping the SSRI. Combination treatment is also viable, but only a small number of combinations have been shown to be effective in double-blinded studies, including the following: lithium plus either a tricyclic or an SSRI; olanzapine (in a dose of 10 mg) plus fluoxetine; triiodothyronine (in a dose of 50 mcg) plus a tricyclic; and, finally, a tricyclic plus an MAOI. This last combination is potentially quite dangerous, and should probably be considered the last option. Regardless of whether one substitutes another single agent, or tries a combination, one must then again provide an "adequate trial," ensuring that doses are adequate and that at least three weeks are allowed to see if a response will occur.

At this point, should the response be minimal or less, one might consider different single agents or different combinations. How far one goes at this point depends largely on the severity of the depression. If it is tolerable, one could consider further medication trials. If, however, there is substantial morbidity or significant risk of death, one should consider ECT.

Although the foregoing schema is in general applicable to most cases, exceptions do occur. First, in severe cases requiring hospitalization, one might consider immediately checking thyroid status and beginning with a rapid titration of a single agent or a combination. Second, for the highly suicidal patient or in those cases where the depression is otherwise life threatening (for example, because of extreme weight loss), moving immediately to ECT may be appropriate, as it remains the most effective and rapid treatment for depression. Third, some debate exists over whether antipsychotics are required for depressive episodes accompanied by psychotic symptoms. In some cases aggressive treatment using the schemas outlined above effects a remission, not only of the typical depressive symptoms but also of delusions and hallucinations. Certainly, this is the case when ECT is used. Most clinicians however will treat such patients with a combination of a second generation antipsychotic and an SSRI.

Before leaving this discussion of acute treatment of a depressive episode with antidepressants, some words are required regarding alprazolam, buspirone, "alternative" treatments such as St. John's wort (hypericum), and certain experimental treatments. Alprazolam in doses of 3 to 6 mg may be as effective as a single-agent antidepressant for mildly to moderately severe depressions. The risk of neuroadaptation and the often extreme difficulty in withdrawing from alprazolam, however, makes this a less than attractive alternative. Buspirone, in high doses (for example, 60 mg or more), likewise appears to be effective in mildly to moderately severe depressions. Its effectiveness relative to other agents, however, is not as yet clear. Of the "alternative" agents, St. John's wort may be helpful with mild depressions; however, its effectiveness in moderate or severe depressions is doubtful. Experimental treatments include transcranial mangnetic stimulation and vagus nerve stimulation. Both have shown promise in treatment-resistant cases, but experience with them is still too limited to justify their routine use. Certainly, if one were contemplated, transcranial magnetic stimulation, a relatively benign procedure, is probably a first choice, given the invasiveness of vagal nerve stimulation.

Once "acute" treatment has effected a symptomatic remission of depressive symptoms, "continuation" treatment is in order. It must be kept in mind that these treatments do not alter the natural course of the depressive episode itself. Rather they merely suppress symptoms. Consequently, if treatment is discontinued shortly after symptoms remit, those symptoms almost invariably return, generally within a few weeks or perhaps a month or longer. Consequently, "continuation" treatment is required until such time as the depressive episode itself has gone into a spontaneous remission. In general this involves a continuation of the "acute" treatment; however, in a minority of cases scaling down the intensity of treatment without a return of symptoms may be possible. For example, if a combination of two or more antidepressants is required, one of the agents may be dropped off and the patient maintained on a single agent or, if a single agent was effective from the start, the dose reduced. One must be cautious here, however, for in most cases patients require for "continuation" treatment a regimen very close or identical to that which worked acutely. If ECT was used, one has the option of either continuing "maintenance" ECT, perhaps on a once-monthly basis, or of using an antidepressant: both paroxetine and a combination of nortriptyline and lithium have been found effective in this regard. Most patients opt for the antidepressant. However, though this is generally effective some patients do relapse, and in these cases a trial of maintenance ECT is probably indicated.

