10

Depressive Disorders

Almost everyone recognizes the experience of feeling depressed. Moodiness is almost universal. Because these experiences are so common, we need to critically examine the boundaries of mood disorders. How does depression differ from sadness? Is it always a disorder in its own right, or can it be just a symptom? The problem is whether to be restrictive or expansive in defining what constitutes depression.

What Is Depression?

Since the time of Hippocrates, *melancholia* has been recognized as a medical illness. In the past, psychiatrists saw this clinical picture as qualitatively different from milder forms of depression (Parker, 2005). Melancholia lasts weeks to months, during which patients suffer from despondency, irritability, and restlessness, with a slowing down of mental processes and movement, diminished appetite, sleeplessness, and powerful suicidal urges. Mood is disproportionate to external stressors, and it is associated with psychomotor retardation or agitation, severe cognitive impairment, prominent vegetative symptoms, and/or psychosis (Parker, 2005).

This is a different picture from mild to moderate depression. Moreover, as psychiatrists have long been taught, depression can be a symptom, a syndrome, or a disorder. The concept that depression is one condition, varying only in severity, has obscured these distinctions. The separation of psychotic and neurotic depression in DSM-I and DSM-II was an attempt, however misguided, to address

this issue. It considered a psychotic (and/or melancholic) picture to be "endogenous," whereas a neurotic depression was viewed as primarily environmental in origin. But that separation was invalid. People with psychotic depression can fall ill after being exposed to stressors, and people with milder forms of depression may also be biologically prone to mood disorders. Thus, depression cannot be subclassified on the basis of etiological factors that are complex and interactive. But we are still left with the following question: Is depression one disorder or many?

The problem with a broad definition of depression is that it makes the diagnosis ubiquitous. Prospective studies find that up to half of the population, and possibly more, will experience changes in mood that meet DSM-IV criteria for a major depressive episode at some time during their lives (Moffitt et al., 2010). These data come from a study that followed people only into their 30s. Parker (2005) noted that other prospective data suggest that almost 80% of the population experiences a major depression during their lifetime. The numbers could easily increase to 100% with the diluting of exclusions for normal reactions such as grief (Wakefield et al., 2007). Yet research in the community shows that bereavement, whether simple or complicated, is not associated with the range of symptoms that characterize classical major depression (Gilman et al., 2012).

Some view the high prevalence of depression as valid, confirming that it is the "common cold of psychiatry." Alternatively, the current definition of major depression may be seriously overinclusive in that it fails to distinguish between problems of living and mental disorder. In this view, overly broad definitions lead to diagnostic inflation.

The Unitary Theory of Depression

More than 40 years ago, in an influential review paper, Akiskal and McKinney (1973) proposed that all depressions lie on a continuum, differing only in severity. They argued that distinctions cannot be

made on the basis of unproven etiological theories and that symptoms, family history, outcome, and treatment response cut across all forms of depression.

The unitary theory was adopted in DSM-III and has held sway ever since. A major depressive episode is diagnosed if patients meet five of nine listed criteria for a minimum of 2 weeks. Severe cases can then be subtyped as psychotic or melancholic. Although the unitary theory became conventional wisdom, it continues to be challenged on the grounds that melancholia is qualitatively distinct (Parker, 2005).

A second, and more serious, problem with the unitary theory is that it does not separate psychopathology from normal unhappiness (Horwitz & Wakefield, 2007). The DSM definition is so broad that it is difficult to imagine anyone who has not met criteria at some point in their life.

An overly short timescale is the most important reason for overdiagnosis. How easy is it, after a loss or serious setback in life, to be depressed for 2 weeks at a time? Given the evidence that most cases of mild depression remit rapidly (Patten, 2008), 4–6 weeks might have provided a more valid cutoff. One could also look for recurrence and chronicity as illness markers.

A third issue is just how "major" is major depression. DSM requires patients to meet five criteria. But nobody knows where the number 5 came from, except that it is more than half of 9. Moreover, a diagnosis can be made on the basis of milder symptoms alone: a low mood plus loss of interest or pleasure, loss of energy, reduced concentration, and insomnia. All these features occur in transitory mood states related to environmental stressors (Horwitz & Wakefield, 2007; Patten, 2008). The counterargument is that research on the DSM-IV criteria in community populations does not find a clear cutoff from normality. However, the criteria for major depression are quite heterogeneous, with the most recent studies (Lux & Kendler, 2010; Lux et al., 2010) showing a mixture of cognitive and neurovegetative criteria rather than a simple measure of severity.

