

Clinically Significant Non-Major Depression

Old Concepts, New Insights

Helen Lavretsky, M.D.

Anand Kumar, M.D.

Clinically significant non-major depression has been underinvestigated despite its high prevalence and public health impact. Although there is an increasing recognition of the importance of non-major forms of depression, their nosological boundaries and neurobiological mechanisms remain largely unknown. The authors discuss the literature pertaining to the current concepts, phenomenology, neurobiology, and treatment approaches to geriatric non-major clinically significant depression. They examine the similarities and differences between various subtypes of depressive disorders and compare non-major, clinically significant depression in elderly patients with non-geriatric adult populations. They draw conclusions from the published literature and propose clinical criteria for the diagnosis of clinically significant non-major depression in elderly persons. (Am J Geriatr Psychiatry 2002; 10:239-255)

Depression in later life has serious health consequences, including increased mortality related to suicide and medical illness and amplification of disability associated with medical and cognitive disorders, often resulting in increased healthcare costs.^{1,2} Although major depression is the most studied and well-defined depressive syndrome, other depressive syndromes and subsyndromal disorders are also associated with significant functional impairment and disability,³⁻⁷ and these clinical categories have only received scant attention in the psychiatric literature.

This article focuses on clinically significant depression that does not meet established criteria for *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM) Major Depressive Disorder (MDD). This category encompasses several clinical subtypes with subtle distinctions. We begin by discussing the clinical

heterogeneity and nosological complexities of these disorders as currently described in the literature. (See Table 1.) We highlight the phenomenological, neurobiological, and therapeutic evidence in support of this category of disorders. Also, we integrate information on elderly patients with data from non-geriatric adult patients with comparable clinical impairment on domains such as epidemiology, neurobiology, and treatment. Finally, we draw conclusions about the validity of this clinical category on the basis of the published literature and recommend future areas of research.

Nosological and Diagnostic Complexities

In current psychiatric practice and research in both elderly patients and younger adult populations, two principal approaches define depression: 1) depressive

Received August 14, 2001; revised September 4, 2001; January 31, 2002; accepted September 6, 2001. From the Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Los Angeles, CA. Address correspondence to Dr. Helen Lavretsky, UCLA-Neuropsychiatric Institute, Room 37-425, 760 Westwood Pl., Los Angeles CA 90095.

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TABLE 1. Summary of the representative studies of non-major, clinically significant depression

Area of Research	Authors	Study Design	Sample	Depressive Subtype	Results
Epidemiology					
1. Community samples	Beekman et al., (1999) ⁶⁰	Literature review by level of "caseness"	Review of 16 community studies of geriatric depression in 22,794 patients	Major depression, minor depression, depressive symptoms	Weighted average prevalence of major depression was 1.8%; minor depression: 9.8%; depressive symptoms: 13.5%
	Heun et al., (2000) ¹¹⁴	Community sample; 86 subjects age 60 and older	Rates of lifetime prevalence	Major, minor, and subthreshold depression	4.9% had a lifetime diagnosis of major depression; 31.8% had either minor or recurrent brief depression
	Steffens et al., (2000) ⁶⁶	90% of Cache County (Utah) elderly community sample	4,559 subjects, ages 65-100 years	Major, minor, subclinical depression	Prevalence of major depression was 4.4% in women and 2.7% in men; lifetime prevalence was 20.4% in women and 9.6% in men, decreasing with age; only 35.7% with major depression were treated with antidepressants
2. Medical illness	Newman et al., (1998) ⁶¹	Community survey in Edmonton, Canada	1,119 community residents age 65 and older, administered the Geriatric Mental State (GMS) Questionnaire and compared with the DSM-III-R diagnoses	Major and minor depression	Prevalence of GMS-AGECAT depression (11.4%) was higher than the DSM-III-R diagnosis of Major (0.86%) or Minor depression (3.6%), which was determined mainly by proportion of dysphoric symptoms on the instrument
	Henderson et al., (1993) ⁵⁸	Cross-sectional prevalence and clinical-correlates study of depression	ICD-10 and DSM-III-R depressive diagnoses	Depressive disorder vs. symptoms	Elderly subjects had many depressive symptoms that did not increase with age; the number of depressive symptoms correlated with neuroticism, poor physical health, disability, and previous depression
	Koenig, (1998) ⁷²	Prevalence of depression in patients with congestive heart failure (CHF)	542 consecutive medical patients	Major and minor depression	Rate of major depression was 36.5% in patients with CHF, vs. 25.5% in patients without CHF; rate of minor depression was 21.5% in patients with CHF, vs. 17% in patients without CHF
	Lyness et al., (1999) ¹¹⁵	Prevalence of depression in primary care patients and associated functional disability	224 outpatients age 60 and older in the Outpatient Family Medicine and Internal Medicine practices	Major, minor, subsyndromal depression	31.7% of patients had a diagnosis of a mental disorder; major depression: 6.5%; minor depression: 5.2%; subsyndromal: 9.9%; and dysthymia: 0.9%; subsyndromal depression is associated with functional disability and medical comorbidity, and often treated with antidepressants

TABLE 1. Summary of the representative studies of non-major, clinically significant depression (continued)

