

# Depression and Medical Illness in Later Life

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In the elderly, depression appearing with medical illness seems to be the rule rather than the exception and leads to significant comorbidity. Effective diagnosis and treatment is therefore essential. Comorbidity invariably leads to conceptual and diagnostic dilemmas, since depression may be both a cause and a consequence of medical illness. Thus, the pathways through which depression and medical illness interact are considered. Treatment issues pertinent to depression comorbid with medical illness are presented, and the utility of reciprocal models that can help formulate treatment plans is discussed. Overall, the need for interventions that improve quality of life for individuals with depression and chronic health problems is highlighted.

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There are many reasons to justify sustained interest in the relationship between depression and medical illness. On a conceptual level, this relationship illustrates the struggle of psychiatry with the "mind-body" divide. Recent systems of classification of mental disorders have sidestepped the issue by taking a purely descriptive approach to the diagnosis of depression.<sup>1</sup> However, in clinical practice, the diagnosis of depressive disorders in people with comorbid medical illnesses has remained a troubling issue. The majority of people older than 65 years have one or more chronic medical illnesses, and morbidity rates rise steeply with age.<sup>2</sup> Since depression is more common among those with medical illness, comorbidity among affective and other medical illnesses is the rule rather than the exception in old-age psychiatry. This may explain why the rate of diagnosis of depression in primary care, less than optimal in younger adults, is often found to be dramatically low in older patients.<sup>3-7</sup> Clinical guidelines for the treatment of depression are based on findings among younger patients, treated at (academic) psychiatric centers. Patients recruited in randomized trials are usually carefully selected, excluding those with comorbid medical conditions. Even in the growing number of trials concentrating on late-life depression, the average age of participating patients is often in the "young-old" range (55-75 years), and comorbid medical

conditions are underrepresented.<sup>8,9</sup> The conclusion must be that very little is known about the efficacy (let alone the effectiveness) of established treatment strategies for depression in the elderly patients doctors see in day-to-day practice.

In lieu of evidence, commonsense reasoning has had a pervasive influence on diagnosis and treatment of depression in elderly patients with medical illness. This commonsense reasoning usually boils down to the motto: "If you have a reason to be depressed . . . you are not depressed." If it is understandable that a patient is sad, anxious, depressed, or dysphoric, then there is no need to make this mood into a clinical entity, and treatment may even be considered harmful. From the perspective of younger, usually healthy doctors, a chronic medical illness is a very good reason to be depressed. Therefore, depressive symptoms occurring in the context of a medical illness are often ignored. Although these types of attitudes have been branded as ageist, they continue to influence clinical guidelines.<sup>8</sup> The primary aim of this article is to review epidemiologic data concerning comorbidity between depression and other medical illnesses, concentrating on issues with clinical relevance and that open fruitful avenues for further research. The article will focus on depression and chronic physical illness, as a complete review of all available evidence is beyond this brief article. Readers are also referred to recent reviews.<sup>10-12</sup>

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## DEPRESSION AND MEDICAL ILLNESS: SOME METHODOLOGICAL REMARKS

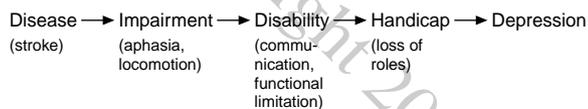
To survey the results of research fruitfully, both depression and medical illness need to be defined in more detail. As is illustrated in Table 1, the level of caseness (symptom, syndrome, or diagnosis) at which depression is defined and measured has profound influence on the

**Table 1. Levels of Caseness of Depression Influence the Associations Found With Medical Illness<sup>a</sup>**

Level of Caseness	Example	Instrument	Prevalence in the Community <sup>b</sup>	Association With Medical Illness
Symptom	Lack of energy, depressed mood	BDI, Zung, CES-D, GDS	Very common	Very strong
Syndrome	Pervasive depression	GMS	10%–15%	Strong
Diagnosis	Major depressive disorder	DIS	< 2%	Modest

<sup>a</sup>Abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, GDS = Geriatric Depression Scale, GMS = Geriatric Mental Schedule, DIS = Diagnostic Interview Schedule, Zung = Zung Self-Rating Depression Scale.

