

Managing Depression in Geriatric Populations

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Background. Late life depression is an increasingly acute public health concern due to the quickly expanding population of elderly in the US. The last few years has witnessed an explosion in the research literature changing our understanding of this disease.

Methods. Published studies over the past decade focusing on the epidemiology, phenomenology, comorbidity, and treatment of depression in the elderly were reviewed.

Results. The prevalence and phenomenology of depression in late-life varies with age. It remains highly prevalent in the elderly population, and certain vulnerable populations of older adults are at special risk. Further, the morbidity of late-life depression on physical health, social support systems, and overall functioning is considerable, making depression a leading cause of disability in elderly adults and a risk factor for mortality and suicide as well. Findings suggest a heterogeneity in etiology and in treatment response among older adults with depression, and differences from younger adults as well.

Conclusions. This paper reviews our current understanding of late life depression and the implications for treatment and prevention. In addition, we review current research questions and future considerations in this field.

Keywords Depression, Treatment, Elderly, Review

INTRODUCTION

Depression in late-life is a serious and frequent cause of emotional suffering in the elderly. Its prevalence is high in the community, but certain vulnerable populations of older adults are at special risk. Further, the morbidity of late-life depression on the individual's physical health, social support systems, and overall functioning is considerable, making depression a leading cause of disability in elderly adults and a risk factor for mortality as well. Because of the serious impact late-life depression has on the individual, compounded by the quickly expanding population of elderly in the US, the last few years has witnessed an explosion in the research literature on late life depression (1). Interesting findings have emerged that have challenged our understanding of this disease and its treatment.

This review will address the major research findings of the past few years regarding the epidemiology and phenomenology, the emerging etiological and mechanistic understandings, and the revised treatment guidelines for late-life depression.

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Epidemiology

Though depression is a serious health issue throughout the life cycle, epidemiologic studies have found that the prevalence of major depressive disorders varies by age. In the US, depression is highly prevalent in older adults (see Table 1). Overall, the estimated prevalence of geriatric major depression in the general population is 1–4%, describing nearly 5 million adults age 65 and older (2–8). However, this does not include the number of older adults that are affected by clinically significant depressive symptoms that do not quite reach the criteria for major depressive episodes. Among community-dwelling older adults, minor depression rates range from approximately 8–16% (2,7,9). There is no significant racial or ethnic difference, but major depression is more common among women compared to men throughout all ages, a difference persisting into late life (10).

The rates of depression in older adults also vary by setting. MDD has been identified in 5–12% of elderly patients treated in primary care settings (6,11–13). Rates of depression in patients admitted to acute medical hospitals have been found to range from 5%–44% (14,15). The prevalence of depression in nursing care facilities may be even higher. Smallbrugge and colleagues (16) evaluated nursing care residents at 14 facilities in the Netherlands and found that depression was present in

17.1% of patients, though other studies have estimated even higher rates of depression—some exceeding 25% (17).

Phenomenology

Age affects the clinical presentation of depression. Brodaty et al. (18) surveyed 810 mixed age patients presenting to a Mood Disorders Unit for admission. They found that melancholic and psychotic depression were more common with older patients compared with younger patients. Significantly, they also found that the clinical presentation and subjective assessment of depressive symptoms differed between the two age cohorts. For older adults with depression, clinician-rated “depression severity” scale scores were increased while patient-rated “subjective” depression scale scores were decreased compared with younger adults with depression. Further, analysis of the data found that the increased severity noted on clinician assessments was related to age and not to depressive recurrence.

The authors suggested two explanations for this disparity: the propensity for older adults to accept depressive symptoms as “normal,” or the possibility of differences in scale items between cohorts. Gatz & Hurwicz (19) have noted that depressive symptom severity ratings may be inflated because of increased endorsement of somatic symptoms resulting from comorbid age-related general-medical problems. The total score is higher because the somatic symptoms of depression may be scored higher due to the real medical problems more often found in older adults. However, the low subjective scale scores noted in depressed older adults (despite potentially increased overall severity of depression types) may be an indication that older adults are less likely to report feeling “sad” or having a “depressed mood.”

Many researchers have observed that in contrast to depressed younger patients who typically report feeling sad, sadness often is not a presenting complaint in older patients with MDD. Husain and colleagues (20) contrasted the presenting symptoms of younger and older adults with depression enrolled in the Sequenced Treatment Alternatives to relieve Depression (STAR*D) Study. They found that older patients had more middle and terminal insomnia, less irritability, and less hypersomnia than younger depressed patients. They were also less likely to hold negative views of themselves or of their future, and were less likely to report previous suicide attempts. Gallo and Rabins (21) have suggested that signs other than reported sadness should be emphasized in diagnosing depression in older adults. These include hopelessness, helplessness, anxiety, complaints of memory loss with or without objective signs of cognitive impairment, anhedonia, slowed movement, irritability, disinterest in personal care, poor adherence to medical or dietary regimens and unexplained somatic complaints.

Two of these symptoms deserve closer scrutiny. The first, unexplained somatic complaints, may be particularly important in the correct diagnosis of late-life depression. Kim et al. (22) applied the Item Response Theory to mixed age depressive adult subjects taking the Beck Depression Inventory (BDI). They noted

that somatic symptoms were much more often reported by older adults with depression than younger adults, especially when depression was more severe. Wallace and Pfohl (23) reviewing responses to the 24-item Hamilton Rating Scale for Depression, found that symptoms of guilt and suicide ideation showed general decline with age, whereas the only symptom showing a significant increase was hypochondriasis. These findings support the long-standing observations that depressed elders frequently focus on somatic complaints when describing depression.

The second symptom of concern, anxiety, is also frequently observed by or reported to physicians by elderly depressed adults as a primary problem (rather than depressed mood), making a correct diagnosis difficult. Anxiety is a frequent comorbid symptom with depression, and may be seen in as many as 65% of older patients with depression (24) even though anxiety disorders are thought to decline with age (25). In fact, several reports suggest that older adults might be more likely than younger patients to manifest a mixture of anxiety and depression (24,26). Because of this, a diagnostic syndrome of “mixed anxiety-depressive disorder” has been proposed as clinically and heuristically useful for older patients (27). Criteria for this disorder are listed in the DSM-IV Appendix (28).