Area of Research	Authors	Study Design	Sample	Depressive Subtype	Results
3. Neurological illness	Burvill et al., (1997) ⁸³	Risk factors for post-stroke depression in 4-month follow-up	191 first-ever stroke patients followed for 4 months	Major and minor depression	17% had major and 11% minor depression at 4 months post-stroke; predictors of depression included functional impairment, living in a nursing home, being divorced
	Cummings and Litvan, (1995) ⁸⁴	Cross-sectional study	33 patients with Alzheimer disease (AD)	Depressive symptoms	Frequency ranged from 6%-33%, depending on definition of depression and instruments used
	Menza et al., (1995) ⁸¹	Cross-sectional comparison of patients with Parkinson disease (PD) and progressive supranuclear palsy (PSP)	19 patients with PSP and 42 with PD	Depressive symptoms	42% of the PSP group had mild-to-moderate depression; 52% of patients had some degree of dementia
Phenomenology	Grayson et al., (1987) ²³	Four diagnostic systems for dementia and depression compared by using Latent Trait Analysis	274 community-dwelling elderly subjects	Depression and dementia	DSM-III, Gurland's system and AGE-CAT and clinician's ratings were used; two distinct clusters of symptoms were identified, and the level of severity (threshold) was identified
	Geiselmann and Bauer, (2000) ⁴	Epidemiological Berlin Aging Study (BASE)	Community sample	Subthreshold depression, dysthymia, major depression	Subthreshold depression had fewer symptoms, with less continuity, with fewer suicidal ideations, thoughts of guilt, or worthlessness
	Oxman et al., (1990) ¹¹⁶	Cross-sectional comparison of older and younger adults	193 outpatients in the Internal Medicine and Family practices	Minor depression	No differences observed between older and younger adults with minor depression
	Pasternak et al., (1994) ¹¹⁷	2-year follow-up	20 bereaved elderly subjects	Subsyndromal depression	Subsyndromal depression was associated with greater functional impairment, worse sleep quality, less perceived interpersonal support, and more intense grieving than nondepressed bereaved subjects
Outcomes	Beekman et al., (1997) ¹¹⁸	Cross-sectional association study of depression and disability	646 community-dwelling older adults, age 55-85 years	Major and minor depression	Associations of major and minor depression with disability and well-being remained significant after controlling for chronic disease and functional limitations; adequate treatment was often not administered, even in subjects with major depression; major and minor depression were associated with increased use of non-mental health services
	Peminx et al., (2001) ¹¹⁹	Longitudinal follow-up of the community sample	2,847 community-dwelling persons age 55-85; 450 subjects with and 2,397 subjects without cardiac disease	Major depression (DSM-III) and minor depression (CES-D ≥ 16)	Depression increased risk of cardiac mortality in subjects with and without cardiac disease; excess cardiac mortality was more than twice as high for major depression than for minor depression

(continued)

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	Penninx et al., (2001) ¹¹⁹	Longitudinal follow-up of the community sample	2,847 community-dwelling persons age 55–85; 450 subjects with and 2,397 subjects without cardiac disease	Major depression (DSM-III) and minor depression (CES-D ≥16)	Depression increased risk of cardiac mortality in subjects with and without cardiac disease; excess cardiac mortality was more than twice as high for major depression than for minor depression
	Penninx et al., (2000) ¹²⁰	Longitudinal follow-up of a community sample (4.5 years)	3,107 older persons (age 55–85)	Major depression (DSM-III) and minor depression (CES-D ≥16)	At baseline, 12.8% had minor depression, and 2% had major depression; minor depression was associated with a significantly greater decline in functional status and performance, as well as with increased risk of death in men; major depression increased risk of functional decline and death in men and women
	Penninx et al., (1998) ⁷¹	Epidemiologic follow-up of community samples (the established populations for epidemiologic studies of elderly subjects)	4,825 persons age 71 years and older followed up at 3 and 6 years	Chronic depression (CES-D) based on cut-off criteria	When present for at least 6 years, depression was associated with a generally increased risk of cancer, after controlling for age, sex, race, disability, hospital admissions, alcohol intake, and smoking
Neuroimaging	Kumar et al., (1998) ¹⁰²	Cross-sectional, quantitative MRI study; whole-brain volumes and normalized measures of prefrontal and temporal volumes	18 subjects with minor depression, 35 patients with late-onset major depression, and 30 normal-control subjects	Major and minor depression	Normalized prefrontal lobe volumes show a significant linear trend with severity of depression, with volumes decreasing with depression severity
Genetics	Anderson et al., (1996) ¹²¹	Family study of subaffective, character spectrum, and primary dysthymia	97 early-onset dysthymic outpatients received diagnostic interview and family history interviews	Dysthymia, subaffective disorder	Subaffective depression subjects had higher rates of major depression, depressive symptoms, and depressive personality features, as well as higher rate of alcoholism in families
	Remick et al., (1996) ⁹¹	Family study	Examined first-degree relatives of probands with depressive-spectrum diagnosis	Probands with minor depression, major depression, dysthymia, and “double” depression	When morbidity risks were calculated using the maximum-likelihood approach for the first-degree relatives, results showed no significant differences in morbidity risk to first-degree relatives
Interventions	Rosen et al., (2000) ¹⁴⁴	6-week open-label study of sertraline treatment of minor depression	12 nursing home residents	Minor depression	75% achieved remission and all tolerated medication well
	Dai et al., (1999) ¹²²	Cognitive-behavioral intervention for minor depression	Elderly Chinese Americans assigned to intervention vs. control	Minor depression	Experimental group showed an improvement; control group did not
	Williams et al., (2000) ¹⁴⁵	Randomized 11-week effectiveness trial	Comparing paroxetine with placebo and problem-solving therapy in primary care (PST-PC)	Minor depression, dysthymia	Paroxetine group showed greater symptom resolution than placebo group in patient with dysthymia and minor depression; patients treated with PST-PC did not show more improvement than placebo group, but their symptoms improved more rapidly than those of placebo patients

Note: The table includes representative studies of late-life major and non-major depression, as well as genetic studies addressing depressive spectrum disorders.

symptoms; and 2) more specific depressive illnesses or disorders defined in terms of duration, number, and type of depressive symptoms. Most nonpsychiatrists typically regard depression in terms of the first construct, whereas psychiatrists apply the second.⁸ Most studies demonstrate that patients with depressive symptoms, even in the absence of a specific depressive disorder, experience considerable morbidity and reduced social functioning.^{8,9}

Only a few of the depressive spectrum disorders currently have official descriptive definitions in the DSM-IV.¹⁰ An even smaller number have gained the status of a “syndrome.” These include Major Depression, Dysthymic Disorder, Mood Disorder Due to a General Medical Condition, Substance-Induced Mood Disorder, Adjustment Disorders, and Depressive Disorder, Not Otherwise Specified (NOS). The last category encompasses several very different and conceptually evolving subcategories, including Minor Depressive Disorder, Premenstrual Dysphoric Disorder, and Recurrent Brief Depressive Disorder. According to DSM-IV, Minor Depression may be subsumed within either Dysthymia, Adjustment Disorder with Depressed Mood, or Depression, NOS. Recognizing these ambiguities and overlap, DSM-IV has published tentative criteria sets for Minor Depressive Disorder, Recurrent Brief Depressive Disorder (RBD), and Mixed Anxiety-Depressive Disorder. This exhaustive list of mood disorders does not however cover all categories of “clinically significant depression.”