<sup>b</sup>Data from Beekman et al.<sup>13</sup>

**Figure 1. The Disablement Process and Depression: Depression and Stroke**

strengths of associations with medical illness. Many of the older studies have defined depression at the symptom level of caseness, reaching very high levels of depression in subjects with medical illness.<sup>12</sup> The definition of pervasive depression is less rigid than in formal diagnostic criteria, but requires a level of severity at which an average clinician would instigate specific treatment of depression.<sup>14</sup> At the diagnostic level of caseness, such as in major depressive disorder, associations with medical illness are much less impressive.<sup>15</sup>

The relationship between depression and stroke is illustrated in Figure 1. Medical illness should not be thought of as a single entity, but as a process involving different stages of disablement.<sup>16</sup> The importance of this becomes clear when reviewing results of recent studies. Moving from left to right in Figure 1, we see that the associations between medical illness (disablement) and depression become progressively stronger.<sup>15,17,18</sup> Therefore, although associations between specific medical illnesses and depression constitute a very important heuristic model, associations with handicap and disability seem to be more important for clinical practice.

A further issue is that associations between medical illness and depression appear to be stronger in studies carried out in more specialized health care settings. Most of the older studies relied on convenience samples of people with medical illnesses. Sampling in specialized clinics, these studies arrived at very high levels of comorbidity with depression. In the community, comorbidity levels are generally much lower.<sup>19</sup>

Many studies have relied on cross-sectional data to assess the relationship between depression and medical illness. There are many reasons why cross-sectional data may be biased, leading to exaggerated estimates of associations between medical illness and depression. Such reasons include

- recall and report bias, i.e., those who are depressed tend to report more negatively about their health<sup>20</sup>
- the impossibility of disentangling cause and effect in cross-sectional studies
- prevalence is the outcome of incidence and prognosis, which cannot be discerned in cross-sectional studies

### DIAGNOSTIC DILEMMAS: INTERPRETING DEPRESSIVE SYMPTOMS IN MEDICALLY ILL PATIENTS

Comorbidity invariably leads to conceptual and diagnostic dilemmas. For example, in many infectious disorders there are signs of “sickness” that, when evaluated with psychiatric rating scales, may mimic depression. Another example is that risk factors for depression following stroke change over the course of time. Directly after the stroke, biological factors probably predominate. Later, the psychosocial implications of the stroke and general vulnerability, such as neuroticism and family history, become more important.<sup>21,22</sup> In early poststroke depressions, it may be argued that affective symptoms are part of the disease, not warranting specific diagnosis. The danger of this argument is that affective symptoms are ignored altogether, leading to lack of treatment of potentially amenable and clinically highly relevant depressive symptoms.<sup>23,24</sup> A descriptive diagnostic tradition, such as adopted in psychiatry, sidesteps the above interpretative dilemmas. It should be realized that a purely descriptive approach to medical diagnosis is rather primitive and unique to psychiatry. In other settings and specialities, etiologic thinking is more prevalent. This difference may help explain why changing attitudes towards depression outside psychiatry has proved to be so difficult.

On a more practical level, distinguishing between symptoms directly caused by medical illness and those attributable to depression may require considerable skill. For example, should profound lack of energy in an elderly patient with anemia be attributed to the medical illness or depression? Considering the 4 dimensions of depressive symptoms listed in Table 2, a hierarchy of utility of symptoms may be constructed. The cognitive symptoms of depression are least susceptible to contamination by symptoms of medical illness. Of the core affective symptoms, sustained, pervasive change of mood remains a reliable indicator of depression, whereas lack of interest or energy is

**Table 2. Four Dimensions of Depressive Symptoms**

Dimension	Examples of Symptoms
Cognitive	Negative thinking, lack of concentration
Affective	Depressed mood, lack of interest
Behavioral	Impaired daily functioning
Physical	Lack of appetite, weight loss, change of diurnal rhythms (sleep), pain

**Table 3. Risk Factors for Major Depressive Disorder in Later Life: Exposure to Risk Factors, Odds Ratios, and Population-Attributable Risks<sup>a</sup>**

