The Varied Clinical Presentations of Major Depressive Disorder

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DSM-IV major depressive disorder (MDD) is a clinical syndrome notable for heterogeneity of its clinical presentation, genetics, neurobiology, clinical course, and treatment responsiveness. In an attempt to make sense of this heterogeneity, clinicians and researchers have proposed a number of MDD "subtypes" based on differences in characteristic symptoms (e.g., atypical, melancholic, psychotic), onset (e.g., early vs. late, postpartum, seasonal), course of illness (e.g., single vs. recurrent, chronic, double), and severity. This article provides a brief review of the status of several of the most common subtypes in terms of their clinical features, biological correlates, course of illness, and treatment implications.

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After decades of research, DSM-IV major depressive disorder (MDD) still qualifies as a clinical syndrome rather than a disease. This in no way diminishes its importance either to the individual or to society. It only indicates that MDD does not yet meet traditional disease criteria, which require a diagnosis attributable to a specific etiologic mechanism with an established pathophysiology and clinical course. Instead, the most salient feature of MDD is, arguably, its very heterogeneity—in terms of its clinical presentation, its genetics and neurobiology, and its clinical course and treatment responsiveness.

After briefly summarizing the epidemiology and impact of MDD, this article reviews current data on the commonly described clinical subtypes of MDD and emphasizes new data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) program.

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MAJOR DEPRESSIVE DISORDER: EPIDEMIOLOGY AND IMPACT

Major depressive disorder is one of the most common of the serious medical and psychiatric disorders, with an estimated 12-month prevalence rate of 6.6% and a lifetime prevalence rate of 16.2%.[1,2] At these prevalence rates, it is estimated that approximately 34 million adults will experience an episode of MDD at some point in their lifetime and that approximately 14 million will suffer from an episode in any given 12-month period. The likelihood of having an MDD episode in the past 12 months was highest in young adults under age 30 years (odds ratio [OR] = 3.0), in women (OR = 1.4), and in individuals currently below the poverty level (OR = 3.8).[1]

Major depressive disorder results in moderate levels of role impairment in 28% of depressed individuals and severe to very severe impairment in 59%.[3] Overall, depressed individuals reported a mean of 35 days in the past year when they were totally unable to work or carry out their normal activities because of their depression. This degree of work impairment is comparable to or greater than what has been reported in previous studies of chronic medical illnesses such as asthma (10.6 days), heart disease (8.8 days), diabetes (6.4 days), and chronic obstructive pulmonary disease (19.4 days).[3] Because of its high prevalence and associated disability, major depression ranks number 2 in the developed world in terms of disability-adjusted life years.[4]

In addition to significant work impairment, MDD is associated with a range of other negative consequences, including a significantly increased (1.5- to 2-fold) risk of myocardial infarction or stroke or developing diabetes.[5–7] Based on a meta-analysis of available community studies, the overall relative mortality risk associated with depression is estimated to be approximately 1.7.[8]

The occurrence of comorbid depression is also associated with a significant worsening of existing medical conditions, resulting, for example, in a 2.3-fold increase in mortality in patients with type 2 diabetes,[9] an 8-fold increase in mortality in patients with congestive heart failure (independent of left ventricular ejection fraction and New York Heart Association functional class), and a 2.6-fold increase in mortality over 2 years in patients with coronary heart disease.[10] The importance of depression as a mortality risk factor is significant given the high prevalence of MDD in patients with ischemic heart disease and myocardial infarction (~20%), stroke (~30%), and diabetes (~12%).[11,12]

A less dire, but even more pervasive, consequence of the comorbidity of MDD and general medical illness is the marked increase in impairment, health care utilization, and total cost compared with patients with general medical illnesses who are not depressed.[13–15] The presence of comorbid MDD is associated with a marked increase in health care utilization, with 40% of high (top 10%) utilizers having a diagnosis of MDD.[15] Even though the presence of depression increases utilization of medical services, it is also a highly significant predictor of nonadherence to prescribed regimens.[16] Overall, the annual cost of depression in the United States, based on a human capital analysis, has been estimated to be approximately $83.1 billion (in 2000; U.S. dollars), of which 31% was categorized as direct medical costs, and 69% was categorized as indirect costs (lost work days and productivity).[17]