The existing clinical and semantic overlap makes any assumptions about the true prevalence of non-major depression somewhat questionable. For example, the term “minor” depression is frequently used to denote all clinically significant forms of depression that fail to meet the criteria for major depression, rather than to the syndrome described in the DSM-IV. The term “subthreshold major depression” emerged to classify patients with fewer than five clinically significant depressive symptoms, thereby not meeting the criteria for the diagnosis of major depression. This patient group was found, in two epidemiological surveys, to have significant impairment in social and occupational functioning.^{11,12} Data are sparse on the clinical course and outcome and on the risk of suicide in patients diagnosed with these conditions.

Historical Perspective

The classification of mental disorders has posed a fundamental challenge to clinicians and researchers in

psychiatry and the behavioral sciences. The basic presumption in medicine—that a classification based on etiology is the most valid—is not applicable in psychiatry, given the lack of clarity about the etiology of nearly all mental disorders.¹³ Descriptive categorization of psychiatric syndromes remains the principal approach to classifying and understanding mental illnesses.^{13,14} A syndrome may be operationally defined as a cluster of related symptoms and signs with a characteristic time course.^{13,14} It may consist of abnormal behaviors, subjective experiences, or a combination of the two.¹³ By definition, primary psychiatric disorders are idiopathic syndromes in which no defined disease processes are known to cause the manifest symptoms and signs.¹⁵ Syndromes are often treated as distinct from one another, and this approach forms the basis of both the DSM and the *International Classification of Diseases* (ICD) for psychiatric disorders. The DSM and ICD systems operationalize diagnostic concepts, standardize the nomenclature,^{16,17} and provide the principal dialects for communication in psychiatry and the behavioral sciences around the world.^{16,17} However, a purely categorical approach has fundamental limitations, potentially impeding our understanding of the nature of these disorders. It is based on the assumption that the psychiatric syndromes are largely distinct from one another and mutually exclusive. This distinction is assumed despite the fact that only a few psychiatric disorders have been adequately validated, and genuine boundaries or points of rarity between the various clinical syndromes and normality remain nebulous. Currently existing constructs of depression frequently overlap or co-exist and often fail to predict disease course and/or treatment outcome.¹⁸⁻²⁰ Summarizing this approach to psychiatric classification, Kendell¹⁴ eloquently says, “Our ignorance of etiology forces us to define most disorders by their symptoms, and syndromes merge insensibly into one another and into normal distress with no obvious natural boundaries or points of rarity to separate them.”

In their classic paper, Robins and Guze²¹ proposed criteria for the validation of clinical syndromes. These comprise the following:

1. Identification and description of the syndrome, either by “clinical intuition” or by cluster analysis;
2. Demonstration of the natural boundaries or “points of rarity” between related syndromes by

- discriminant-function analysis, latent class analysis, and other statistical approaches;
3. Follow-up studies establishing a distinctive course and outcomes;
 4. Therapeutic trials establishing a distinctive treatment response;
 5. Family studies establishing that the syndrome “breeds true”;
 6. Association with some more fundamental abnormality—histological, psychological, biochemical, or molecular.

Few, if any, syndromes or disorders in the DSM classification have been validated with standardized criteria. The majority of existing clinical studies are based on narrowly-defined samples that exclude much of the variability of the affective phenomena under consideration.¹⁵ They include psychiatric patients with categorically-defined depressive disorders, and one must be especially cautious when concluding that different samples of depressed patients are phenomenologically distinct from one another.

The dimensional approach to classifying psychiatric disorders is an alternative described in various research studies.²²⁻²⁸ This approach conceptualizes behavioral syndromes as occurring along more than one dimension. For example, depression and anxiety may be conceptualized as two “parallel” dimensions, as opposed to distinct, mutually exclusive categories.²³ Also, the vegetative and “psychic” or cognitive aspects of mood may be treated as two coexisting dimensions in patients with clinical depression. Psychometric techniques, such as the latent trait analysis, have been used to model the relationship between variables and to identify clusters of symptoms forming a dimension.^{22,24,29-32} The widely used categorical approach is helpful when considering specific interventions for individual disease states. The dimensional approach more accurately captures symptoms and syndromes as overlapping clinical phenomena that reflect underlying traits and core psychopathological processes of mental illnesses.³³

Diagnostic Controversies

The instability of psychiatric diagnoses over time has raised questions about the validity of the contemporary diagnostic classification system of depression. Angst and colleagues^{34,35} reported that there is little stability among the specific subtypes of depression expe-

rienced by those who continue to manifest depression during the follow-up period. Changes in clinical presentation and severity of depression are frequently encountered over time. Categories such as “subsyndromal” (SSD), “subclinical,” or “subthreshold” depression have been described to denote clinically significant symptoms of depression that linger over a period of time.³⁴⁻³⁷ The results of the 1996 International College of Neuropsychopharmacology (CINP) President’s Workshop supported the conclusion that unipolar major depressive disorder is a pleomorphic mood disorder consisting of a cluster of depressive subtypes existing in a relatively homogeneous, symptomatic clinical continuum. This extends from subsyndromal depressive symptomatology through minor depressive episode, dysthymic disorder, major depressive disorder, and “double depression.” The workshop³⁸ argued that subsyndromal and minor depression represent clinically significant depressive subtypes commonly observed during the course of illness in patients with unipolar major depressive illness. Similarly, in research on geriatric depression, the emphasis is shifting from studying, almost exclusively, major depressive syndrome toward studying non-major depressive disorders.³⁹ Whereas the exclusively etiological approach identified only the most severe cases of depression,⁴⁰ the inclusive approach to diagnosing depression predicts outcomes most accurately. It is also supported by the observation that while the prevalence of MDD decreases with age, the prevalence of minor depression and depressive symptoms appear to actually increase.