Because depression is a life long illness, some researchers have suggested that late-onset versus earlier-onset (or recurrent) major depressive episodes may represent distinct phenomenological entities (29). Epidemiologically, about 30% of cases of major depression in old age represent late-onset depression (1). Clinical studies have reported differences in etiology and symptoms between early-onset depression and late-onset depression in late life though findings have not been consistent. Findings of higher rates of family mood disorders in patients with early onset depression (30,31) have suggested an increased genetic susceptibility for earlier age of onset, while a different etiological mechanism for late-onset depression has been suggested due to increased findings of vascular pathology (32,33). Phenomenologically, some researchers suggest that late-onset depression may have increased symptoms of guilt, anxiety, and apathy (34,35), though this has not been found by others (31,36). However, in contrast to early-onset (or recurrent) depressions in late-life, late-onset depressions are associated with more cognitive and executive dysfunction, characterized by specific deficits in tasks of attention and executive function. These deficits are associated with increased anhedonia and, significantly, cardiovascular comorbidity (37).

Etiology and Mechanism

Depression varies in prevalence and phenomenology by age, but it also varies within the older age cohorts. This suggests that the etiology and mechanisms of depression are multiple and attributable to a balance of biological, social, and psychological concerns. To review the risk factors identified in each domain is beyond the scope of this paper. However, Blazer and Hybels (38) have identified specific risk and protective

factors especially relevant to depressive symptoms and disorders of late life. These include biological risks (such as genetic polymorphisms or mutations, low levels of DHEA, cortical and subcortical ischemia, and Alzheimer's disease) and psychological protective factors (such as socio-emotional selectivity and wisdom).

Overall, the influence of genes appears to be less powerful for depression in late life compared with younger adults. As noted previously, a history of family mood disorders is less common in elderly depressed with late-onset disease than elderly depressed with early-onset, and less in the general elderly depressed population compared with younger cohorts (31,39). Yet, genes do continue to play a significant part in elderly depression. Twin studies of older adults in Sweden have shown that genetic influences accounted for 16% of the variance in total depression scores (as measured by the Center for Epidemiologic Studies Depression Scale [CES-D]) and 19% of somatic symptoms. However, genetic influences had minimal effect on the variance of specific symptoms of depressed mood and affect (19).

Support for specific genetic markers identified to be potentially related to late-life depression has not been consistent. For example, despite early optimism, no association between the apolipoprotein E4 allele and depressive symptoms was found in a community sample (40). Better support has been identified for genes that seem to relate cerebral vascular lesions and associated depression. Hickie and colleagues (41) found that patients with late-onset major depression exhibited a higher frequency of C677T mutation of the methylene tetrahydrofolate reductase (MTHFR) enzyme compared with controls. They suggested that this mutation may place older persons at risk for major depression associated with cerebral vascular lesions (vascular depression). Depression is also one of the initial symptoms of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a disease associated with the notch 3 gene. Finally, genetic influences of serotonin modulation may continue to be seen in late-life depression. An analysis of three longitudinal twin studies of the elderly in Sweden (mean age 73) found an association between the 5-HTR_{2A} gene promoter polymorphism and depressive symptoms for the A/A genotype (42).

These preliminary findings have suggested that genetic polymorphisms or mutations may predispose older adults to develop depressive symptoms through vascular changes in the brain (43,44). Interestingly, the association of depressive symptoms and vascular risk factors has long been recognized (45). In fact, depression is a frequent outcome of stroke, occurring in approximately one-fourth of all stroke survivors (46). It has been hypothesized that depression itself may predispose to vascular disease through a variety of mechanisms such as effects of hypocortisolemia, immune activation, depression-related platelet aggregation leading to increased thrombosis, or by depression-related poor compliance with medical treatment for an underlying illness (such as diabetes, obesity, etc). It is also suggested that depression and vascular disease may be associated by a shared underlying etiology, such as atherosclerosis (see 47).

MRI investigations have shown that depression is linked with white-matter hyperintensities (WMH), areas of bright regions seen in the brain parenchyma on T2-weighted MRI scans. These lesions are thought to represent vascular injury to white-matter tracks and are frequent findings on MRI scans as people age. However in certain individuals, these WMH may contribute to the disruptions of neural circuits associated with depression (32,33,48). Diffusion tensor imaging (DTI) is a relatively novel MRI technique that is thought to be particularly useful in assessing the disruption of neural white matter circuits. It does so by measuring the direction of water molecule movement in brain tissue. When unrestricted by any barriers, water moves (or diffuses) randomly in all directions. However, when constrained by barriers such as neuronal cell walls, water moves/diffuses along the planes of those barriers. It is hypothesized that WMH represent a disruption of the relatively ordered direction of neuronal tracts, and can be measured by a decrease in the directional diffusion of the water molecules seen in DTI. Studies of elderly depressed subjects have found a reduction of white matter fractional anisotropy (FA) values in widespread regions of the frontal and temporal lobes of depressed patients representing disruption of white matter tracts (49). Taylor et al. (50) specifically found that microstructural changes noted on DTI in the white matter of the right superior frontal gyrus are associated with late-life depression. White matter microstructural abnormalities lateral to the anterior cingulate has also been associated with a low rate of remission from depression (51).

Because of this, researchers have proposed a new classification of depression: vascular depression (32,33). This diagnosis is associated with features of increased lassitude, a history of hypertension, and poorer outcomes, but not a family history of mental illness or loss of libido (52). Impairments noted in vascular depression resemble impairments in frontal lobe syndromes. Cognitive and executive function testing has supported the neuroanatomic findings. This may also explain why late-onset depressed adults demonstrate more impairment in visuospatial ability, memory, speed of information processing and executive functioning deficits (37,53,54) (findings consistent with late-life depression discussed above).

