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Subsyndromal depression in the elderly: underdiagnosed and undertreated

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Abstract

Major depressive illness is present in about 5.7% of US residents aged ≥65 years, whereas clinically significant nonmajor or "subsyndromal" depression affects approximately 15% of the ambulatory elderly. Risk of developing subsyndromal depression increases as elderly people get older. Because they have numerous distressing ailments, everyday life can be burdensome for many elderly persons. Almost one third of Americans aged 75 years or older rate their health as "fair to poor." Yet, the physical discomforts experienced by so many elderly individuals are unlikely to generate a clinically significant depression unless other ingredients such as loneliness, impairment of mobility, loss of a spouse, a serious financial reverse, and—probably most important—genetic susceptibility are added to the psychophysiological mix. Because depression damages quality of life and is usually eminently treatable, it is essential that physicians and other health professionals be trained to recognize true depression and distinguish it from confounding conditions caused by medications, organic brain disease, or short-term grief reactions. In the medically ill elderly, depressive symptoms may be overlooked because of the assumption that they are a part of the concurrent medical illness. Diagnosis of depression in the elderly can be greatly assisted by use of age-specific screening instruments such as the Geriatric Depression Scale. Ultimately, brain imaging and biochemical and physiological measurements may prove useful in diagnosis. The presence of somatic concomitants of depression such as severe neck and low back pain should alert the clinician to the possibility of an underlying mood disorder. Suicide and suicide attempts occur all too frequently in the depressed elderly; therefore, screening for late-life depression is urgently required among the elderly in primary and residential health care settings.

1. Introduction

Approximately 2 million (5.7%) of the 35 million US residents who are aged 65 years and older have a major depression such as unipolar or bipolar disorder, or dysthymia. Another 5 million (14.3%) may have "subsyndromal" or "subthreshold" depression, namely, depressive symptoms that fail to meet the full diagnostic criteria for a major depression [1,2]. The risk of major depression increases up to 3-fold if a first-degree relative has the illness [3].

The prevalence of major depressive illness appears to diminish as people get older [4]; however, the incidence of clinically significant nonmajor forms of depression increases steadily with advancing age and rises steeply among those older than 80 years [5,6]. Although minor and other nonmajor forms of clinically significant depression are much more prevalent than major depression among the elderly, prevalence estimates depend on the setting in which the survey is conducted and the criteria used to define the depressive disorder under scrutiny. Nevertheless, despite the somewhat confusing terminology used to describe them, the nonmajor depressions are associated with significant functional impairment and psychosocial disability. Moreover, in this nonmajor category, a significantly increased risk remains of developing a major depression, having an accident, or experiencing a serious illness [7].

A number of terms have been used to describe clusters of depressive symptoms that do not meet the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for this disorder. Lavresky and Kumar [8] have pointed out that among problems associated with the *DSM-IV* classification and other nosologies are the following: (1) many of the syndromes in the *DSM* classification await validation with standardized criteria; (2) existing clinical studies have been based on narrowly defined samples that exclude much variability; (3) there is little stability among specific subtypes of depression. Over time, these subtypes can change materially in clinical presentation; (4) diagnostic categories into which depression is divided are largely, if not entirely, symptom-based and are

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not anchored in more fundamental anatomic, physiological, or molecular disorders. In the words of Judd et al [9], "During the long-term course of (depressive) illness, major, minor, dysthymic, and subsyndromal syndromes wax and wane within the same patient, and these symptomatic periods are interspersed in the overall course with times when patients are remitted and symptom-free."

Among medical outpatients aged 65 years or older, the prevalence of "depression" has been reported to range from 7% to 36%, increasing to 40% in the hospitalized elderly. Blazer and Williams [10] found that 14.7% of a community sample of persons aged 65 years or older had "substantial depressive symptoms." Minor depression is said to affect up to 50% of residents in long-term care facilities [4,11]. Among institutionalized elderly patients, up to 70% reported feeling "depressed, sad, or blue" to the extent that such feelings created problems in their daily activities. Among 708 elderly inhabitants of nursing homes and congregate apartments, 12.2% had major depression, and an additional 30.5% experienced less severe but, nevertheless, marked depressive symptoms [4,8].