It is clear from the emerging literature that clinically significant depression that does not meet criteria for MDD is responsible for considerable psychosocial and functional compromise.^{35-37,39,41} Also, the relationship of these categories to MDD is dynamic and tends to change over time. Prospective longitudinal data from the studies of young adult patients reveal that subthreshold depression and other forms may be both an antecedent to and sequela of MDD, thereby providing evidence for the validity of the spectrum concept of depression.³⁵ Despite the broad impact and clinical relevance of these factors, information on the natural course, neurobiological correlates, and treatment response of non-major depression is fragmentary at the present time. Several nosological entities may be subsumed under the rubric of non-major, clinically significant depression, thereby complicating the overall picture both conceptually and clinically.

DIFFERENTIAL DIAGNOSIS

Minor Depression

Minor Depressive Disorder is now included in the DSM-IV as a "potential category," with a set of diagnostic research criteria proposed for further studies.¹⁰ The essential feature of minor depression is one or more periods of depressive symptoms that are identical to major depressive episodes in duration (2 weeks or longer), but which involve fewer symptoms and less impairment. An episode involves either a depressed mood or loss of interest or pleasure in nearly all activities. In total, at least two, but fewer than five, additional symptoms must be present. During the episode, these symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. In some individuals, there may be near-normal functioning, but this is accomplished with significantly increased effort. The diagnosis of Minor Depression is excluded if there is a history of a major unipolar or bipolar mood disorder or a psychotic illness. Using this construct, minor depression may be conceptualized as part of a depressive spectrum defined by the number of symptoms and their severity, as well as the duration of the episode.

The recommended DSM-IV criteria notwithstanding, definitions of minor depression vary among different investigators, which contributes to the confusion of dealing with this group of disorders. Broadhead and associates¹¹ defined minor depression with mood disturbance as the presence of 2 weeks of depressed mood or anhedonia plus one or more other symptoms of depression. Minor depression without mood disturbance is defined as one or more symptoms of depression for 2 weeks, without depressed mood or anhedonia.^{5,41} Minor depression without mood disturbance was included because of a concern that individuals with depressive symptoms may have a depressive spectrum disorder without depressed mood or anhedonia. Bruce and colleagues⁴² defined "dysphoria" as 2 weeks or more of feeling "sad, blue, depressed, or when you lose all interest and pleasure in things you usually cared about or enjoyed." Skodol and colleagues⁴³ defined minor depression as presence of one or more symptoms of depression, one of which must be dysphoria or anhedonia. According to Beck and Koenig,⁵ diagnoses of major depression or dysthymia must be excluded.

Little is known of the natural history of minor de-

pression. About 20% of those diagnosed with minor depression have had a lifetime diagnosis of major depression.⁷ As many as one-third to one-half of patients with major depressions do not have a full recovery and have residual symptoms consistent with minor depressive syndrome.^{5,7} Minor depression is associated with considerable discomfort, disability, and morbidity,⁴⁴ as well as with the excessive use of non-mental health services.³ Despite the obvious mental and public health significance of this group of disorders, only a few studies have focused on minor depression. The existing studies consistently report undertreatment of depressed elderly patients in primary care and nursing home settings, a factor that underscores the importance of the recognition of non-major depression.^{4,44-48}

Subsyndromal "Depressive Spectrum"

The category of subsyndromal "depressive spectrum" disorders (SSD) has been proposed by different investigators in the course of their conducting longitudinal studies of large populations of adult and geriatric patients. In a 15-year follow-up, community-based, cohort-study, Angst and colleagues³⁴ studied the longitudinal course of young adult patients diagnosed with MDD, dysthymia, recurrent brief depression (RBD), and minor depression. They found very little stability for the specific types of depression among those who continued to manifest depression during the follow-up period: 51% of patients with MDD and 44% of those with RBD met criteria for another subtype of depression. When stability was observed, the same subtype occurred in combination with the development of another subtype. Among subjects with a single subtype, severity was greatest among those with dysthymia, whereas individuals with combined subtypes had greater severity than those with a single subtype. Despite the demonstrated close relationship between subthreshold and threshold depressive disorders, there was also a need for maintaining the threshold criteria in diagnostic approaches because of the lack of predictive value of minor depression and depressive symptoms for the illness outcome. They suggested that symptom threshold and recurrence, but not the minimum duration of depressive episodes, should serve as a basis for classification.

Judd and colleagues³⁶ have observed, in their prospective naturalistic follow-up study of 431 adult patients initially diagnosed with MDD, that depressive symptoms at threshold for minor depression or dysthy-

mia (27%) and subthreshold depressive symptoms (17%) were more common than MDD (15%). SSD was operationally defined as any two or more concurrent symptoms of depression (DSM), present for most or all of the time, for at least 2 weeks, associated with evidence of social dysfunction, occurring in individuals who do not meet criteria for the diagnosis of minor depression, major depression, and/or dysthymia. SSD was initially subcategorized into SSD with and without depression. The former overlapped considerably with the DSM-IV category of Minor Depression. Therefore, the revised criteria only included patients who did not meet criteria for Minor Depression; that is, without the 14-day depressed mood/anhedonia requirement. They suggested that the most common SSD symptoms include insomnia, feeling tired, recurrent thoughts of death, and trouble concentrating. They also proposed that the symptomatic course is dynamic and changeable, thus representing a symptomatic continuum of a single disease category.

Other Diagnostic Categories

A number of mood disorders may be considered in the differential diagnosis of non-major clinically significant depression (DSM-IV).¹⁰ Adjustment Disorder with Depressed Mood is diagnosed if the depressive symptoms occur in response to a psychosocial stressor. Criteria for Depressive Disorder, Not Otherwise Specified (NOS) differ from those for MDD in the number of presenting symptoms; that is, fewer than five symptoms can be present. Depressive symptoms occurring in response to the loss of a loved one are considered bereavement. Substance-Induced Mood Disorder is due to the direct physiological effects of a drug of abuse or the side effects of a medication (e.g., steroids). Mood Disorder Due to a General Medical Condition is diagnosed when depression is considered to be due to the direct effect of a general medical condition. Recurrent Brief Depressive Disorder is defined as an episode lasting less than 2 weeks but longer than 2 days, that recurs at least once per month for 12 consecutive months. In summary, the same combination of signs and symptoms, occurring in the context of diverse antecedents (medical and psychosocial) have been classified and categorized as distinct clinical entities in standard psychiatric nosology.