If previous editions of DSM had required more than five criteria, that would also have helped to separate major depression from

transient mood states. It would also have been useful to have criteria that *must* be present rather than mixing and matching like a menu at a Chinese restaurant. As it stands, the only required feature among the nine is low mood (or a loss of interest and pleasure). The bar is set too low, and scoring severity does not address the problem. For example, subclinical cases with four or even fewer symptoms are also distressed. Yet one could say much the same about three, two, or even one symptom.

Finally, because even a seven-digit phone number is too long to be remembered by most people unless written down, clinicians do not actually remember nine criteria when making a diagnosis. Zimmerman et al. (2011a) found that simplifying the criteria list to five criteria instead of nine (low mood, loss of interest, guilt or worthlessness, impaired concentration or indecisiveness, and death wishes or suicidal thoughts), of which three would be required to make the diagnosis, gives much the same result as DSM-IV. Even so, simplifying the algorithm does not address the question as to whether depression is too broadly defined. Parker et al. (2010) proposed an alternative procedure in which psychotic, melancholic, and nonmelancholic types are immediately identified rather than being afterthoughts to an overall diagnosis of major depression. This was designed to encourage clinicians to recognize psychotic and melancholic depressions, which require different methods of treatment and respond differently to therapy.

In summary, more than 40 years after Akiskal and McKinney (1973), we still cannot conclude whether severe, moderate, and mild depression are points on a single spectrum or separate syndromes. Yet major depression is a heterogeneous diagnosis that can mislead clinicians about treatment. There is no clinical value in overidentifying this diagnosis.

Exclusions for Diagnosis

Should depression be diagnosed if a stressor is present that would make almost anyone unhappy? DSM-IV allowed for the exclusion of

extended periods of symptomatic distress following bereavement, but it did not apply the same rule to other losses. Life events such as divorce or job loss can also produce symptoms that resemble grief. Depressive symptoms, whether caused by bereavement or by other life stressors, are similar (Wakefield., 2012), and excluding grief helps to distinguish the normal from the pathological (Wakefield et al., 2011). Why not extend the exclusions to recognize that when people suffer losses, they can be expected to have transient depressive symptoms?

DSM-5 has moved in the opposite direction. Initially, it wanted to remove the grief exclusion entirely, expanding the range of diagnosis. This decision reflects a failure to take into account the social context in which symptoms develop. Grief produces symptoms that are similar to depression, but that does not prove they are one and the same. Although it is true that some patients with grief go on to develop severe depression, separating them helps clinicians to describe patients with different outcomes and different treatment needs (Parker et al., 2011). Arthur Kleinman (2012), an expert in psychiatric anthropology, expressed his disagreement with the change by describing how his grief for the recent death of his wife could have been diagnosed as a major depression.

Wakefield and First (2012) proposed a solution that would involve raising the bar for severity and determining the extent to which symptoms are contextual. The fact that some patients remain depressed several months after bereavement could be taken into account by rewriting the criteria. Thus, those who have 2 weeks of depressive symptoms after a loss would be diagnosed as having a normal reaction, whereas those who suffer for extended periods could still be diagnosed with a major depression.

The solution eventually adopted by DSM-5 in May 2012 is that clinicians are warned not to diagnose major depression if grief, even when prolonged, best accounts for symptoms. It also provides a category, for now relegated to Section III, called "persistent complex bereavement disorder." This compromise avoids removing the bereavement exclusion entirely, which would have meant that many more patients would be diagnosed with, and treated for, depression.

Perhaps this has already happened—many people take antidepressants without a diagnosis of major depression (Mojtabai & Olfson, 2011).

Wakefield (2010) suggests that DSM's diagnostic expansiveness reflects the nature of today's outpatient practice. Psychiatrists do not want to be limited to severe disorders but, rather, want diagnoses that justify treating whatever problems they see. Perhaps this would make little difference if treatment mainly consisted of counseling or psychotherapy. But the diagnosis of major depression leads physicians to prescribe drugs—despite the evidence that less severe cases do not consistently respond at more than a placebo level (Kirsch et al., 2008). And once patients are put on antidepressants, clinicians are afraid to stop them for fear of a relapse.

Fortunately, most antidepressants are not very toxic, even when taken on a long-term basis. But the diagnostic system should not encourage physicians to prescribe drugs that may or may not work and that patients tend to go on taking for years. Recent data show that 11% of all Americans older than age 12 years are taking an antidepressant (Pratt et al., 2011). Evidently, psychiatry and primary care have come to view unhappiness as a mental disorder.