The vascular lesions may also increase older patients' vulnerabilities toward the development of subsequent depression, particularly in the face of life-event stressors or changes in social support (52). Heiden and colleagues (55) studied the clinical and MRI WMH findings of 31 depressed elderly subjects at baseline and again 5 years later. They found that subjects with greater extent of WMHs had more severe depressions (as measured by the HAM-D), more severe longitudinal courses of depression, and a lower Mini-Mental State Examination (MMSE) score. Holley and colleagues (56) ascertained that the depressogenic effect of stress was stronger in the presence of significant vascular risk. Thus, vascular disease may disrupt mood regulation circuits in the brain, which in turn increases vulnerability to depression by decreasing a person's ability to respond to stressful events.

Recent interest in etiologic mechanisms of late life depression has also focused on structural changes in certain regions of the brain. Volumetric neuroimaging research currently suggests that elderly depressed have significant abnormalities in the frontal lobes (particularly the orbital frontal cortex), the temporal lobes (especially the hippocampus and amygdala), and basal ganglia—areas related to the cortical-striatal-pallidal-thalamus-cortical pathway (see 57). These findings are largely consistent with MRI findings in younger depressed adults.

The etiological mechanisms for these findings are still unclear, but interesting hypotheses have emerged. For example, studies of the hippocampus in elderly depressed subjects have found decreased volumes. Sheline and colleagues (58) suggested that the changes in hippocampal volume may be related to glucocorticoid toxicity caused by an excess in stress hormone levels induced by a long duration (or early onset) depressive illness. However, Steffens and colleagues (59) have argued that the hippocampal volume loss may be related to an early dementia process in which depression is a preclinical symptom of dementia. Taylor and colleagues (60) have suggested that the hippocampal reductions may be related to a more complex interaction of depressive illness and genetic vulnerability. They suggest that early-onset subjects homozygous for the s/s allele of the serotonin transporter gene may have decreased hippocampal volume attributable to increased susceptibility to the increased glucocorticoid levels causing neurotoxic effects on the hippocampus, whereas late-onset depressive subjects homozygous for the l/l allele may have decreased hippocampal volume attributable to increased susceptibility to subcortical ischemic disease causing increased risk for depression and dementia.

The association of dementia and late life depression remains a major concern to researchers and clinicians. As noted above, cognitive and executive problems are not infrequently seen in late life depression, especially when associated with vascular changes or late-onset. The depression/dementia syndrome may have a large overlap of common pathophysiology (61). Depression is frequently associated with Alzheimer's disease (AD). Further, older adult depressed patients who present with associated cognitive impairment have an increased risk of developing AD over the next 5 years, even when the cognitive problems resolve (62). However, a recent study published by Ganguli and colleagues (63) has challenged this assumption. In their sample of 1,265 depressed older adults (age 67 and older) who were followed for 12 years, 171 eventually developed dementia. They found that depressive symptoms were indeed associated with cognitive impairment, but the depressive symptoms were not associated with the subsequent development of cognitive decline leading to dementia.

Studies of neurotransmitter involvement in depression have recently focused on reduced serotonin function and abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis. In younger adults, the role of the 5HT system in relapse of depression has been studied using acute tryptophan depletion (ATD). This technique involves consumption of a balanced

amino acid drink that is lacking in tryptophan, thus reducing peripheral tryptophan levels by 70%–80% as well as central serotonin synthesis (64). Findings in younger adults have shown profound reductions in mood during ATD in patients who had recovered from depression (65,66). This technique was applied to 16 elderly adults who had recovered from a depressive episode (67). Contrary to findings in the younger populations, there was no evidence of mood change in the elderly though cognitive functioning (particularly working memory) did appear to decline transiently. The authors suggested that older recovered adults may be more sensitive to acute disturbances of the 5HT system than younger recovered adults. In a related study, Porter et al. (68) did not find that elderly patients recovered from depression had any greater vulnerability in the hypothalamic 5HT pathways to ATD, though there was reduced reactivity of the HPA axis compared with healthy subjects.

In summary, biological vulnerability to depressive symptoms are significant in late life, though they may be different than those faced in early adulthood. There appear to be genetic vulnerabilities, though the most promising associations currently noted are related to vascular changes and the serotonergic changes which may also be seen in mid-life depressions. Finally, however vascular changes may occur, these appear to be directly related to late-onset depression.

Clinical Implications

Prognosis

In most longitudinal clinical studies, major depression in older adults exhibits a chronic remitting course (69–72). Mitchell and Subrahim (73) conducted a meta-analysis reviewing studies that examined age at presentation/recruitment versus studies of age at first episode of depression. They found that when controlling for confounding variables, remission rates of depression in patients in late life were little different from those in midlife, but relapse rates appear higher. They also found that elderly patients with early-onset depression are more likely to have had a higher number of previous episodes, which adversely influences prognosis compared to elderly depressed patients with late onset of illness. Husain et al. (20) recently reviewed the relationship between current age and depression severity, course of illness, presenting symptom features, and comorbid symptoms on the 1,498 subjects enrolled in the Sequenced Treatment Alternatives to relieve Depression (STAR*D) Study. Older patients (ages 51–75) endorsed longer durations of illness, more major depressive episodes, a later age of onset of their first major depressive episode, and more general medical comorbidities.

Suicide

Suicide rates increase with age and are very high among those 65 years and older, ranging from 5–10% of the depressed

population (74). In 2001, 5,393 Americans over age 65 committed suicide. Of those, 85% (n=4,589) were men and 15% (n=804) were women (75). Women appear to have a higher incidence of suicide attempts (76), while men have a higher incidence of suicide completion. Because of this, late life suicide is characterized by less warning and higher lethality (77). Firearms were used in 73% of suicides committed by adults over the age of 65 (75).