Risk Factor	Exposure (%)	Odds Ratio (95% Confidence Interval)	Population-Attributable Risks (%)
Recent partner loss	2.4	12.78 (3.09 to 52.76)	8.6
Events, 0–6 years	15.4	1.51 (0.73 to 3.14)	5.8
Events, war	14.6	2.08 (1.03 to 4.2)	11.0
Functional limitations	35.8	2.37 (1.35 to 4.18)	27.5
Chronic medical illness	64.8	1.37 (0.76 to 2.46)	16.5

<sup>a</sup>Data from Beekman et al.<sup>15</sup>

usually more difficult to interpret. With regard to the behavioral correlates of depression, both in medical illness and in depression, levels of daily functioning and well-being may be impaired, leaving their attribution to the judgment of the clinician. The physical signs of depression, finally, are the most difficult dimension of symptoms to diagnose accurately.

This difficulty is reflected in the instruments most suitable to screen for depression in older or medically ill populations. The Geriatric Depression Scale (GDS),<sup>25</sup> the Hospital Anxiety and Depression Scale (HADS),<sup>26</sup> and the Center for Epidemiologic Studies Depression Scale (CES-D)<sup>27</sup> all have either totally deleted or played down the importance of physical symptoms of depression, diminishing the overlap with and overestimation of depressive symptoms in the medically ill. Whereas ignoring the physical symptoms of depression in medically ill people may be fruitful for screening purposes, it is not a viable option in diagnosis. The existing diagnostic instruments differ in their attempts to solve this problem. However, the diagnosis of the physical symptoms of depression in elderly, medically ill people remains a complex clinical decision, requiring considerable skill and experience that cannot be accurately simulated by existing instruments.

**COMORBIDITY PATTERNS**

Taking leave of the above conceptual and methodological difficulties, how do depression and medical illness interact? As both are common in later life, their co-occurrence is partly due to chance. However, a consistent finding of a huge body of research is that there is a strong, more-than-chance association between medical illness and depression in later life.<sup>10,12</sup> Indeed, the intimate relation-

**Table 4. Physical Illness as a Cause of Depression: Mechanisms**

Type of Effect	Physical Illness	Mechanism
Biological	Stroke	Damaged brain tissue (left frontal)
	Parkinson's disease	Imbalance of neurotransmitters
	Rheumatoid arthritis	Immune system, cytokines
	Hyperparathyroidism	Hypercalcemia
	Cushing's disease	Hypercortisolemia
Diabetes mellitus		Genetic association
		Vascular association
Psychosocial	Many illnesses	Hypothalamic-pituitary-adrenal axis
		Threat; mourning; loss of roles, status, or functioning; deprivation
Iatrogenesis	Long list of drugs	Mostly unclear

ship with medical illness is one of the hallmarks of geriatric depression, a key difference from depressive disorders of younger adults. Both for theoretical and clinical reasons, it is important to trace comorbidity patterns. Depression may be both a cause and a consequence of medical illness, and each disorder may be of etiologic as well as prognostic significance for the other. Moreover, depending on the type, severity, and stage of the medical disorder, the nature of the association with comorbid depression may change, leading to highly complex and changing patterns of comorbidity.

**Medical Illness as a Risk Factor for Depression**

As would be expected, numerous studies have found medical illness to be a strong etiologic and prognostic factor for late-life depression.<sup>9,12,18,28,29</sup> Indeed, most authors agree that medical illness is a dominant risk factor for depression in the elderly, dwarfing the effects of all other factors.<sup>18,28,30</sup> Table 3 contains results of a community-based study in the Netherlands, in which the impact of risk factors is expressed in 2 different ways.<sup>15</sup> From an etiologic perspective, the relative risk of depression associated with exposure to risk factors is the appropriate analysis. Table 3 shows that recent loss of the partner carried by far the strongest relative risk for depression in this study (those exposed to partner loss had a 12 times greater chance of being depressed when compared with those not exposed). Both chronic medical illness and functional limitations carried modest to weakly elevated risks of depression. However, relative risks do not take the prevalence of the risk factor into account. From a public health perspective, population-attributable risks, in which the prevalence of the risk factor is accounted for, are the analyses of choice. Table 3 clearly shows that, because chronic illness and functional disability are far more common than partner loss, these factors do indeed dominate the risk profile of elderly in the community.