DOES GERIATRIC “NON-MAJOR DEPRESSION” DIFFER FROM DEPRESSION IN YOUNGER ADULTS?

Some similarities and differences exist in phenomenology and disease course of depression in elderly patients and in younger adults.⁴⁹⁻⁵¹ Unlike major depression, with its preponderance of biological and melancholic features, the clinical presentation of minor depression is variable.⁵² Blazer and colleagues⁹ identified a symptom cluster profile unique to people over 60 years old, characterized by depressed mood, psychomotor retardation, poor concentration, constipation, and poor self-perception of health. This cluster was associated with cognitive deficits and physical illness and did not correspond to any particular DSM category. The spectrum of geriatric depression also extends to patients with underlying medical or progressive dementing illnesses who may develop depression during the course of those illnesses. In bereavement, subsyndromal and minor depression stood between major depression and no-depression in terms of their effect on the overall adjustment to widowhood,⁵³ thus, supporting the “spectrum” concept. Prigerson and colleagues⁵⁴ identified distinct patterns of symptoms in complicated grief and bereavement-related depression that were associated with enduring functional impairment. Similarly, some investigators have identified clinical features of dysthymia that are clearly different in elderly patients; these include the late onset, medical comorbidity, cognitive deterioration, and frequent adverse life events.⁵⁵⁻⁵⁷

Epidemiology and Clinical Features

The nosological status of minor depression, together with the variability in diagnostic criteria, contribute to the variability in prevalence estimates of these disorders.^{26,58,59} Relevant factors include differences in diagnostic systems, severity threshold, and duration of illness required for the diagnosis of various affective states/disorders.^{60,61} Despite these methodological considerations, there is broad consensus on the prevalence and clinical impact of non-major forms of mood disorders in both the community and more specialized clinical settings.

A. Community samples. Minor and other non-major forms of clinical depression are more prevalent in adult and elderly populations than MDD. Re-analyzing the Ep-

idemiologic Catchment Area data, Judd and colleagues³⁷ reported a 1-year prevalence of "subsyndromal depression" of 11.8% using the criterion of more than two symptoms for at least 2 weeks. This figure exceeds the 9.5% 1-year combined prevalence for all the DSM-defined mood disorders. Tannock and Katona⁸ suggested that depressive symptoms or subsyndromal cases of minor or mild depression are very common in the elderly population. Blazer and Williams⁶² found that 14.7% of their community sample over age 65 had substantial depressive symptoms. Despite methodologic differences, there is an emerging consensus that the prevalence of minor depression changes with age: there is an increase in symptoms in people in their 30s, a decrease in middle age, a steady increase in old age, and a very steep increase in people over age 80.^{5,63} This phenomenon appears unrelated to the increased mortality, somatization, or increased institutionalization among depressed elderly persons.^{5,40} There is also a suggestion of mitigation of severe depression with age.^{63,64} Caine et al.¹⁵ argue that much of the affective spectrum symptomatology in elderly community populations is not captured by our current diagnostic entities. Most, although not all, studies also suggest that prevalence rates are higher in women and among older people living under adverse socioeconomic circumstances.^{65,66}

B. Long-term care settings. The prevalence rates of minor depression have been estimated in special populations and settings. For example, it affects up to 50% of residents in long-term care facilities and up to 25% of patients in primary care settings.^{44,67} In all settings, the prevalence of depressive symptoms is two- to four-fold higher than major depression.^{48,67} Among institutionalized elderly patients, up to 70% feel "depressed, sad, or blue" at least enough to cause minor problems in their day-to-day activities.⁴⁸ Elderly nursing home and congregate-apartment residents were screened for symptoms of depression. Of 708 survey respondents, 12.4% met the DSM-III-R criteria for Major Depression. Another 30.5% of the total sample reported less severe, but nonetheless marked, depressive symptoms. Such "minor" depressive syndromes were much more common among congregate-housing than nursing home residents. Possible major depression was more prevalent among newly admitted residents of both housing components.

C. Medical settings. Most patients with mental illness are seen exclusively in primary care medicine.^{5,11,12} Primary care settings have therefore been the recent focus of studies of minor depression. It is estimated that 3% to 16% of medical outpatients suffer from minor depression. Up to 64% of medical outpatients will complain of depressed mood.⁵ Studies of depression in medically ill patients usually report the negative impact of depression on the rate of recovery, as well as its overall impact on disability, and increased cost of care.^{5,47,68-72}

D. Geriatric depression in medically ill patients. A review of the literature from 1965 to 1995 found the reported prevalence of minor depression in medical outpatients to be 3% to 16%.⁵ Up to 64% of medical inpatients complained of depressed mood. In a study of 542 patients age 60 and older, Koenig⁷² reported higher rates of major and minor depression in patients with congestive heart failure (CHF) than in cardiac patients without CHF (ratio of 1.5-2:1). Compared with non-depressed CHF patients, those with depression were more likely to have comorbid psychiatric disorders, severe medical illness, and severe functional impairment.⁷² Patients often remained depressed for a prolonged period, and more than 40% failed to remit during the year after their discharge.⁷² When the major and minor depression groups were compared directly, no significant differences were observed between them on salient clinical and psychosocial measures.