Another significant risk associated with depression is suicide. Based on the results of a meta-analysis of available studies, the risk of suicide has been estimated to range from 2.2% (in outpatients with less severe illness) to 8.6% (in more severe depression with a history of hospitalization for suicidality and depression).[18] Greenberg et al.[17] report that, of the $83.1 billion economic burden of depression, $5.4 billion (7%) was attributed to suicide-related mortality costs. Suicide is one of the top 10 leading causes of death in the United States, with more than 30,000 deaths per year.[19]

MAJOR DEPRESSIVE DISORDER SUBGROUPS

Major depressive disorder is a heterogeneous syndrome in terms of its clinical presentation, neurobiology, family history, onset and course of illness, and treatment response. Empirically derived depression, or "subtypes," have been proposed based on differences in symptom presentation, onset characteristics, course of illness, and severity. These proposed MDD subtypes are neither comprehensive nor mutually exclusive. Whether depression subtyping is merely a useful clinical shorthand, or has only speculative/heuristic value, depends on whether the proposed subtype meets 1 or more of the following 3 criteria: (1) the subtype has implications for treatment selection, (2) the subtype has prognostic implications in terms of treatment response or outcome, or (3) the subtype delineates a disorder with specific genetic and/or neurobiological features.

SYMPTOM-BASED SUBGROUPS

In the past 40 years, 4 MDD subgroup-based cross-sectional symptom features have been widely discussed: atypical, melancholic, psychotic, and anxious depression. Atypical depression is reviewed in detail in another article in this issue (see Thase[20]).

Melancholia

Historically, melancholia is the subgroup with the most ancient lineage, antecedent even to the concept of depression. The term *melancholia* derives from the Greek words με‘λαινα χολε (*melaina chole*) meaning "black bile" and originated in the humoral etiology of the illness. The modern concept of melancholic depression largely overlaps with "endogenous" depression and is differentiated from "exogenous" depression, which is thought to occur as a reaction to life stressors. Empirical research has not consistently confirmed a difference in precipitating stressors between endogenous/melancholic depressions and exogenous depressions.[21] However, factor analyses appear to support the occurrence of a melancholic subtype of MDD characterized by an autonomous depressed mood with pervasive anhedonia that is minimally responsive to positive external events.[22,23] In the current DSM-IV nosology, "with melancholic features" is an illness specifier. Several biological parameters seem to differentiate patients with melancholic symptom features from other depressed patients, including shortened rapid eye movement latency, excessive cortisol secretion, and other hormonal and biological changes.[24,25] Generally, MDD with melancholic features appears to consistently respond better to antidepressant medication than placebo.[26]

Psychotic Depression

Psychotic depression is characterized by delusions and/or hallucinations that are usually mood-congruent (e.g., somatic or sinfulness delusions, or disparaging auditory hallucinations) and typically occurs in patients reporting severe depressive symptoms. Approximately 18% of people with MDD have psychotic features.[27] The psychotic and melancholic subtypes are distinguished from other MDD subtypes by marked hyperactivity of the hypothalamic-pituitary-adrenal axis with hypercortisolemia,[28,29] and for at least the psychotic subtype, by significant cognitive deficits in selected areas (e.g., processing new information, verbal memory, and executive function).[30,31] Clinical experience suggests that patients with psychotic depression are more treatment resistant and have a poorer long-term prognosis, especially if the psychotic features are mood incongruent. While a number of studies recommend the combined use

of antidepressants and antipsychotics,[32] a recent Cochrane review found no evidence for a clear benefit of combination therapy over antidepressant monotherapy.[33,34] That review also highlighted the inadequate nature of the clinical trials database in psychotic depression.[34] Of note is that patients meeting criteria for psychotic depression were excluded from the STAR*D study.[35,36]