2. Disabilities associated with the aging process

For many elderly persons (particularly the "oldest old" [age 85 years and older]), everyday living can be a burdensome experience. The elderly are increasingly subject to muscular aches, joint pain and stiffness, diminishing physical mobility, decreased vitality, loss of strength and endurance, reduced hearing and visual acuity, insomnia, anxiety, cognitive decline, and decreased resilience. These are only some of the ailments the elderly are called upon to bear.

If "dysphoria" is taken to mean "feeling unwell" or "not feeling good," it is not surprising that many elderly individuals who are not necessarily depressed are dysphoric. On the other hand, if "dysphoria" means feeling "unhappy" rather than (or as well as) "unwell," then dysphoria would have to be an important feature of geriatric depression [12]. Hence, when the term is used in a medical context, its precise meaning should be specified.

In the National Health Information Survey 2002 [13], 31.4% of respondents aged 75 years and older rated their health as "fair to poor" (self-rated health is a strong and independent predictor of long-term health [6]), 29% felt that walking a quarter of a mile would be difficult or impossible, and 21% stated that they would have difficulty in climbing 10 steps without resting. In addition, 36.6% of those in the $\geq$75-year category gave a history of heart disease, 51.8% of high blood pressure, and 11.1% of stroke.

Because symptoms associated with poor self-rated health such as pain, daily discomforts, and low energy resemble symptoms of a "generalized cytokine-induced sickness response," Lekander et al [14] examined self-rated and physician-rated health, circulating levels of interleukin (IL) 1β, IL-1β receptor antagonist, IL-6, and tumor necrosis factor α (TNF-α) in 265 consecutive primary care patients. They found that poorer subjective health was associated with higher concentrations of inflammatory cytokines and that self-rated health was a stronger predictor of cytokine concentrations than physician-rated health. Based on their findings, the authors suggest that an individual's health perceptions may be coupled to circulating cytokines.

Given that that almost one third of Americans aged 75 years or older self-rate their health as being fair to poor, it is not surprising to learn that the plasma concentrations of certain inflammatory cytokines increase with aging [15]. Interestingly, the proinflammatory cytokines are powerful modulators of corticotropin-releasing hormone (CRH) secretion. CRH, in its turn, stimulates enhanced hypothalamic-pituitary-adrenal axis activity with increases in circulating adrenocorticotropic hormone and cortisol—hormones reported to be elevated in major depression [16]. Clearly, the extent to which the concentrations or patterns of circulating cytokines associated with geriatric depression differ from those in nondepressed elderly controls needs further investigation (see below).

For Americans currently 75 years old, the odds are almost 2:1 against surviving to 85, 3.5:1 against surviving to 90, and 9:1 against surviving to 95 [17]. Awareness of the rapidly escalating risk of becoming disabled or dying as one gets older and more frail exacerbates feelings of insecurity about the future. The ever-increasing enrollment of elderly persons in assisted care facilities—often well in advance of any immediate need for them—attests to the pervasiveness of these fears and uncertainties, the desire to avoid loneliness, and the need for the kind of security offered by such institutions [18].

Although they may cause significant discomfort (one definition of dysphoria), the frequent and sometimes chronic pains, anxieties, and disabilities experienced by elderly do not necessarily generate clinically significant depression. Other ingredients such as impairment of physical mobility, loneliness, loss of professional identity, and genetically determined susceptibility to depression usually have to enter the psychological mix before clinical depression emerges in elderly persons.

Indeed, the ability of an illness or a distressing experience to give rise to clinical depression depends in part on the inherent vulnerability of the elderly individual and on the severity and duration of the adverse circumstance.