A number of studies evaluated the impact of depression on outcomes. Depression was associated with excess disability in visually-impaired patients,⁶⁸ poor treatment in elderly patients with non-insulin-dependent diabetes (Type 2),⁶⁹ and increased risk of falls and fractures.⁷⁰ Chronic depression, when present for at least 6 years, may also increase risk for cancer in elderly women, according to a recent epidemiological study.⁷¹

E. Depression in patients with degenerative and neurologic disorders. Many diseases of the central nervous system (CNS) are associated with increased prevalence of depression. Mood disturbances are commonly observed in neurodegenerative disorders, including probable Alzheimer disease (AD) and Parkinson disease (PD) and after ischemic injury to the brain (post-stroke depression).⁷³⁻⁸⁴ However, depression is not invariably seen in all degenerative disorders, and the prevalence and profile of the mood and behavioral aberrations are relatively disease-specific. This suggests that specific

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neurobiological mechanisms and pathways may be responsible for mood disorders in certain conditions.⁷³⁻⁷⁵

In AD, both major depression and other clinically significant forms of depression that do not meet threshold for MDD have been described.⁷⁵⁻⁷⁹ In certain study samples, clinically significant minor depression and depressive symptoms are more prevalent than MDD and have been reported in 20% to 40% of patients diagnosed with AD.⁷⁶⁻⁷⁹ Prevalence estimates of depression in AD vary widely, from 0% to as high as 86% in some samples. Estimates of depression in PD also vary widely. Studies using more stringent criteria for the diagnosis of depression suggest that the true prevalence of depression in PD may be between 20% and 40%.⁸⁰ Approximately half these patients would meet criteria for MDD, and the rest would show features consistent with minor depression and dysthymia. Differences in diagnostic instruments and in the clinical methods used to diagnose depression (patient interviews as opposed to caregiver reports) probably contribute to these discrepant findings.⁷⁵ Also, the overlap in clinical features between AD, PD, and affective disorders also complicates the diagnosis of depression in these disorders.⁷⁵ The prevalence of depression is low in patients with frontotemporal dementia (FTD) and progressive supranuclear palsy (PSP), thereby indicating that mood disturbances are not a natural consequence of all forms of neurodegeneration.^{81,82,84} Impairment in neurotransmitter function and selective atrophy in the forebrain nuclei have been offered as explanations for the depression in neurodegenerative disorders.^{81,82,84}

Depression after vascular injury to the cerebral hemispheres is now a well-recognized clinical entity. Post-stroke depression may present as minor or major depression and occur within 12 to 24 months after the cerebrovascular accident.⁸³ Major as well as less severe forms of depression occur in patients with neurodegenerative and vascular disease.⁸⁵ This observation, together with the absence of any biological rationale to treat these categories as being distinct, lend credence to the notion that major and other forms of depression may represent a clinical continuum, rather than distinct clinical entities.

Genetics

The results of the association studies in behavioral genetics have been inconsistent. The explanations of these inconsistencies include the lack of the diagnostic

precision in defining phenotypes, as well as biases from population stratification (the mixture of individuals from heterogeneous genetic backgrounds).⁸⁶ These artifacts may occur because population stratification (or admixture) due to ethnic or other confounding factors can generate significant population differences in marker allele frequencies. Sher⁸⁶ suggested that a major problem of association studies in psychiatric diseases is that psychiatric diagnoses are not biologically real disease entities: a syndromal psychiatric diagnosis such as depression includes etiologically, pathologically, and prognostically heterogeneous disorders. For this reason, genetic studies have not yet addressed subsyndromal depressive-spectrum disorders.

On the "syndromal" level, traditional familial studies, designed to study heritability of depression, find a relationship between major depression, bipolar depression, schizoaffective disorders, alcoholism, panic disorder, eating disorders, and personality disorders, thereby establishing a rather broad range of related spectrum-disorders.⁸⁷⁻⁹⁰ Remick and colleagues⁹¹ examined first-degree relatives of probands with the diagnoses of minor depression, major depression, dysthymia and "double" depression in adults. When morbidity risks were calculated for the first-degree relatives using the maximum-likelihood approach, the results showed comparable risks of depression in first-degree relatives of probands with MDD, minor depression, and dysthymia. They drew the conclusion that, from a genetic perspective, major depression, recurrent depression, minor depression, and double depression were indistinguishable.

There are no published genetic studies in elderly patients examining the relationship of major depression to other forms of mood disturbances. The few genetic studies of depression in elderly patients have focused primarily on the apolipoprotein-E genotype, a known risk factor for AD,⁹²⁻⁹⁵ and its relationship to late-onset depression⁹⁶ and cerebrovascular disease in late-life depression.⁹⁷ However, the results of these studies are inconsistent, and many investigators do not find any relationship between apolipoprotein-E genotype and behavioral symptoms such as depression in either cognitively intact or impaired patients.⁹⁸⁻¹⁰⁰ Therefore, genetic studies of affective disorders,⁹²⁻¹⁰¹ although limited, appear to support the concept of a continuum of depressive disorders and suggest that further studies should also include milder forms of clinically significant depression.

Neuroimaging, Cognitive, and Polysomnographic Studies

Most neuroimaging studies in mood disorders are largely restricted to patients with MDD. Magnetic resonance imaging (MRI) studies demonstrate that patients with late-life MDD have smaller focal brain volumes and larger high-intensity lesion volumes in the neocortical and subcortical regions than control subjects.^{102,103} The focal reductions in brain volume have been identified in the prefrontal region, hippocampus, and the caudate nucleus. The physiological correlates of MDD in late life include widespread reductions in glucose metabolism and cerebral blood flow on PET, Xenon-133 inhalation, and single photon emission computed tomography (SPECT).¹⁰³ Glucose hypometabolism in MDD occurred in neocortical and subcortical regions.¹⁰³ Cerebral blood flow and metabolism were reduced in prefrontal cortical regions, superior temporal, and anterior-parietal areas.¹⁰⁴

Our recent study¹⁰² demonstrated that patients with late-onset minor depression had smaller prefrontal lobe volumes than age-matched nondepressed control subjects. Our findings indicate that patients with minor depression present with specific neuroanatomical abnormalities that are comparable with the major depression group but significantly different from control subjects.¹⁰² Normalized prefrontal lobe volumes showed a significant linear trend with the severity of depression, with volumes decreasing with illness severity. Whole-brain volumes did not differ significantly among the groups. These findings suggest common neurobiological substrates for all clinically significant forms of depression with a late onset and support the "spectrum" hypothesis of depression. Neuroanatomical abnormalities may represent one aspect of a broader neurobiological diathesis to mood disorders in late life. Although these findings are intriguing, they clearly need to be replicated before more definitive conclusions can be drawn. Additional studies combining neuroimaging with focused postmortem and other neurochemical studies are also required to further elucidate the biological basis of late-life mood disorders. Studies are underway to examine the extent to which structural abnormalities of the brain, such as hyperintensities on MRI, covary with functional deficits.