Anxious Depression

Anxious depression is a subgroup that has been variously defined as MDD with prominent anxious symptoms, or MDD with a comorbid anxiety disorder. In the STAR*D study, 46% of patients met criteria for anxious depression, defined as a Hamilton Rating Scale for Depression (HAM-D) anxiety/somatization factor score greater than or equal to 7.[37] Demographically, patients with anxious depression were significantly less educated, older, and more likely to be unemployed. Clinically, the anxious depression subgroup was more severely depressed and was more likely to have suicidal ideation, even after adjustment for depression severity. In terms of overlap with other symptom-based MDD subgroups, patients with anxious depression were more likely to have melancholic features and less likely to report atypical symptom features. As might be expected, anxious depression was associated with a significantly increased risk of concurrent panic disorder (OR = 1.3), somatoform disorder (OR = 1.5), and hypochondriasis (OR = 1.4). In the STAR*D study, patients diagnosed with anxious depression using Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) criteria were significantly less likely to achieve remission (OR = 0.77, $p < .002$); there was no difference in treatment response in the anxious depression group defined by HAM-D criteria.[38] This inconsistent finding reflects previous reports in which some, but not all, studies found reduced response rates in the anxious subgroup.[39–43] One of the most potentially important consequences of anxious depression is the persistence of residual anxiety post–antidepressant treatment. Such residual anxiety symptoms have been reported to significantly predict an increased risk of relapse.[44,45]

ONSET-BASED SUBGROUPS

The circumstances or events associated with the onset of an episode of MDD have long been used as an empirical method for subtyping. Perhaps the best-established onset subtypes of MDD are seasonal affective disorder and postpartum depression. In addition, age-at-onset subtypes (early vs. late-life) have been examined, as well as subtypes relating to the nature of the triggering event (e.g., trauma).

Seasonal Affective Disorder

Seasonal affective disorder (SAD) can be diagnosed only if recurrent episodes demonstrate a regular temporal relationship between episode onset and a particular time of the year, typically in the fall. Most often, depressive symptoms remit fully between seasonal episodes. As might be expected, the prevalence of seasonal affective disorder varies with latitude, ranging from a prevalence of less than 2% in Florida to ~10% in northern New England.[46,47] Subsyndromal seasonal worsening of mood appears to be at least 2 to 3 times as common as seasonal symptoms that meet DSM-IV criteria for MDD.[48–50] Seasonal affective disorder has not been associated with specific differences in neuroendocrine dysfunction or neurotransmitter levels or a specific pattern of circadian dysregulation (e.g., phase delay or advance).[51]

For the past 20 years, exposure to bright light (2000–10,000 lux for 30–120 minutes daily) has been the recommended nonpharmacologic therapy for SAD. A meta-analysis of bright light treatment studies of SAD[52] found an effect size of 0.84, which was only modestly greater than the effect size of 0.73 for bright light therapy of nonseasonal MDD. Bright light was not found to be an effective adjunctive therapy in patients with nonseasonal MDD who were also being treated with antidepressants. These results suggest some degree of specificity for bright light therapy and SAD.[52]

Postpartum Depression

Postpartum depression is the most common serious complication of childbirth, occurring in 13% of women who deliver.[53] However, a number of these patients actually have had depression prior to delivery. When the onset is postpartum, it typically occurs within the first 4 to 8 weeks after delivery, and the average duration is 7 to 8 months, though 20% of individuals experience a chronic course, with durations of 2 years or longer. The recurrence rate during subsequent pregnancies appears to be high (~50%).[54]

Postpartum depression is thought to be triggered in at-risk women by the steep postpartum decline in reproductive hormones. At-risk women appear to be those who have strong family and/or personal histories of MDD (nonpostpartum) or who have a history of premenopausal dysphoric disorder.[55] The hormonal hypothesis has been elegantly supported by a small study in nonpregnant women in which leuprolide administration, followed by transient challenge with estradiol and progesterone, was used to simulate a postpartum hormonal state.[56] Five of the 8 women with a history of postpartum depression (62.5%) and none of the 8 women in the comparison group developed significant mood symptoms during the withdrawal period.

There are few well-designed treatment studies that evaluate the efficacy of available antidepressants for postpartum depression. Postpartum depression is a different entity than postpartum psychosis, which occurs in 1 in 500 to 1 in 1000 births, and there is some evidence to suggest that the latter is more likely to entail bipolar disorder. In general, it is uncertain whether women who suffer from postpartum depression have a different clinical course or pattern of comorbidity than women with other types of depression.