3. Diagnosis of depression in the elderly

The patterns of depressive symptoms that occur in the elderly are appreciably different from those manifested in younger-age groups. Some of the differences are illustrated in age-specific screening instruments such as the Geriatric Depression Scale (GDS, 15-item version [19]) shown in Table 1. Blazer and Williams [20] have described a cluster of symptoms unique to the elderly that includes (in addition to depressed mood) poor concentration, psychomotor retardation, poor self-perception of health, and

Table 1
Geriatric depression scale—short form[a]

Geriatric Depression Scale (short form)	
Are you basically satisfied with your life?	yes NO
Have you dropped many of your activities and interests?	YES no
Do you feel that your life is empty?	YES no
Do you often get bored?	YES no
Are you in good spirits most of the time?	yes NO
Are you afraid that something bad is going to happen to you?	YES no
Do you feel happy most of the time?	yes NO
Do you often feel helpless?	YES no
Do you prefer to stay home, rather than going out and doing new things?	YES no
Do you feel like you have more problems with memory than most?	YES no
Do you think it is wonderful to be alive now?	yes NO
Do you feel pretty worthless the way you are now?	YES no
Do you feel full of energy?	yes NO
Do you feel your situation is hopeless?	YES no
Do you think that most people are better off than you are?	YES no

Scoring: 1 point for each response that is in capital letters. Scoring cutoff: normal (0-5), above 5 suggests depression.

[a] Reprinted with permission from Sheikh and Yesavage [19].

constipation. Cognitive deficits and physical illness were also prominently associated with the cluster. It should be noted that the combination of features described by Blazer and Williams does not fall under any *DSM* category.

As in younger-age groups, clinically significant depression in the elderly (ie, an unduly prolonged mood disorder sufficiently incapacitating to warrant medical attention) needs to be distinguished from the "normal" short-term reactions that occur in response to any of a number of emotionally stressful events such as bereavement, a serious financial setback, an undesired move to an unfamiliar environment, or development of a painful or disabling illness. Improved techniques for identifying the various types of depression have been developed in recent years; however, clinical depression in the elderly remains seriously underdiagnosed and undertreated [8,21]. An analysis of diagnosis and treatment of depression in the elderly Medicare population based on claims data from 1992 to 1998 disclosed that, after 1992, the rate of depression diagnosis more than doubled, reaching 5.8% in 1998 [22]. This increase—which presumably reflected increasing attention being given to the problem—shows how much room for diagnostic improvement there was in the 1990s. One can only wonder how much room remains for further improvement.

In the medically ill elderly, depressive symptoms may be overlooked because of the assumption that they are a part of the concurrent medical illness. Indeed, many of the symptoms of depression such as dysphoria, fatigue, loss of appetite, and sleep disturbance resemble those associated with a somatic illness. In addition, elderly patients often may fail to complain of symptoms of depression, considering them to be normal concomitants of aging.

Yet, because depression in the elderly damages quality of life, is associated with a significantly enhanced risk of suicide, and is usually eminently treatable, it is extremely important that the attending physician be trained to recognize depression and distinguish it from the other disorders (eg, organic brain syndromes [dementias], and normal grief reactions) often associated with, and which may mimic, clinical depression.

Rating scales are indispensable in screening for depression in elderly patients, including those who reside in assisted living facilities and nursing homes [23]. Such instruments are especially helpful to family physicians and other nonpsychiatrists who suspect that a patient may be depressed. Useful criteria for the diagnosis of clinically significant nonmajor (subsyndromal) depression in the elderly have been proposed by Lavretsky and Kumar [8]. Bonin-Guillaume et al have written that "inventories are better than interviews and should be integrated into semi-standardized interviews which do not last more than 30 minutes" [24]. Vinkers et al [25] have reported that, in the Leiden 85-Plus Study, the 15-item version of the GDS detects change in depressive symptoms after the death of a partner, "a negative life event that is the most important risk factor for depression in the elderly." The authors conclude that the GDS-15 is sufficiently sensitive to detect longitudinal changes in depressive symptoms.

4. Somatic markers of depression

4.1. Low back and/or neck pain

Several authors have recently described severe back and/or neck pain as being strong predictors of major depression at a wide range of ages [26-28]. Currie and Wang [26] used the short form of the Composite International Diagnostic Interview to examine the prevalence and correlates of major depression in persons with chronic back pain using data from the Canadian Community Health Survey in a sample of 118 533 household residents. Rates of major depression were estimated at 5.9% for pain-free patients and 19.8% in those with chronic back pain. The rate of major depression increased in linear fashion with greater pain severity. In another Canadian study, Carroll et al [27] found an independent and robust relationship between depressive symptoms and onset of neck and low back pain. In comparison with the lowest quartile of scores (the least depressed), those in the highest quartile of depression scores had a 4-fold increased risk of troublesome neck and low back pain. Carrington Reid et al [28] studied 754 members of a large health plan who were 70 years and older. They used a score of 16 or greater on the Center for Epidemiologic Studies–Depression Scale to identify the presence of depressive symptoms. The authors found that, in this elderly group, the presence of depressive symptoms was independently associated with the occurrence of disabling back pain (adjusted odds ratio = 2.3).