Table 4 summarizes some of the pathogenic pathways through which medical illness is thought to cause depres-

**Table 5. Depression as a Cause of Medical Illness: Mechanisms**

Type of Effect	Mechanism
Biological	Agitation, lack of sleep, depletion of reserve capacity Nutritional deficiencies and metabolic dysregulation Immunologic dysregulation Cardiovascular dysregulation
Symptom presentation	Changed perception of the body Changed perception of pain
Nihilism and hostility	Inadequate self-care Lack of compliance with medical advice Disturbed interaction with caregivers/medical personnel
Iatrogenesis	Side effects of psychopharmacologic agents

sion (see Robertson and Katona<sup>12</sup> for a series of reviews). Depending on the specific disease, different biological pathways to depression have been studied,<sup>31–36</sup> and depending on the psychosocial impact of the illness, several corresponding pathways have also been assessed.<sup>10,37–40</sup>

### Depression as a Risk Factor for Medical Illness

Increasing awareness of the immense consequences of depression have provided great impetus for recent research. In later life, as among younger adults, depression has been shown to have a profound impact on well-being, daily functioning, and use of medical services.<sup>41–44</sup> A series of studies<sup>36,45–48</sup> suggests that depression, especially major depressive disorder, carries a higher risk of mortality. This excess mortality is probably only partly due to suicide and mostly due to cardiovascular and other morbidity.<sup>36</sup>

Table 5 summarizes some of the pathways through which depression is thought to influence medical illness. As in Table 4, there are both biological and psychosocial pathways for which increasing evidence is being gathered. The long-standing interest in this area is illustrated by the Malzberg study,<sup>45</sup> which showed that mortality among subjects with involuntional melancholia was 6 times higher than in controls. Cardiovascular disorders accounted for an estimated 40% of mortality among the depressed, which was 8 times higher than in the controls.<sup>44</sup> In later studies, these findings have been confirmed. A total of around 40% to 50% of patients with acute myocardial infarction have a history of depression.<sup>46</sup> In 283 cardiovascular patients 10 days post–myocardial infarction, 45% had symptoms of depression, and 18% met the criteria for major depressive disorder.<sup>49</sup> Symptoms of depression 5 to 15 days post–myocardial infarction are a significant predictor and independent risk factor for mortality at 6 months (3 times greater than in nondepressed patients).<sup>36</sup> More detailed analyses of the impact of depression on cardiovascular homeostasis are being carried out.<sup>36,47</sup>

### Depression and Medical Illness: A Reciprocal Model

The exact pathway through which depression and medical illness interact may vary between individuals and

across time. Very few studies are equipped to trace complex comorbidity patterns, if only because repeated measures covering considerable lengths of time are necessary among large numbers of elderly people. The few studies that come close to these requirements suggest that a reciprocal model is indeed the most appropriate model and that the pathway from medical illness to depression is the stronger and more direct pathway.<sup>50</sup> From a clinical perspective, a reciprocal model, including all 4 stages of disablement, helps to structure the information needed to plan treatment (see Figure 1). Moreover, reciprocal models, theoretically frustrating as they may be, afford a great number of therapeutic possibilities.<sup>10,39</sup>

### TREATMENT ISSUES

Most of the pharmacotherapeutic trials pertaining to depression, even those concentrating on older people, generalize poorly to the elderly patients seen in day-to-day practice.<sup>8</sup> In other areas of treatment, such as psychotherapy, even fewer data are available. A negative effect of comorbid medical illness on efficacy of antidepressant medication has been fairly consistently demonstrated.<sup>8,9</sup> However, this should not lead to therapeutic nihilism. Most studies, including studies carried out in selected groups of patients with both a physical illness and depression, show reasonably favorable outcomes.<sup>11,12</sup> Treatment can work, but it often takes more effort. To be effective, a treatment plan should not be limited to depression. Using Figure 1, several treatment options will usually apply. Gurland and Wilder<sup>10</sup> distinguished 3 basic types of intervention: primary treatment of depression, treatment of physical illness/impairments, and interventions relevant to both conditions. Examples of the latter 2 are physical rehabilitation, restoration of physical independence, control of pain and other discomforts, bolstering of social support, and cognitive therapy for improving attitudes and coping capacity.<sup>10</sup> These interventions cannot cure physical illness, but they can have an effect on the more general and subjective aspects of physical health and on associated mood changes. The finding that the impact on mood of these more general aspects of physical health is more salient than the effect of specific diseases is therefore highly relevant for the treatment of depression in the elderly.