Early Versus Late-Onset MDD

Early versus late-onset MDD is a commonly reported subgrouping. In the STAR*D study, approximately 38% of patients reported an early onset of MDD, defined as the first episode occurring before age 18 years.[57] Previous studies have reported early-onset MDD to be associated with an increased likelihood of a wide, but inconsistent, range of clinical and demographic variables. Among the most consistently reported are a familial loading for MDD, an increased risk of bipolar disorder, higher rates of comorbidity (especially anxiety disorders), and increased suicidality.[58–63] After adjusting for current age and duration of MDD, the STAR*D study found that early-onset MDD was significantly more common in women than men (40% vs. 30%) and was more likely, as might be expected, to be associated with lower educational attainment. Early-onset MDD was also associated with higher rates of obsessive-compulsive disorder and posttraumatic stress disorder (PTSD) and greater irritability and suicidal ideation. In the STAR*D study, early age at onset had no influence on treatment response.[34]

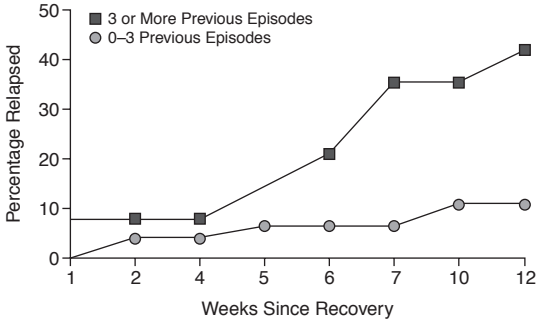
Community data from the latest National Comorbidity Survey indicate that ~50% of individuals have a first onset of MDD after age 32 years and ~25% of individuals have a first onset after age 44 years.[64] In contrast to early-onset MDD, there is no consensus on how late-onset MDD might usefully be defined. Furthermore, the clinical features and treatment response characteristics of late-onset MDD (as distinct from late-life depression) have not been well studied.

COURSE OF ILLNESS-BASED SUBGROUPS

The DSM-IV delineates 5 distinct longitudinal course of illness patterns: single, recurrent, or chronic MDD and, among the chronic subtypes, chronic major depressive disorder or dysthymic disorder, upon which acute episodes of MDD are superimposed. The recurrent subtype exhibits 2 varying patterns, depending on the degree of recovery between the acute episode. Individuals who report persistent depression between full episodes may be difficult to distinguish from individuals with double depression, unless a careful history reveals an initial acute episode of MDD that is antecedent to chronic, low-grade depressive symptoms.

It is uncertain whether these course of illness subgroups have distinct biological correlates. Furthermore, there is no good evidence that course of illness is a prescriptive predictor of differential response to 1 class of treatment relative to another. However, the course of illness subtype has significant treatment implications for long-term management, since chronicity and risk of recurrence are strong predictors of the need for aggressive use of maintenance therapy. For example, patients reporting 3 or more prior episodes have more than a 4-fold increased risk of relapse in the first 3 to 4 months posttreatment (Figure 1).[65]

Figure 1. Cumulative Probability of Relapse in Unipolar Major Depression Based on Number of Previous Episodes[a]



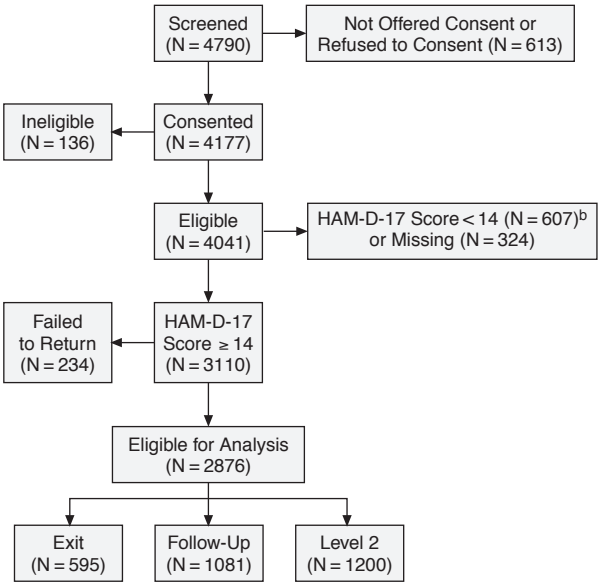
[a]Adapted with permission from Keller and Boland.[65]