Older adults who are suicidal are also more likely to be divorced or widowed, living alone, and experience stressful life events (financial problems, interpersonal problems) and have a greater prevalence of depression, substance abuse (78,79) and physical illness (74,77,80–82). In a review of suicide risk among psychiatric inpatients in Denmark, Erlangsen and colleagues (83) noted that affective disorders had almost a twofold higher risk of suicide among psychiatric inpatients than other types of disorders, while patients with dementia had a significantly lower risk ratio of 0.2. More than half of suicides occurred either within the first week of admission or discharge. In the US, most elderly suicide victims were seen by their primary care provider a few weeks prior to their suicide attempt and diagnosed with their first episode of mild to moderate depression (81). Contrary to expectation, elderly persons who commit suicide do not have increased rates of severe or terminal illness (84).

Mortality

In community studies, there was no clear association between depressive symptoms and all-cause mortality among older participants of the ECA study when other known causes of mortality were included in the logistic analysis (85). However, in clinical populations a relationship between depression and mortality has been consistently found. Murphy and colleagues (86) examined all-cause mortality in a 4-year follow up study involving 120 depressed elderly psychiatric inpatients compared with 197 age- and gender-matched control subjects. Among the depressed women, mortality was twice the expected rate; among the men, it was three times the expected rate. Many researchers (87–90) have found that elderly patients hospitalized for medical illness had a higher mortality rate during the hospitalization than matched controls who were not depressed. Rovner and colleagues (91) also found greater death rates among elderly nursing home patients with depression.

Health Service Utilization

Depression in late life leads to an increased use of hospital and outpatient medical services (19% increase in number of outpatient encounters, 30% increase in total outpatient charges) (92–94). Unlike younger patients, who are more prone to see a specialist regarding physical and psychological health, most older adults tend to seek care from their primary care physicians. For example, Garrard et al. (95) reported that the prevalence rate of elderly outpatients who are treated in the primary

care sector varies between 17–37%. However, despite the common prevalence, late-life depression is often under-recognized and under-treated, particularly in non-psychiatric settings (96). It has been suggested that this may be due in part to expectations by the primary care physician (“depression is a normal part of age or illness”), or the fact that (as noted above) elderly depressed tend to express more somatic complaints rather than sadness complaints. Thus missed cases occur because the term “depressed” is never used as a subjective complaint.

Koenig (97) surveyed 404 consecutively admitted subjects with CHF (157 who met criteria for major depression) and found that fewer than 50% of patients with major depression received treatment, and only 12% had psychiatric consultations. Fewer than 50% of patients with MDD in primary care settings receive treatment with antidepressants (93,98–101) or see a mental health specialist (102–104).

Disability

Major depression is a leading cause of disability in adults. In elderly patients, both depression and medical illness have an additive effect on disability and lead to an increase in mortality and nursing home placement (63,96,105–108). Depression severity is a predictor of variance in instrumental activities of daily living (IADL) (109). Treatments that result in a reduction in the severity of depression leads, one year later, to a reduction of approximately 50% in the number of days burdened by disability (110).

Comorbidity

Medical Comorbidity

As noted previously, depression is a risk factor for medical illnesses and may worsen the course of the comorbid illnesses (111,112) while medical illness is a risk factor for the development or worsening of depression and can mask depressive symptoms (98,113). In an analysis of 1,801 depressed older adults, Harpole and colleagues (114) found that patients suffered from an average of 3.8 chronic medical conditions. Therefore all discussions of the biological etiology of depression must respect the interaction of depression and medical illness, because depression among the medically ill in late-life is common (1). This is especially noteworthy due to the high prevalence of depressive symptoms in general medical inpatients, primary care practices, and extended health care services.

The interaction between medical illness and depression is complex. Kraaij and colleagues (115) conducted a meta-analysis of 25 studies evaluating negative stressors and their relationship with depression. Health status consistently was associated with depressive symptoms in older adults. Fiske and colleagues (116) also found that health status was correlated with depression, but new illnesses did not necessarily predict worsening of depressive symptoms longitudinally. This suggests that older and younger adults' reaction to illness and depression may not be different.

Medical illnesses are much more likely to occur in older adults, but it should be noted that most older adults who experience significant medical illnesses do not become depressed.

The interaction between depressive disorders and comorbid medical illnesses are significant for the wide variety of associations. Special attention has been given to several conditions that are prominent in the elderly, such as cardiovascular disease, lung diseases, endocrine disturbances (especially thyroid diseases, diabetes, and obesity), orthopedic problems (such as hip fractures), neurological diseases (such as Parkinson's disease or stroke), cancer, chronic pain, Huntington's chorea and multiple others. For the purposes of this review, three common medical conditions comorbid with depression in the elderly will be highlighted: coronary heart disease, cancer, and neurological disease (see Krishnan et al. (113) for more in depth discussion on medical comorbidities).

Coronary Heart Disease. Studies have consistently found high rates of depression associated with cardiovascular disorders. For example, for patients admitted to the hospital for diagnostic cardiac catheterization or an acute myocardial infarction, studies have shown consistently that approximately 20–30% have major depression (117,118). For patients with congestive heart failure, estimates of the prevalence of major depression have ranged from 17% to 37% (119). Depressed elderly are also more likely to have associated cardiac risk factors when compared with non-depressed elderly (120). Tiemeier et al. (121) assessed 4,019 older adults and found a strong association between atherosclerosis and depression in the elderly (see discussion of vascular depression above).

The morbidity of depression and comorbid CHD is significant because patients with comorbid depression have worse medical outcomes compared with those without depression (122). This included increased risk for re-hospitalization days after angioplasty or CABG (108, 123), greater mortality after MI (118,124), and more disability (125). Further, depression itself can be an independent risk factor for heart failure among elderly women (126) or an independent predictor for further cardiac events (117,127). Data from the Cardiovascular Health Study (128) show that in older adults, depression is associated with increased mortality after controlling for disease severity, indicators of subclinical disease, demographic factors, and other biological and behavioral risk factors. Significantly, even minimal symptoms of depression are associated with increased mortality after myocardial infarction (129).