Epidemiological research, based on DSM criteria, tends to support the idea that depression is ubiquitous. In the National Comorbidity Survey, a large-scale epidemiological study, lifetime prevalence was 16.6% (Kessler et al., 2005a). But these numbers could be an underestimate. Forgetting about a depressive episode once it resolves is generally adaptive. When researchers used prospective rather than retrospective data (Moffitt et al., 2009), up to half of all individuals in the general population meet criteria at some point in their life up to age 32 years.

The problem is that community studies of depression include mild cases that do not require medical treatment (Patten, 2008). Thus, these high numbers are seriously misleading. Moreover, there is little point in screening to move people into the mental health system.

The problem of false positives casts a shadow on all epidemiological studies of mood disorders. Enthusiasm for antidepressant

treatment has led to the idea, supported by mental health advocates, of screening the general population to diagnose all forms of depression including subthreshold cases. This would have the unfortunate effect of shifting the focus of psychiatry from severely ill patients, who we are already hard pressed to treat properly, to normal people who have transient episodes of depression from which they will recover. Even if depression is the common cold of psychiatry, a cold should not be confused with pneumonia.

The unitary theory, incorporated into the DSM system, arose from a specific *theory* about mood disorders, consistent with the tendency to view all mental illness as biological and on a continuum with normality. Yet none of the current categories of depression reflect unique pathological processes or endophenotypes. Even in melancholia, which can sometimes be associated with endocrinological changes (Parker et al., 2010), biological markers are not consistent enough to be used to validate diagnoses. In mild to moderate depression, we have no markers at all.

Current mood disorder categories fail to help clinicians select specific treatment methods, which require more than a simple diagnosis. The unitary concept of major depression is a poor guide to therapy because patients are heterogeneous and drug responses are unpredictable in nonmelancholic depression. Healy (2009) has even spoken of the *creation* of major depression, given that the category is not well validated and not always all that "major."

DSM-III addressed variations in clinical presentation by allowing additional codes for severity within the broader diagnosis of major depression. But it is one thing to include these options in the manual and another to get clinicians to use them. What seems to have happened is that treatments designed for melancholic depression are being applied to depression of any kind (Paris, 2010a).

The editors of DSM-III had, at one point, considered introducing a category of "minor depression" to describe less severe symptoms. In the end, that category fell into a larger wastebasket: "mood disorder, not otherwise specified." Patients with transient symptoms who do not meet five criteria for major depression for 2 weeks can also be diagnosed with an "adjustment disorder with depressed

mood," although that diagnosis is not sufficiently utilized. Finally, patients with chronic but subclinical symptoms can be diagnosed with dysthymia (now called *persistent depressive disorder*) if they meet only two criteria (present most of the time during a 2-year period). Although clinicians often see these patients, this is a poorly researched category that could include milder mood disorders and/or depressed feelings associated with other diagnoses, particularly personality disorders, and that do not respond consistently to antidepressants.

Changes in DSM-5

There are no major revisions for classifying depression in DSM-5, but some changes need to be noted. As in previous editions of the manual, a major depressive episode still requires the presence of five out of nine criteria (low mood, loss of interest, weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, worthlessness, reduced concentration, and thoughts of death), accompanied by clinically significant distress. Then a major depressive disorder (single episode or recurrent) can be diagnosed.

There are some changes in the definition of major depression. First, the core mood criterion includes hopelessness, which might broaden the diagnosis. Second, the bereavement exclusion is replaced by a call for clinical judgment in distinguishing normal reactions to significant loss. Third, the new persistent depressive disorder category combines dysthymia, in which patients retain subthreshold symptoms during a 2-year period, with other chronic cases. New specifiers of major depressive disorder include perinatal onset, mixed features, and anxious distress.

It has long been known that anxiety and depression cannot readily be separated and are often, if not usually, found in the same patients (Goldberg & Goodyer, 2005). A proposed change in DSM-5 was for a comorbid anxiety dimension plus the addition of a new disorder called mixed anxiety–depression (three symptoms of major depression plus two of anxiety). Wakefield (2012) expressed

concern about the low bar for this diagnosis. In any case, the proposal was dropped in 2012 after it did not prove reliable in clinical trials.

Another change concerns the definition of mixed episodes (in which depression and mania can be found in the same patient at the same time). The manual offers a "mixed features" specifier applicable to manic, hypomanic, and major depressive episodes. This allows clinicians to score subthreshold symptoms, making it more likely that mixed episodes will be identified. That may or may not be a useful idea.