In the STAR*D program, approximately 75% of patients reported 2 or more prior episodes, and ~55% of patients reported high levels of recurrence (≥ 3 previous episodes).[66] Early age at onset (even after controlling for age) and positive family history of depression were significant predictors of high risk of recurrence. Patients with the recurrent depression subtype tended to have more severe depressive symptoms and to have more anxious, somatic, and cognitive symptoms. The chronic depression subtype was more likely to occur in first-episode MDD compared with recurrent MDD (44% vs. 19%). While this may simply be attributable to the fact that one must recover from an episode before the episode can recur, it also suggests the possibility that those variables contributing to risk of subsequent recurrence (onset) may be different from the variables that contribute to the risk for illness persistence (vs. remission; offset).

A separate STAR*D analysis examined the clinical correlates of chronic depression, defined as the occurrence of an episode of MDD lasting 2 years or longer.[67] Approximately 20% of STAR*D patients had the chronic subtype of MDD. In this sample, chronic MDD was associated with significantly higher rates of concurrent generalized anxiety disorder (GAD), greater general medical illness burden, and history of suicide attempts. Chronic MDD was more common in black and Hispanic patients and was associated with socioeconomic disadvantage. The findings from these 2 STAR*D analyses were generally consistent with the previously published literature and tend to support the distinction between the chronic MDD and the recurrent MDD subtypes.

Conceptualizing MDD in terms of course of illness subtypes underscores the importance of correctly recognizing the classic phases of treatment and keeping in focus the only acceptable outcome, which is full symptom remission. The persistence of depressive symptoms in individuals with nonremission is associated with significant negative consequences, including marked impairment in functioning, significant increased risk of MDD recurrence, an increased likelihood of developing various forms of comorbidity (e.g.,

Figure 2. STAR*D Participant Flow (level 1)[a]



[a]Adapted with permission from Trivedi et al.[38]
[b]Some of these patients were eligible for entry into level 2.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, STAR*D = Sequenced Treatment Alternatives to Relieve Depression program.

Table 1. Baseline Demographic and Social Characteristics of STAR*D Outpatients With Nonpsychotic Major Depressive Disorder[a]

Characteristic	Value (N = 2876)
Female, %	63.7
Age, mean ± SD, y	40.8 ± 13.0
Race, %	
White	75.8
Black	17.6
Hispanic	13.0
Other	6.6
Marital status, %	
Never married	28.7
Currently married	41.7
Widowed/divorced	29.6
Employment status, %	
Employed	56.2
Unemployed	38.2
Retired	5.6
Clinical setting, %	
Primary care	37.9
Psychiatry	62.1
Insurance status, %	
Private	51.1
Public	14.2
None	34.7

[a]Adapted with permission from Trivedi et al.[38]

substance abuse, medical, psychiatric), increased health services utilization, and shortened life span (due to suicide or medical illness).[6,7]

SEVERITY-BASED SUBGROUPS

A final depression subgroup typology is to categorize MDD by illness severity. In clinical settings, conceptualizing MDD in terms of illness severity is widely used. High severity has been identified as a significant predictor of a lower likelihood of achieving remission in at least two 8- to 12-week studies.[68,69] In the STAR*D study, depression severity was identified as a significant negative predictor of remission (OR = 0.83, $p < .0001$).[34] However, depression severity was not found to be a significant independent predictor of nonremission on a multivariate regression analysis.