Cancer. Cancer remains a frequent cause of morbidity and mortality among the elderly. Many studies have documented the comorbidity of depression in various cancers from 1–42% (130). Patients with cancers of the pancreas, lung, or head and neck are especially at risk (131), though the diagnosis of cancer is a crisis point for many people and all report differing amounts of distress. Aragona et al. (132) found that 62% of newly diagnosed breast cancer patients had some depressive symptoms. Comorbid depression is associated with increased functional impairment and poorer quality of life (133).

Neurological Disease. As noted before, neurological diseases in the elderly, especially the elderly depressed, are common.

Studies have suggested that the prevalence may range from 10–40% (134). A recent study (135) interviewing 300 newly evaluated elderly with neurological disease found that 27% had a comorbid major depressive episode. The depression tended to persist, with 48 of the 54 patients still reporting significant depressive symptoms at 8 months. In a review of studies from around the world, the prevalence of major depression after stroke was noted to be approximately 20%, while the prevalence of minor depression was 19% (46). Left side stroke is more likely to lead to early onset (<3 months) of depression, while a right sided stroke may more likely lead to a later-onset depression (136). For patients with Alzheimer's disease, the prevalence of depression is approximately 20% as well, while up to 30% may have minor depression (61). In mild cognitive impairment, significant depressive symptoms are noted in up to 36% of patients (137). Comorbid depression in Parkinson's disease (PD) ranges from 15–50% (138,139), and depression may be an early hallmark for the development of PD (140).

Depression is an independent risk factor for physical disability in patients with neurological illnesses (135). Studies have found that increased cognitive impairment post stroke is related to comorbid depression (46). Comorbid depression is also a strong independent risk factor for mortality after stroke (141,142). For patients with mild cognitive impairment, comorbid depression is a predictor of progression to Alzheimer's disease (137). The presence of depression in dementia is also a source of increased disability and mortality (143).

Psychiatric Comorbidity

Co-occurring psychiatric disorders are associated with poorer treatment responses in late life MDD. The prevalence of anxiety disorders in elderly MDD has been reported between 10–50% (5,144–147), primarily generalized anxiety disorder and phobias. Anxious depression tends to be more prominent in the “younger old,” and have greater suicidal ideation, more impairment of subjective social support, more severe depressive symptoms, and a longer time to remission (146,148).

With a prevalence of 15–30%, elderly patients with MDD have a 3–4 fold higher risk of having a comorbid alcohol use disorder compared with non-depressed elders (149). Personality disorders occur in 10%–30% of patients with late life major depression, particularly in patients with early onset depressive illness. Cluster C disorders predominate, while Cluster B diagnoses are rare. The presence of a Cluster C personality disorder comorbid with late life depression was associated with a longer time-to-response during acute treatment and non-response in continuation or maintenance treatment (150).

Treatment and Management

Psychopharmacologic

Antidepressants have become the “foundation” and primary treatment for moderate to severe depression in older adults (1).

In the past few years there have been several systematic reviews and meta-analyses of current published evidence on the efficacy and treatment challenges for pharmacologic intervention in late-life depression (112,151–154). The main conclusions of these studies reviewing antidepressant treatment for late-life depression are briefly summarized:

1. **Efficacy:** All classes of antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) have similar efficacies.
2. **Tolerability and Safety:** The intensity of adverse events as measured by withdrawal rate from clinical trials may be similar across classes,
3. **Treatment Factors:** Antidepressants should be given for at least four weeks to have a beneficial effect compared to placebo.

Efficacy

As with all summarizing statements, it should be noted that each of these points must have some qualifications. First, as many of the reviews and critiques pointed out (112,151,153,154), there are relatively few placebo-controlled studies examining efficacy in late life depression. This is especially true for the newer antidepressants (e.g., venlafaxine, duloxetine, etc.), requiring information on their use in older adults to be inferred from trials conducted in younger adults. However, several recent studies have demonstrated similar efficacies of duloxetine (155,156), venlafaxine (157), and bupropion (158) when compared with other antidepressants.

Secondly, generalization from the studies to the general elderly population is somewhat limited since most of the available clinical trials had small study sample sizes of late-life depression patients. In the past three years, four studies have been published that have increased the power of their findings by using larger samples. These include placebo-controlled trials with fluoxetine (159), paroxetine (160), and sertraline (161,162). Table 2 lists all published placebo-controlled trials of antidepressants available in the US for late-life depression.

Thirdly, it should be noted that not all studies demonstrated efficacy in late-life depression. Taylor and Doraiswamy (151) note that of the 12 placebo-controlled trials they examined for antidepressant efficacy in late-life depression, 71.5% of the trials reported significantly greater efficacy with drug than placebo. Trials that were published that did not separate from placebo are noted in the comment section of Table 2.

Fourth, generalization from the clinical trials to the individual elderly depressed patient may be difficult because many of the studies did not include subjects with comorbid medical illnesses or cognitive impairments (frequent findings in elderly patients) (151). Several specific studies did address samples with comorbid medical illnesses, or included sub-analyses for comparison of comorbid medical illnesses. Citalopram (163) and fluoxetine (164) have been found effective in the treatment of post-stroke depression compared to placebo, and for maintenance therapy. Sheikh et al. (162) examined a large group of elderly depressed with and without comorbid medical illness. They found sertraline to be efficacious and well-tolerated in elderly depressed compared with placebo regardless of the presence of comorbid medical illnesses. Interestingly, two studies in medical inpatients (165,166) both failed to differentiate active drug from placebo. Evans and colleagues (165) though did find that patients with serious physical illness who completed 5 weeks or more (N=37) showed a significant improvement in mood if treated with fluoxetine compared with placebo. Systemic review by Wilson et al. (154) found that all classes of antidepressants remained effective for the treatment of late-life depression in patients with physical illnesses. However, older patients and patients with late-onset depression are at increased risk of medical comorbidity, which continues to be a risk factor for poor antidepressant tolerability (see below).