A further point refers back to the discussion of levels of caseness. Evidence suggests that associations with medical illness are stronger when a broader definition of depression is used. Indeed, in a recent study, minor depression was strongly associated with physical illness, whereas major depression was not.<sup>15</sup> If this finding is corroborated, it would imply that in elderly people with major depressive disorder, primary treatment of depression should not be delayed, whether or not there are comorbid physical illnesses. Given the severe consequences for well-being and functioning in minor depression,<sup>40,43</sup> delay-

ing primary treatment may also be questioned. However, as yet very little is known about the efficacy of treatment of minor depression, especially among elderly individuals with physical illness. Therefore, strong recommendations cannot be made in this area.<sup>51</sup>

## CONCLUSION

In geriatric psychiatry, comorbidity is a rule rather than an exception. Disentangling comorbidity patterns among depression and other medical conditions is both a theoretical and methodological challenge, opening several fruitful areas of future research. Efficacy, effectiveness, and large-scale implementation of treatment remain understudied. Examples of unresolved issues are the effectiveness of standard pharmacotherapeutic treatment in day-to-day practice and in primary care, effects of treatment of minor depression, and the efficacy of psychotherapeutic intervention in elderly patients with comorbid medical conditions.

In practice, the exact interactions between disorders will often remain elusive, especially in nonpsychiatric settings such as primary care. However, treatment of late-life depression should be centered in primary care, if only because of the sheer numbers of elderly people involved. Adopting a reciprocal model of comorbidity is clinically useful, because it leads to a pragmatic and structured approach to treatment and because it offers many opportunities for intervention. In recent guidelines, the advice has been given to first treat any (underlying) medical disorder, deferring primary treatment of depression. Given recent epidemiologic findings, this advice is questioned: in major depressive disorder certainly, and in minor depression possibly, primary treatment should not be deferred. Frail elderly people have compromised reserve capacity in most homeostatic and psychosocial areas. Any intervention that may better their quality of life and bolster motivation and other resources needed to live with chronic physical health problems deserves active implementation.

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## Discussion

# Depression and Medical Illness in Later Life

**Dr. Thompson:** It would be useful for us to clarify the reasons why we are going against the guidelines laid down by the U.S. consensus panel and advising physicians to treat depression, regardless of physical morbidity. The first is humanitarian. If we have a treatment that works, should we be withholding it? The second relates to the finding that major depressive disorder is strongly linked to handicap; resolution of the medical illness will still leave major depressive disorder.

**Dr. Salzman:** A third consideration is that depression is linked to prolonged healing of the primary disorder, and morbidity is enhanced by depression, so treating the depression can improve the clinical outcome. Frasure-Smith and colleagues' data [*JAMA* 1993;270:1819–1825] on myocardial infarction (MI) show that treating depression enhances the response to healing and the treatment of the medical illness.

**Dr. Zisook:** The study implies such an enhancement, but we don't yet have the treatment data. We need a study to document the implication.

**Dr. Sadavoy:** But, if we are talking about aggressive pharmacologic intervention in a severely ill individual, you might want to defer it for several reasons.

**Dr. Montgomery:** Obviously, guidelines are not to be interpreted as rules for every patient, but, on the basis on Frasure-Smith and colleagues' data, depression is the best predictor of death. You don't want to wait before treating the depression.

**Dr. Salzman:** I wonder if the increased risk of suicide in the over-85 age group, especially in those with a serious physical illness, stroke, or MI, could be reduced by treating their depression. These people tend not to be treated actively because physicians are concerned about side effects, but we now know that we can use selective serotonin reuptake inhibitors (SSRIs) in this group.