It appears that the occurrence of disabling back and/or neck pain in community-dwelling elderly persons is a strong predictor of an underlying depression. For this

reason, it is appropriate to look for and rule out depression in elderly individuals who complain of severe neck and/or low back pain.

5. Some biologic concomitants of depression

Depression is usually diagnosed on the basis of a psychiatric evaluation that commonly includes the physician's observation of the patient's behavior, a medical-psychiatric history, interviews with the patient's spouse or near relatives, exclusion of confounding factors such as drug-induced or substance abuse–induced depressive symptoms, and application of 1 or more rating scales of the kind described above.

Although there are currently no laboratory tests for depression readily available to clinicians, it seems likely that—in the future—supplementary information of diagnostic value will be obtainable from brain imaging, various physiological tests, and measurement of concentrations in blood of biologically active agents such as cytokines, prostaglandins, homocysteine, neurotrophins, and hormones reflecting activity of the CRH and locus ceruleus–norepinephrine systems.

5.1. Depression-associated morphological changes in brain

There is increasing evidence that structural abnormalities occur in the brains of elderly patients in association with depression. For instance, Ballmaier et al [29] used high-resolution magnetic resonance imaging to study the brains of 24 elderly patients with major depression and 19 group-matched comparison subjects. They found highly significant bilateral volume reductions in gray matter in the anterior cingulate, the gyrus rectus, and the orbitofrontal cortex. There were also significant bilateral white matter volume reductions and significant cerebrospinal fluid volume increases in the anterior cingulate and gyrus rectus. The authors suggested that the prominent bilateral gray matter deficits in the anterior cingulate, gyrus rectus, and orbitofrontal cortex "may reflect disease-specific modifications of elderly depression."

The depression-related changes in brain morphology described by Ballmaier et al appear to be reversible—at least to some degree. Evidence for such plasticity has been provided by Nobuhara et al [30] who carried out diffusion tensor imaging studies in 8 late-life depressed patients and 12 healthy controls. The patients were scanned before and after electroconvulsive therapy (ECT) treatment, with fractional anisotropy (FA) being determined in the frontal and temporal regions and the corpus callosum. Before ECT, the investigators found a significant white FA reduction in widespread frontal and temporal brain regions in the depressed patients. A significant increase in frontal white matter FA was observed after a course of ECT. Thus, the findings of Nobuhara et al provide additional evidence for the reduction of frontal white matter associated with depression in the elderly and for at least partial restoration of white matter integrity in association with effective treatment.

In light of changes that appear to occur in portions of the brain's anatomy in association with the occurrence of major depression in the elderly, it is noteworthy that deep brain stimulation (DBS) slightly above and lateral to the right nigrostriatal area elicited several reproducible 4-week-long episodes of acute depressive dysphoria in a 36-year-old woman with medically refractory Parkinson disease and a history of intermittent depression [31]. The DBS-elicited mood disorder was transient, resolving spontaneously in 4 weeks. This finding, added to the observation that ablation of the olfactory bulbs in rodents causes a depressionlike syndrome reversible by chronic treatment with various antidepressants known to act on neurotransmitters implicated in mood disorders [32], provides additional support for the belief that the subjective symptoms of depression are expressions in behavior and consciousness (as articulated by the patient) of 1 or more distinct perturbations in brain architecture and neurotransmitter function.

5.2. Possible humoral markers of depression

There is recent evidence that plasma levels of TNF-α are markedly elevated in patients with severe depression, compared with sex- and age-matched healthy controls [33]. In a series of 15 depressed patients followed up longitudinally with measurement of TNF-α before, during, and after repeated ECT, clinical improvement was accompanied by a gradual and significant decline in TNF-α concentration, eventually reaching levels comparable to those observed in healthy controls. Depressed patients not receiving ECT showed elevated TNF-α levels throughout the study period.