In order to better assess the impact comorbid medical illnesses have on late-life depression, 1,801 patients were enrolled at 18 primary care sites through the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial. Patients were treated by a care manager who offered education, care management and antidepressant treatment or brief psychotherapy under the supervision of a psychiatrist and primary

Table 1 Studies of Incidence and Prevalence of Major Depression in Late Life in Community Samples

Authors	Study/Location	Age	Sample Size	Instrument	Prevalence	
					Depression	Minor Depression
Blazer et al. 1987 (3)	Epidemiologic Catchment Area Study USA	65+	1,300	CES-D	0.8% (women 1.4%; Men 0.4%)	2% dysthymia 4% minor depression
Copeland et al. 1987 (194)	Liverpool, England	65+	1,070	GMS-AGECAT	2.9%	8.3%
Newman et al. 1998 (195)	Edmonton, Canada	65+	1,119	GMS-AGECAT	11.2% (women 14.1%; Men 7.3%)	
Beekman et al. 1995 (5)	Netherlands	55–85	3,056	CES-D	2.0%	12.9%
Steffens et al. 2000 (7)	Cache County, Utah, USA	65–100	4,559	DIS, modified	3.7% (women 4.4%; Men 2.7%)	0.2% dysthymia 1% minor depression
Chong et al. 2001 (196)	Taiwan	65+	1,500	GMS-AGECAT	5.9%	15.3%
Chen et al. 2004 (197)	Hiefei, China	65+	1,736	GMS-AGECAT	2.2%	

Table 2 Placebo-controlled Clinical Trials of Antidepressants Available in the United States

Study	Medication	Dose	Sample	Age	Duration (weeks)	Outcome Measure	Results
Andersen, 1994 (163)	Citalopram Placebo	10–40	33 33 ^c	67	6	HAMD	Study focused on elderly with post stroke depression. Response ($\geq 50\%$ reduction in HAMD) rate was significant with 59% of citalopram and 27% placebo improved
Branconnier, 1983 (198)	Imipramine Bupropion (low) Bupropion (high) Placebo	150 150 450	18 18 18 9	63	4	HAMD	Both higher and lower doses of bupropion, and imipramine were effective compared to placebo.
Cohn, 1984 (199)	Imipramine Nomifensine Placebo	137.5 152.5	21 21 20	66	4	HAMD	Both nomifensine and imipramine were superior to placebo.
Evans, 1997 (165)	Fluoxetine Placebo	20	38 38	80	8	HAMD	Study focused on depression with comorbid physical illness. Response ($\geq 50\%$ reduction in HAMD) rate was 67% for fluoxetine and 38% for placebo. No significant difference between the two groups.
Georgotas, 1987 (200)	Nortriptyline Phenelzine Placebo	25–125 15–75	75 total	55+	7	HAMD	Nortriptyline and phenelzine were more effective than placebo. Effects observable by week 4.
Gerner, 1980 (201)	Imipramine Trazodone Placebo	145 305	9 12 13	68	4	HAMD	Trazodone and imipramine were significantly better than placebo. Trazodone was better tolerated than imipramine.
Halikas, 1995 (202)	Mirtazapine Trazodone Placebo	5–35 40–280	50 50 50	62	6	HAMD	Mirtazapine showed efficacy for depression compared with placebo.
Jarvik, 1982 (203)	Imipramine Doxepin Placebo	25+ 25+	12 10 10	67	26	HAMD	Response ($\geq 50\%$ reduction in HAMD) rate was 50% for imipramine, 52% for doxepin and 19% for placebo. Remission rate was 45% for imipramine and doxepin (combined group) and 12% for cognitive behavior therapy group.
Kane, 1983 (204)	Imipramine Bupropion (low) Bupropion (high) Placebo	146 150 323	12 11 10 5	64	4	HAMD	No difference was noted in efficacy between the four groups. Authors believed sample size was too small to determine efficacy.

Katz, 1990 (205)	Nortriptyline Placebo	65	18 12	84	7	HAMD	Study focused on elderly frail patients in an institutional setting. Nortriptyline was more effective than placebo.
Merideth, 1984 (206)	Imipramine Nomifensine Placebo	150 150	20 22 19	68	5	HAMD	Response was seen in 78% of nomifensine group, 64% imipramine group, 20% placebo group. Nomifensin had better side effect profile than imipramine
Nair, 1995 (207)	Nortriptyline Moclobemide Placebo	75 400	38 36 35	69	7	HAMD	Remission (≤ 10 HAMD) rate 33% for nortriptyline, 23% for moclobemide, and 11% for placebo. Nortriptyline was significantly better than placebo, but moclobemide was not.
Nyth, 1992 (208)	Citalopram Placebo	10-30	88 45	77	6	HAMD	Response rate of 60% for citalopram vs 24% for placebo.
Rapaport, 2003 (160)	Paroxetine	25-50	106	70	12	HAMD/ CGI	Response (CGI of 1 or 2) rate was 72% for paroxetine CR, 65% for paroxetine IR, and 52% for placebo. Remission (HAMD ≤ 7) rate was 43% for paroxetine CR, 44% for paroxetine IR, and 21% for placebo. Both active treatments were more effective than placebo
Roose, 2004 (209)	Citalopram Placebo	10-40	84 90	80	8	HAMD	No difference in response ($\geq 50\%$ reduction in HAMD) or remission (HAMD ≤ 10) rates between citalopram and placebo.
Schneider, 2003 (161)	Sertraline Placebo	50-100	371 376	70	8	HAMD	Sertraline showed significant improvement compared to placebo across HAMD and CGI endpoints, though the effect size was small (0.25).
Schweizer, 1998 (210)	Imipramine Buspirone Placebo	89 38	60 54 58	72	8	HAMD	Efficacy of treatment with low-dose imipramine was 70%, buspirone was 61%, and placebo was 42%. Imipramine/placebo difference seen as early as week 2. Buspirone/placebo difference only at week 8.
Sheikh, 2004 (162)	Sertraline Placebo	50-100	360 368	70	8	HAMD	Study included depressed with physical illnesses. Sertraline was efficacious compared with placebo regardless of comorbid medical illness.
Tollefson, 1995 (159)	Fluoxetine Placebo	20	286 291	67.7 \pm 7.7	6	HAMD	Response ($\geq 50\%$ reduction in HAMD) rate was 44% for fluoxetine vs 32% for placebo. Remission (HAMD ≤ 8) rate was 31 for fluoxetine vs 18% for placebo.
Wakelin, 1986 (211)	Fluvoxamine Imipramine Placebo		33 29 14	65	4	HAMD	Fluvoxamine and imipramine were superior to placebo