Preliminary unpublished observations from our laboratory suggest that patients with minor depression have neuropsychological impairment levels that fall in

between patients with MDD and control subjects. In a study of patients with late-onset major and minor depression and normal-control subjects, we asked whether cognitive abilities decreased with increasing severity of depression. Our results indicate that in domains such as verbal recall, executive functioning, processing speed, maintenance of set, and working memory, patients with minor depression (operationally defined using modified DSM-IV criteria) had scores that fell between the MDD and control groups. This decline in cognitive performance parallels a similar group trend in brain-volume demonstrated with MRI.¹⁰²

Polysomnographic findings in adult patients with subthreshold depressive depression demonstrated shortened REM latency, increased REM sleep, redistribution of REM to the first part of the night, classic diurnality, high rate of family history of mood disorders, and positive response to antidepressant medication and sleep deprivation.¹⁰⁵ Among primary care referrals to a sleep disorders center, short REM latency was found in a large number of patients without subjective mood change but with somatic manifestation of depression. Rather than being incidental, the REM disturbances in the foregoing studies appear consistently in the subthreshold affective group, which suggests a common neurophysiological substrate for subthreshold and melancholic depression.¹⁰⁵ Functional imaging studies of subsyndromal mood disorders in late life are lacking, but they could provide additional information about the pathophysiology of these conditions as compared with syndromal depression.

TREATMENT

To date, studies of treatment of non-major depressive disorders are limited in number. Very little is known about treatment strategies in clinically significant non-major depression. Most existing studies focus on dysthymia and minor depression in primary care.^{39,46,106,107}

Descriptive studies have established that in treating depression, primary care providers use one or more of three modalities: watchful waiting, medication, and referral to the specialty sector.¹⁰⁸ Used most commonly, watchful waiting return visits provided sympathetic listening and a show of interest, and, in some cases, brief, "common sense" counseling and suggestions for tension-reduction.¹⁰⁸ Return visits also permitted the provider to

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monitor the patient's symptom level. In approximately 50% of the instances when a referral to a specialist was considered, the patient refused to accept it because of cost, possible stigma, or problems with access.¹⁰⁸ The use of medication is virtually the only active treatment given by primary care providers, but the evidence of efficacy of psychopharmacologic interventions in non-major depression is currently lacking.

Open-Label Pharmacologic Trials of Minor Depression

Only a few open-label trials among adult outpatients and nursing home residents find promise in alleviating depressive symptoms. In an open-label study of fluvoxamine, patients with minor depression and subthreshold depression associated with dysfunction and disability demonstrated improvement in depression and functioning.¹⁰⁹ In an open-label trial of sertraline involving 12 nursing home residents who met the DSM-IV criteria for Minor Depressive Disorder, 75% of patients reached remission by Week 6. All patients were able to tolerate sertraline.⁴⁴

Treatment of Depression in Neurological and Degenerative Disorders

Although the high prevalence of clinically significant depression has been reported in many neurological and neurodegenerative disorders, there have been only 13 relevant placebo-controlled trials of antidepressants, of which only 3 had more than 10 subjects enrolled.⁸⁵ Positive results were reported in the trials of citalopram in depressed patients with AD and post-stroke depression and with use of desipramine in patients with multiple sclerosis and brain injury.⁸⁵ Nearly half of the trials did not report drug-placebo differences. These studies examined the use of imipramine, maprotiline, or clomipramine for depressed patients with AD, trazodone for patients with poststroke depression, and amitriptyline for patients with depression and epilepsy. Beneficial effects of nortriptyline were complicated by significant problems with orthostatic hypotension.⁸⁵ Likewise, delirium and cardiovascular morbidity occurred in patients taking nortriptyline for post-stroke depression.⁸⁵ Although it is clear that depression comorbid with neurological illness compounds disability and worsens outcomes, clear evidence in support of effective pharmacological approaches is lacking.⁸⁵

Psychotherapy and Combined Treatments

In the United Kingdom, with its general practice-based healthcare delivery system, attention had been paid to developing brief, practical psychological treatments that could be provided in the primary care setting itself. Problem-solving therapy (PST) is based on behavioral medicine principles and teaches a patient that there can be a relationship between problems experienced and emotional symptoms, particularly in the case of depression and anxiety.^{110,111} It is a collaborative treatment, with the therapist and patient focusing on regaining a sense of control over life's problems, which are likely to be important factors in resolving emotional symptoms. PST is brief, lasting 4 to 6 sessions, for a total of 2 to 4 hours, with most sessions fitting into a 30-minute clinic visit. Non-mental health practitioners could provide such treatment. Gath and Catalan¹¹⁰ and Mynors-Wallis,¹¹¹ at Oxford, reported a high level of patient acceptance and satisfaction with the treatment, as patients readily understood and accepted the practical value of acquiring problem-solving skills. The British investigators concluded that PST in primary care (PST-R) was an effective alternative to medication treatment in their primary care patients; it performed better than placebo and was as effective as amitriptyline.¹¹² In the recent American randomized 11-week effectiveness trial comparing paroxetine with placebo and PST in primary care (PST-PC), the paroxetine group showed greater symptom-resolution than the placebo group. Paroxetine showed moderate benefit for depressive symptoms and mental health functioning in elderly patients with dysthymia and more severely impaired elderly patients with minor depression. The benefits of PST-PC were smaller, had slower onset, and were more subject to site differences than those of paroxetine. Patients treated with PST-PC did not show more improvement than placebo, but their symptoms improved more rapidly than those of placebo patients during the latter treatment weeks. PST-PC/placebo differences were more pronounced in the minor depression group than in patients with dysthymia.⁴⁵

Current Trials of Pharmacological and Combined Treatment of Depression in Primary Care Settings

Several ongoing collaborative trials are addressing the effectiveness of pharmacologic and nonpharmacol-

ogic treatments of depression in primary care setting. Two current collaborative trials are the NIMH-supported Prevention of Suicide in the Primary Care Elderly Collaborative Trial (PROSPECT) study,¹⁰⁶ and the Hartford Foundation-supported Improving Mood: Promoting Access to Collaborative Treatment for Late-Life Depression (IMPACT) study, both are evaluating the effectiveness of models in practices by nurse health specialists.¹⁰⁷ The PROSPECT study was designed to evaluate the extent to which intervention targeting depression in older primary care patients with depression could reduce risk factors for suicide, including suicidal ideation, hopelessness, and depression. The Department of Veterans Affairs (the VA Unified Psychogeriatric Biopsychosocial Evaluation And Treatment program [UPBEAT]) project on mental health services in primary care is evaluating the relative effectiveness of integrated mental health services delivered in the medical care setting versus referral to mental health professionals for older primary care patients with depression, anxiety disorders, and alcohol abuse problems.¹⁰⁷ All three of the trials include patients with non-major depression.