As noted, continuation treatment should persist for as long as the depressive episode would last in the natural course of events. In cases where the patient has a prior history of depressive episodes of fairly uniform and discrete length, this may be taken as a reliable guide for the duration of the current episode. In most cases, however, such guidance is not available. Either no prior episodes occurred, or, if they did, they were of such indistinct onset and remission that their length could not be reliably estimated. In these cases prolonged continuation of treatment until the patient has been symptom free for at least four consecutive months is prudent. This guideline, empirically determined, rests on several assumptions: first, that no acute treatment is perfect; second, that given the waxing and waning nature of depressive symptoms, in the natural course of events, at times symptom severity is expected to rise to a "peak" that could "break through" the treatment and cause some symptoms in the patient; and third, the longer a patient goes without a "breakthrough," the more likely the depressive episode is

finally undergoing a natural remission. When the time does come to cease continuation treatment, given the fact that a small risk of relapse still exists, one may want to time the cessation of treatment with respect to events in the patient's life. For example, a patient may not wish to be exposed to any risk of relapse when starting a new job, assuming any major new responsibility, or facing any major stress. In most cases it is prudent to hold off cessation of continuation treatment until the patient feels that life has become manageable and is likely to remain so. In any case one may want to see the patient at least one more time, perhaps 2 or 3 months after cessation of continuation treatment to make sure that the depressive episode has indeed remitted.

Given that the majority of patients have a subsequent episode, asking the patient to consider preventive treatment is appropriate. Such preventive treatment is generally recommended when either the euthymic interval between episodes is less than 2 years or, based on past experience, one can predict that a future episode would be sufficiently severe as to cause significant suffering or complications. Another impetus for the recommendation of preventive treatment are recent studies suggesting that episodes "beget" future episodes in a "kindling" process, suggesting that control of present episodes may reduce the risk of an increased frequency of episodes in the future. If the patient does opt for preventive treatment, an extension of the continuation regimen of an antidepressant is usually effective; whether cognitive-behavior therapy or ECT is effective is not clear. Should patients decline preventive treatment, one should review the prodromal symptoms experienced in the past. Thus explicitly forewarned, patients may be better able to recognize early symptoms in the future and secure treatment before the symptoms become severe and disabling.

Upon first examining the patient, one should consider all three phases of treatment: acute, continuation, and preventive. For many physicians the choice of treatment for the acute phase is influenced by what has been shown effective in both the continuation and preventive phases. Clearly then, antidepressant treatment currently appears best suited; if an antidepressant regimen works for acute treatment, then in all likelihood the treatment will be effective for both the continuation and preventive phases.

An additional treatment option involves phototherapy. Mounting evidence supports the use of phototherapy for patients whose depressive episodes display a seasonal pattern with onset in the winter and remission in the spring. Patients are exposed to full-spectrum light at 2500 lux for about 2 hours every morning. If a response is not seen within about a week, consideration might be given to increasing the duration to 4 or even 6 hours. Although some patients appear to respond to exposure at other times, for example at midday or in the evening, or to shorter durations with higher intensity of exposure (to as little as a half hour at 10,000 lux), starting with the 2-hour morning "dose" and proceeding from there is prudent. Some patients with a seasonal pattern may respond to phototherapy, both as acute treatment and as continuation treatment. Some, however, require the addition of an antidepressant to achieve full relief. Because phototherapy is time consuming and for many patients simply impractical, one should bear in mind that major depression whose course is marked by a seasonal pattern also responds to antidepressants without the use of phototherapy.

Indications for hospitalization include the following: a significant risk of suicide; significant disability caused by symptoms of depression, making patients unable to maintain themselves at home or at work; significant concurrent illness (for example, certain cardiac conditions) that requires intensive monitoring; or acute treatment with ECT (continuation treatment with ECT generally may be done on an outpatient basis). At times the decision to hospitalize is easy, for example when the patient has recently made a suicide attempt, is in danger of being fired because fatigue and poor concentration make work impossible, or has recently had a myocardial infarction. Most patients, however, fall into a "gray zone," and in these cases carefully considered clinical judgment is required.

Deciding when to discharge a patient also requires considerable judgment. Though one may wish to wait until the depressive symptoms are fully remitted, such a strategy is usually grossly impractical given the burden, financial and otherwise, attendant on a long hospital stay. In practice, one waits until an uninterrupted "trend" toward improvement has been established. Given that setbacks often occur early in treatment, one should not discharge the patient at the first blush of improvement. Rather one may want to wait until the patient has been definitely "on the mend" for at least 3 or 4 days in a row before considering discharge. The patient's support system must also be considered. Those with little outpatient support may require longer inpatient care to allow for a fuller degree of recovery before discharge. When the patient is discharged with a potentially lethal prescribed medicine, one may want to limit the number of tablets dispensed to a sublethal amount.

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