care expert. Recent published findings (114) noted that patients with comorbid medical illnesses had higher severity of depression at baseline, but responded to treatment as well as those without comorbid illness. The number of medical comorbidities was not a factor in treatment response.

In addition, Alexopoulos et al. (167) studied treatment response in 112 nondemented elderly patients with major depression with citalopram, focusing on executive function and medical burden. They found that the patients with disturbances in executive function were more likely to have poor outcomes, though impairment in other Dementia Rating Scale (DRS) cognitive domains did not significantly influence the outcome of depression. They concluded that this disparity (which suggested problems in frontostriatal-limbic integrity in late life depressed patients) supported observations of the role of specific frontostriatal-limbic pathways (see etiological discussion above). These results underline the observation (151) that there is a significant heterogeneity in geriatric depression, and that current definitions of depression do not fully capture the large spectrum of depressive disorders. For example, the mixed results noted in the medical inpatient trials and nursing home populations, as well as the high placebo response rate, suggests that depression may be experienced due to psychosocial reasons (less family support, bereavement, loss of independence, etc.) which complicate treatment and may be less amenable to pharmacologic therapy.

Fifth, some researchers have suggested that depression in late life has a relatively poor prognosis compared with depressive episodes in younger patients. Recently, Mitchell and Subramaniam (73) conducted a systematic review of comparative studies evaluating the response relationship of elderly and middle aged depressed patients. They found that when confounding variables were controlled, remission rates of depression in the elderly are similar to those in midlife. However, they also noted that relapse rates appear to be higher for the elderly group.

Tolerability and Safety

Tolerability of antidepressants in elderly is a difficult topic in which to make firm summarizing statements. As noted above, withdrawal rates between SSRIs and TCAs were comparable on systemic review of clinical trials; however, this may not necessarily mean that all antidepressants are equally tolerable among sub-populations or individuals. When a sub-analysis was conducted by Mottram et al. (153) comparing classical TCAs (amitriptyline, clomipramine, doxepin, and dothiepin) with SSRIs (paroxetine, citalopram, fluoxetine and fluvoxamine) and removing the "related TCAs" (trazodone and mianserin) from inclusion, both TCA and SSRI classes had similar efficacy but the classical TCA recipients were more likely to be withdrawn due to "side effects." These findings probably reflect the different side effect profiles of each class. As noted by Mottram et al. (153), classical TCA recipients experienced more gastrointestinal (a ratio of 4.6 side effect

experiences for each 10 TCA recipients compared to 2.9 experienced by 10 SSRI recipients) and neuropsychiatric side effects (4.1 side effects experienced by 10 classical TCA recipients compared to 2.3 side effects experienced by 10 SSRI recipients). Other side effects, especially anti-cholinergic and sedating effects must be considered individually for each medication. Because of the side effect profiles, Cole et al. (168) have suggested that tricyclic antidepressants may have more contraindications for their use in older depressed patients, especially those with medical complications.

Treatment Considerations

As note above, efficacy of antidepressant have been found to be similar among the various classes of antidepressants, but the choice of agents is usually determined by patient characteristics such as prior response, tolerability (see above), drug interactions, compliance, and frailty (169). While a recent evidence-based analysis of treatment guidelines for late-life depression found that either antidepressants alone or in combination with psychotherapy was recommended, no specific antidepressant or class of antidepressant was recommended (152). In 2001 an expert consensus panel recommended that based on the literature available at that time, the first-line treatment for depression was an SSRI (specifically citalopram) (170).

Actual clinical practice found a variety of treatment patterns. A recent polling of the APA's Practice Research Network members (171) found that for late-life depression, members used a combination of medication and psychotherapy in 52% of the time, while they used medication only 39% of the time. Seventy-six percent of geriatric depressed patients received antidepressants, of which 59% were on stable doses. SSRIs were the most commonly used (30%), followed by tertiary amine TCAs (12%) and secondary amine TCAs (5%). The most common SSRI used was fluoxetine.

As noted in the summaries, reviews of the literature suggested that antidepressant trials should last at least 4–6 weeks. Some studies however, have suggested that older adults may take longer to recover from depression than younger adults (4) and recovery may continue through week 12. A recent study by Mulsant and colleagues (172) evaluated 472 late-life depression patients through 12 weeks of treatment. They found that if patients have shown at least a partial response by the fourth week of treatment, then most became full responders within the next four weeks. However, if patients did not show any response by the fourth week, then the potential for full response during the following 8 weeks was very low. One study (173) evaluated the use of citalopram augmented with methylphenidate for the treatment of acute major depression in elderly subjects. They found that the combination of citalopram and methylphenidate demonstrated an accelerated response compared with citalopram monotherapy, though both treatment arms showed efficacy over the 10 week period.

In their comparison of treatment response between older and younger adults, Mitchell and Subrahim (73) found that

older patients responded similarly to younger adults, but that older adults had higher relapse rates. This suggested that the duration of treatment for depression in older people may need to be carefully considered. Klynsner et al. (174) found that the SSRI, citalopram, compared with placebo helped prevent relapse when used up to 48 weeks (32% vs. 67%) in late life depression. The expert consensus panel (170) recommended continued treatment with antidepressants for at least 12 months after remission. This recommendation may be updated since in a more recent study, Reynolds et al. (175) found that elderly depressed patients that responded to treatment with paroxetine were less likely to have a recurrence if they continued to receive treatment for at least two years. Some clinicians (169) have suggested that treatment for recurrent late-life depression should be for (12–36) months, while high risk recurrent patients should be treated for at least 3 years to lifetime.