At present, treatment approaches to non-major clinically significant depression remain unclear. However, the results of a large, multi-site trial for minor depression and dysthymia in primary care⁴⁵ offer some hope in improving the outcomes of depression. In the absence of evidence to the contrary, antidepressant medications and psychotherapeutic interventions,¹¹³ alone or combined, are currently the recommended course of treatment.

CONCLUSIONS

There are similarities and differences in the manifestations of clinically significant depressive disorders. There is an emerging consensus from epidemiological, longitudinal, and genetic studies supporting the idea of a continuum of depressive disorders, ranging from the very mild "subthreshold" to major unipolar and bipolar disorders. Evidence from neuroimaging and neuropsychological studies lends additional support to this thesis. All forms of clinically significant depression are associated with considerable economic and psychosocial consequences. Current approaches to studying affective illness, which adhere to traditional nosological categories, may no longer be adequate for the next gener-

ation of studies into the biological and psychosocial correlates of this group of disorders. Rigid definitions of the phenotype, without fully integrating clinical realities, greatly limits the scope of studies aimed at elucidating the true biological basis of mood disorders.

Applying the classical criteria outlined by Robins and Guze²¹ for the validity of a diagnostic category, one would be hard-pressed to draw meaningful distinctions between major and non-major forms of depression in elderly patients and non-geriatric adults with depression. Dividing patients with these forms of affective illness into encapsulated categories would require us to ignore clinical and scientific realities for the sake of nosological simplicity. Mood disorders need to be conceptualized and studied along multiple dimensions, including severity, duration of illness, and treatment response. Also, although there are similarities between geriatric and non-geriatric depression with regard to phenomenology and other clinical features, there are also important differences that make the independent study of elderly patients crucial to our understanding of depression in late life.

Our desire to draw sharp boundaries between serious mental disorders and transient states of distress has contributed to our neglect of the biological and psychosocial basis of non-major forms of depression. Clearly, the sustained and more extreme forms of mood disturbances are easier to conceptualize as clinical disorders. The precise distinction¹¹³ between mood changes, as a normal emotional response to the vicissitudes of life, and depression, as a clinical disorder, is more nebulous in mild depressive states. Operationally defining a condition is often a necessary first step in trying to establish its clinical and biological correlates and demarcating its boundaries from other conditions and normality. However, any operational definition needs to be clinically meaningful and should reflect all relevant dimensions of the condition. Defining a minimum "floor effect" for the severity of depression, duration of symptoms, and overall psychosocial functioning, and integrating these domains cohesively would be an important first step in defining a plausible phenotype. In elderly patients, cognitive and medical aspects are additional dimensions that need to be considered. A phenotype encompassing all of the relevant dimensions could then serve as the basis for genetic, neurobiological, and psychoneuropharmacological studies.

We propose clinical criteria for the diagnosis of clinically significant non-major depression (CSNMD) in el-

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derly patients (Table 2). These criteria are consistent with operational definitions of minor depression used in other clinical studies but broader in clinical and methodological scope.^{102,116} We believe this is an important first step in understanding and elucidating the phenomenological and neurobiological basis of clinically significant mood disorders, especially in elderly patients.

Traditional approaches to classifying psychiatric disorders may no longer be adequate for the next generation of studies into the biological correlates and treatment approaches to patients with these groups of

disorders. As more evidence accumulates from well-designed multicenter studies, we will be in a position to make more definitive statements and recommend more precise guidelines for both the diagnosis and management of this complex group of disorders.

Dr. Kumar is at the UCLA Department of Psychiatry and Biobehavioral Sciences.

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TABLE 2. Proposed diagnostic criteria

- 1) Presence of low mood and/or loss of interest in all activities most of the day, nearly every day, and
 - 2) At least two additional symptoms from the DSM checklist:
 - a. significant weight loss when not dieting or weight gain (e.g., a change in more than 5% of body weight in 1 month), or decrease or increase in appetite nearly every day
 - b. insomnia or hypersomnia nearly every day
 - c. psychomotor retardation or agitation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
 - d. fatigue or loss of energy nearly every day
 - e. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
 - f. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
 - g. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
 - 3) The symptoms cause clinically significant distress or impairment in social and occupational functioning
 - 4) 17-item Hamilton Rating Scale for Depression (Ham-D) score of ≥ 10 , or Geriatric Depression Scale Score of ≥ 12 ¹²³
 - 5) Duration of at least 1 month;
Duration subtypes:
 - a. Duration from 1–6 months;
 - b. Duration from 6–24 months;
 - c. Duration >24 months
 - 6) The symptoms may be associated with precipitating events (e.g., loss of significant other)
 - 7) Organic criteria:
 - objective evidence from physical and neurological examination and laboratory tests, and/or history of cerebral disease, damage, or dysfunction, or of systemic physical disorder known to cause cerebral dysfunction, including hormonal disturbances and drug effects;
 - a presumed relationship between the development or exacerbation of the underlying disease and clinically significant depression;
 - the disturbance occurs exclusively to the direct psychological effect of alcohol or a substance use;
 - recovery or significant improvement of the depressive symptoms following removal or improvement of the underlying presumed cause
 - 8) Exclusion criteria:
There has never been:
 - an episode of mania or hypomania;
 - a chronic psychotic disorder, such as schizophrenia or delusional disorder.Previous history of major depressive episode is not an exclusion criterion.
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