Depressive symptoms also have been associated with increased IL-1β plasma levels. A common polymorphism in the promoter region of IL-1β has been linked to altered synthesis of this agent, and McCulley et al [34] have hypothesized that this common genetic polymorphism is a risk factor for the occurrence of depression in Alzheimer disease.

It has been reported that the serum concentrations of brain-derived neurotrophic factor (BDNF) in a series of 118 unrelated healthy volunteers were associated with depression-related personality traits [35]. In these subjects, BDNF correlated significantly with the depression-related factor neuroticism (r = 0.212, P = .022), leading the authors to propose that low BDNF levels, in combination with depressive personality traits, might constitute a risk marker for vulnerability to mood disorders.

Finally, as pointed out by Akiskal et al [36], many outpatients with "subsyndromal" depression have been shown to have shortened rapid eye movement (REM) latency, increased REM%, and redistribution of REM to the first part of the night. Such REM disturbances appear consistently on consecutive nights of polysomnography in patients with subthreshold affective disorder.

Clearly, the practical usefulness to clinicians of brain, biochemical, and polysomnographic studies such as those

described above remains to be established. However, if certain changes in brain morphology, neurological function, or in concentrations of circulating substances known to be associated with geriatric depression prove to be helpful markers for the presence of the illness (and possibly its severity), the availability of such "tests" will add a sorely needed biologic dimension to the currently limited diagnostic armamentarium.

6. Suicide in the elderly

Although individuals aged 65 years or older comprise approximately 13% of the US population, 18% of all suicide deaths in 2000 occurred in this group. The highest suicide rates have been recorded in white men aged 85 years and older (59 deaths per 100 000), which is more than 5 times the national US rate of 10.6 per 100 000. Overall, men are more likely than women to die by suicide, with the overall sex ratio being 4:1. Among US residents aged 85 years or older, men are 14 times more likely to commit suicide than women [37].

A recently reported Canadian survey has found that many common illnesses are independently associated with an increased risk of suicide in the elderly [38]. This risk is greatly increased among individuals with multiple illnesses, Specific illnesses associated with suicide included (with odds ratios of risk shown in parentheses) congestive heart failure (1.71), chronic obstructive lung disease (1.62), seizure disorder (2.95), urinary incontinence (2.02), anxiety disorders (4.65), depression (6.44), psychotic disorders (5.09), bipolar disorder (9.20), moderate pain (1.91), and severe pain (7.52). Almost half of the patients who committed suicide had visited a physician in the preceding week.

A group of Swedish investigators analyzed consecutive records of 85 men and women who had committed suicide and undergone forensic examination and compared the findings with those from 153 control subjects [39]. These workers found that visual impairment, neurological disorders, malignant disease, and a heavy burden of physical illness were independently associated with an increase of suicide in elderly people. Serious physical illness appeared to be a stronger risk factor for suicide in men than in women. Yet another Swedish study that focused on life events and psychosocial factors in elderly suicides showed that somatic illness, family discord, and financial trouble were significant risk factors. Other risk factors were mental disorder, low educational achievement, and a history of previous suicide in the family [40]. Factors associated with a decreased risk included active participation in an organization and having a hobby. Multivariate logistic regression analysis showed mental disorder and family discord to be particularly important risk factors for suicide among elderly men and women.

Suominen et al [41] reported recently on their investigation of the health care contacts among elderly individuals attempting suicide. They studied all consecutive 1198 suicide attempters treated in hospital emergency rooms in Helsinki, Finland, between 1997 and 1998, dividing the subjects into 2 groups—those 60 years and older (n = 81) and those younger than 60 years (n = 1117). They found that, during the 12 months immediately before the attempt, the majority of elderly suicide attempters had a contact with a health care agency, but their mood disorders were likely to have remained undiagnosed before the index attempt. Only 4% had been diagnosed with a mood disorder before the attempt, but 57% after. The authors emphasize that, to prevent suicidal behavior, screening for "late-life depression" is urgently required among the elderly in primary health care settings. Moreover, health care professionals and paraprofessionals seriously need further education in recognition, diagnosis, and treatment of mood disorders in elderly patients.

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