**Dr. Zisook:** This is true especially treating with a medication that decreases platelet serotonin levels. There is a lot of indirect evidence that depression causes physical illness, in particular cardiovascular disease. It would be good to have a prospective hypothesis and test it.

Heart rate variability is a factor worth investigating. Good data indicate that depression adversely affects heart-rate variability, so, if you've got somebody who is impaired immunologically and has impaired heart-rate variability, that's a good setting for the development of cardiovascular disease.

**Dr. Beekman:** Is there any evidence that a successful intervention aimed at depression actually reduces cardiovascular risk factors?

**Dr. Zisook:** Some data suggest that paroxetine does. For example, in contrast to nortriptyline in patients with major depression and ischemic heart disease, paroxetine inhibited platelet activation, suggesting that it may reduce platelet activation in vivo and could thereby positively impact ischemic heart disease-related mortality in this population [*Pollock BG, et al. J Clin Psychopharmacol* 2000; 20:137–140]. In addition, another study found that paroxetine, again in contrast to nortriptyline, had no sustained effects on heart rate variability [*Roose SP, et al. JAMA* 1998;279:287–291]. I don't know of data on other SSRIs, but the paroxetine data are impressive, showing decreased variability and platelet changes.

**Dr. Beekman:** Quite a few centers throughout the world are starting research in this very important area.

**Dr. Montgomery:** What we are doing is identifying depression as a serious condition and saying that you should pay close attention to its treatment, regardless of what else is going on.

**Dr. Beekman:** A very important idea is that depression has more adverse consequences in subjects who are compromised in other areas. So, the more physically ill you are, the more detrimental it is to have concomitant depression. This is totally different from the current way of thinking.

**Dr. Salzman:** How do we communicate to the public in a way that is scientifically acceptable that depression must be treated?

**Dr. Montgomery:** A lot more scientific evidence supports the treatment of depression than hypotension, for example.

**Dr. Zisook:** But a link exists between depression and cardiovascular disease, since they are the 2 major causes of disability in the world.

**Dr. Sadavoy:** What's actually happening with patients? We are not suggesting that there is a biological predisposition associated with disability, but a change in self-concept and view of the world that produces, in the first instance, an experience of demoralization that may progress along different pathways. If we take that kind of formulation, our treatment interventions will also have to take different pathways. We need to determine the core deficits, which will determine the most effective prevention.

**Dr. Montgomery:** I agree that we should not simply talk about improving mood. What we need to talk about is depression as a serious disorder that needs treatment and present evidence-based information on effective treatments. I would be careful about taking a model that says

demoralization needs to be dealt with to prevent the evolution of the depression. The model may be interesting, but I don't think that it should be applied. We must focus on depressive disorders that have reached the stage at which treatment responses can be seen.

**Dr. Thompson:** What about prevention? In the elderly who have a physical illness, for example a stroke, is there some way of preventing the endpoint of major depressive disorder or important depression through intervening with the social and psychological complex of that person's experience?

**Dr. Sadavoy:** We have to acknowledge that these are important issues even though we may not have answers.

**Dr. Zisook:** You could argue for high vigilance in that population.

**Dr. Thompson:** There is some work on the psychology of aging. The question is whether, for example, the elderly people who maintain morale through the insults of getting older have less family history of depression. Is depression related to the social and psychological context, or is there a biological factor in these people?

**Dr. Beekman:** If you look at depression developing soon after a stroke, biological factors are probably very important. But depression can occur after the first month because people have to cope with disabilities and role changes. Over time, the risk factors associated with the incidence of depression change, and they become more general. They look more like other types of depression, so family histories, neuroticism, and other life events become more important. Thus, the timing in the history of the physical illness plays an important part in how you should conceptualize depression. This is well documented for stroke, but the same model seems to apply to Parkinson's disease or rheumatoid arthritis. But, whatever the model, the message remains that you should not defer treatment of major depression.

**Dr. Salzman:** And data show that the longer depression exists, the harder it is to treat. We should also remember that older people probably take longer to respond.

**Dr. Sadavoy:** There is also the fact that minor depression progresses to major depression, so early intervention is important.

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