CLINICAL SUBTYPES AND TREATMENT RESPONSE: A CLOSER LOOK AT A STAR*D TREATMENT RESPONSE ANALYSIS

The STAR*D study was designed to evaluate the effectiveness of antidepressant treatment in real world outpatient settings. The goal was to obtain outcome data that would be highly generalizable to clinical practice, while retaining sufficient methodological rigor (in terms of diagnosis, measurement, and treatment delivery) to ensure the validity of the results.[35]

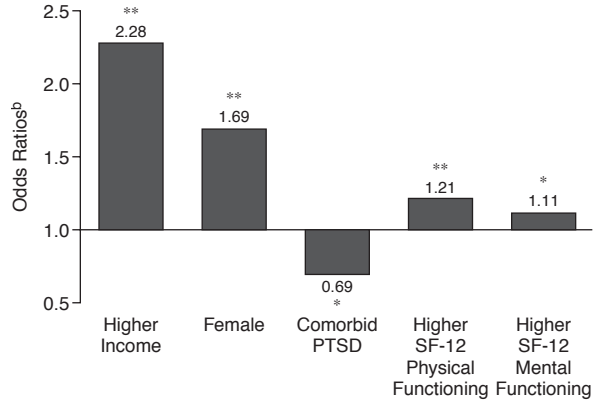
One important STAR*D analysis examined baseline demographic and clinical correlates of achieving remission, including such depression subgroup variables as early versus late onset, presence or absence of chronicity, presence or absence of psychiatric or medical comorbidity, and high versus low severity.[36]

The STAR*D study recruited outpatients who met DSM-IV criteria for MDD in 23 psychiatric and 18 primary care practice settings. In the initial phase, patients received flexible doses of citalopram for up to 14 weeks (Figure 2). Remission was defined as an exit score of less than or equal to 7 on the 17-item HAM-D (primary outcome) or a score of less than or equal to 5 on the 16-item QIDS-SR (secondary outcome).[36]

The baseline demographic and social characteristics of the patient sample are summarized in Table 1. A little more than one third of patients reported early-onset MDD, and approximately one fourth met criteria for chronic depression. The most common depression subgroups were recurrent depression, experienced by approximately 75% of patients and with an average of 6 lifetime episodes of MDD reported, and anxious depression, reported by 53% of patients. Axis I comorbidity was the norm, with only 35% of patients reporting "pure" MDD and fully 38% of patients meeting criteria for 2 or more comorbid Axis I disorders. Anxiety disorders were, by far, the most common form of Axis I comorbidity, especially social phobia, GAD, and PTSD. Data from the latest National Comorbidity Survey[1] indicate that anxiety disorders occur prior to the onset of MDD in greater than 75% of cases.[36,37]

The mean daily dose of citalopram at the acute phase endpoint was 41.8 mg. Remission rate was 28% using

Figure 3. Results of a Stepwise Logistic Regression Analysis: Significant Predictors of Depression Remission in STAR*D[a]



[a]Based on Trivedi et al.[38]
[b]Variables with odds ratios > 1 predict a higher likelihood of achieving remission.
*p < .01.
**p < .0001.
Abbreviations: PTSD = posttraumatic stress disorder, SF-12 = 12-item Short Form Health Survey, STAR*D = Sequenced Treatment Alternatives to Relieve Depression program.

HAM-D criteria and 33% by QIDS-SR criteria. The QIDS-SR response rate was 47%. A stepwise logistic regression analysis was performed to identify the demographic, social, and clinical variables, which were significant independent predictors of remission. The large sample size (N = 2876) permitted inclusion of a large number of candidate predictor variables. The results of the regression analysis identified only 5 variables as being significant predictors of remission, only one of which (the presence of comorbid PTSD) was a negative predictor, associated with a 39% reduction in the odds of achieving remission (Figure 3). With the exception of PTSD, the results of the analysis are notable for the absence of specific clinical predictor variables.[38]

CONCLUSION

As noted at the beginning of this review, the diagnosis of major depressive disorder is marked by its heterogeneity of clinical presentation, neurobiology, course of illness, and treatment response. The urge to delineate clinical subtypes of MDD is a natural response by thoughtful clinicians and researchers to this heterogeneity. Major depressive disorder subtypes clearly have heuristic value, but with a few exceptions (e.g., psychotic depression and the unipolar vs. bipolar distinction), the validity of empirically derived subtypes remains tantalizingly out of reach.

Drug names: citalopram (Celexa and others), estradiol (Estrace, Menostar, and others), leuprolide (Viadur, Lupron, and others), progesterone (Prometrium, Crinone, and others).

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