Another idea is the addition of severity dimensions for major depressive episodes. This procedure depends on an unweighted symptom count based on self-report instruments such as the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) or clinical ratings such as the Clinical Global Impression (CGI; Guy, 1976). Scoring symptoms formally could have advantages over clinical impressions of severity, but it is not really objective because clinical judgments still have to be made.

The category of premenstrual dysphoric disorder has moved from the appendix of DSM-IV into the mood disorders section of DSM-5. Premenstrual dysphoric disorder lists 11 possible symptoms, of which 5 have to be present (associated with clinically significant distress). The list describes mood swings and irritability that occur during most cycles and that remit when menstruation occurs. This disorder had been considered for inclusion in DSM-IV but was considered to require more study. The concern was that common symptoms that many women experience could be medicalized. The rationale behind the change in DSM-5 is that, as has been known for some time, this syndrome can be treated effectively with antidepressants (Steiner et al., 1995). Concerns remain about the potential stigmatization of normal mood changes in women and that diagnostic criteria may be too easily met, leading to unnecessary pharmacological treatment in patients whose symptoms are mild.

Finally, disruptive mood dysregulation disorder, a category that applies to children aged 6–18 years, has been added. As noted in Chapter 9, this category was introduced to discourage the diagnosis

of bipolar disorder in children. But because this condition has a number of features in common with disruptive behavior disorders, it will be further discussed in Chapter 13.

First (2011) reviewed changes in mood disorder classification in light of a cost–benefit analysis. He expressed concern about false positives (i.e., diagnosing patients who are unhappy with depression) and about clinical utility and problematic implementation, given that busy clinicians are unlikely to carry out complex scoring that might best be reserved for researchers. As with so many other revisions in the manual, the changes have not been subjected to the kind of detailed testing needed to determine what effect they will have on practice.

Implications of Diagnosis for Treatment

In contemporary medicine, clinicians tend to assume that *any* patient meeting DSM criteria for major depression has to be put on antidepressants. Some physicians are afraid of lawsuits if they do not prescribe. The name of the diagnosis (particularly the word "major") and the name of the drugs ("antidepressants") are often sufficient for a knee-jerk prescription. Few follow the British guidelines published by the National Institute for Clinical Excellence (2007), which sensibly recommend that physicians watch and wait for a few weeks before putting patients with mild to moderate depression on any drugs.

The adoption of a single category of major depression is an important support for the idea that all cases require similar treatment. Yet compared to placebo, severe depression responds much more consistently to antidepressants than mild to moderate symptoms (Kirsch et al., 2008; Shelton & Fawcett, 2010). This issue is still controversial, and some meta-analyses (e.g., Gibbons et al., 2012) have supported a wider response to drugs. Nonetheless, a general principle in medicine is that treatment response is easier to measure when symptoms are severe.

We should be humbled by research findings showing that antidepressants are not consistently superior to placebo in producing remissions in patients with milder symptoms. Placebo effects are low in severe depression but strong enough in milder depressions to closely match the efficacy of drugs. Differences in response based on initial severity have long been observed: Although drugs are almost always necessary in severe depression, psychotherapy is just as effective in milder cases (Elkin et al., 1989). These treatment effects support the conclusion that "major depression" is a heterogeneous condition—not one diagnosis with varying levels of severity (Parker, 2005).

The unitary theory of major depression also underlies the concept of "treatment-resistant depression"—that is, a scenario in which depressive symptoms do not respond well to drug treatment. This concept, based on the idea that depression *should* respond, has led to the wide use of augmentation and switching strategies. Some of these procedures can be useful, but much recent research, particularly the STAR-D effectiveness study (Rush et al., 2006; Valenstein, 2006), has suggested that antidepressants, although useful, are greatly overrated. Approximately two-thirds of patients eventually remit from depression after treatment, but many recover with time alone.

In summary, a diagnosis of major depression is, by itself, a poor guide to practice. Inconsistent efficacy of treatment occurs because drugs are being prescribed to a heterogeneous group, some of whom have a true mental disorder and some of whom are just unhappy.

In the history of medicine, physicians have expressly aimed to treat disease on the basis of a detailed understanding of the mechanisms behind pathology. But just as often, physicians develop cures and only then go in search of diseases. We should be cautious about rushing to offer panacea-like treatments and to justify this practice by creating overly broad diagnostic categories. Depression remains a central focus of clinical practice, but it is classified in a broad and misleading way that fails to distinguish between cases that require pharmacotherapy and those that may not. The result can be both overdiagnosis and overtreatment.