While physician practices are important, equally important are the response and receptiveness of elderly patients to receiving treatment. Givens and colleagues (176) recently explored the attitudes that elderly may have toward antidepressant. They found four themes that characterized resistance to antidepressants: (1) fear of dependence; (2) resistance to viewing depressive symptoms as a medical illness; (3) concern that antidepressants will prevent natural sadness; (4) prior negative experiences with medications for depression. They postulated that improved treatment response could be obtained when these issues were addressed.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) has long been documented to be an effective in the treatment of late life depression (177,178), especially psychotic depression (179). Efficacy may be also more pronounced in late-life depression comorbid with cerebrovascular disorders, dementia, and Parkinson's disease (180). ECT should also be considered for use in depressed patients who have had a failure to thrive, severe suicidal ideation, or previous good response to ECT. There is no evidence that ECT causes any kind of brain damage, although transient memory impairment is the main adverse effect (181,182). ECT may be an alternative to treatment with antidepressants, but a recent meta-analysis (180) could not draw firm conclusions as to whether ECT is more effective or safer than antidepressants.

Other Somatic Interventions

There is very limited evidence for the use of other somatic treatments in late life depression. Three studies have not shown transcranial magnetic stimulation (TMS) to have any effect on depression in older adults after two weeks (183–185), though one study reported modest improvement in depressive symptoms when compared with sham treatment in stroke patients with refractory depression (average age 64) (186). No studies are currently available on the use of vagal nerve stimulation or deep brain stimulation in the elderly depressed.

Psychotherapy

In a recent article reviewing the evidence for psychotherapeutic interventions in late life depression, Mackin and Areal (187) noted that as recently as 1991, the National Institutes of Health (NIH) consensus statement on treatment for late-life depression ranked psychotherapy as a third-line treatment due to the limited evidence available at that time. Since then, many clinical trials and other types of studies have been conducted developing treatment manuals and refining therapeutic approaches. So successful have been efforts in developing specialized psychotherapeutic approaches for elderly depressed that four meta-analyses (188–191) and one systematic review (187) have been conducted on the emerging data.

Many different psychotherapeutic and psychosocial interventions have been described in the treatment of late-life depression. These include cognitive behavior therapy (CBT), interpersonal psychotherapy (IPT), reminiscence therapy, life review therapy, brief dynamic therapy, psychoeducation, and dialectic behavior therapy (DBT). It is beyond the scope of this article to review each of these, though it should be noted that the most commonly studied psychotherapies have been the “manualized” therapies, CBT, IPT, and DBT (187). The process of manualization has allowed these treatments to be evaluated in a clinical trial format. The result has been a strong demonstration of success for acute treatment of late-life depression, as well as relapse prevention or with comorbid personality disorders. It has also been shown to be efficacious for the treatment of minor depression as well.

Several studies have suggested that behavioral intervention, especially in the medically ill depressed, may be an extremely effective intervention. Koenig (119) reported that in his series of patients with CHF admitted to a medical hospital and then followed over a (6–24) week period, patients with minor depression responded best (unrelated to antidepressant usage), while even subjects with major depression improved, (those with less severe medical illness more than those with more severe illness). Alexopoulos et al. (192) followed a series of 63 subjects with COPD and depression admitted for pulmonary rehabilitation. Approximately 51% of subjects met criteria for response (50% or greater reduction in depressive symptoms scores from baseline), and 39% met criteria for remission (final Hamilton Depression scale score equal to or less than 10). They noted that social support and satisfaction with treatment were predictors of improvement and that improvement of depression may be the result of behavioral interventions rather than the use of antidepressant drugs. Finally, the recent publication of results from the IMPACT study found the brief therapy and psychoeducation interventions, along with antidepressants, to be effective in the primary care setting as well (114). Evidence based guidelines for treatment now include combination treatment of antidepressants and psychotherapy as first line options for late-life depression (152). A recent pole of geriatric psychiatrists (171) found that combined antidepressant/psychotherapy treatment was the most common

treatment approach for geriatric patients (52%), followed by antidepressant treatment only (39%).

There is much more limited evidence that psychotherapy is effective in maintenance treatment. While there are several studies in non-geriatric depressed samples that support the efficacy of psychotherapy interventions in the prevention of recurrences, the data for older adults is mixed. Reynolds et al. (193) found that therapy was helpful in the prevention of recurrences among the young-elderly (ages 60–75), while a more recent study focusing on the older-elderly (ages >70) did not find monthly maintenance therapy effective. It has been postulated that this negative finding occurred due to increased medical illness in the older group, or due to a sampling bias. Most of the older-elderly group were in their first episode depression compared with the younger-elderly group who had higher recurrent depressive episodes in. Late-onset depression (as discussed earlier) is a clinically heterogeneous group whose depression may more likely represent a preclinical stage of dementia and thus less ability to participate meaningfully in therapy.

SUMMARY

Depression in late life remains a challenge for the clinician as well as a major public health concern. It is highly prevalent in the community, but it also has an especially high risk among medical and nursing care patients. Thus, good recognition and treatment of depression must be a concern for the primary care provider as well as the psychiatrist. This may be a challenge at times, because phenomenologically late life depression may differ somewhat from depression in younger adults. Specifically, older depressed individuals may complain less of “sadness” and more of “somatic complaints”. Late life depression also tends to present as more of a chronic illness with frequent relapses. Suicide is highly prevalent, and depression itself is an independent risk factor for mortality and disability. Despite this, the prognosis is good with adequate treatment. Current antidepressants available in the US have shown great utility in treating depression. Yet optimal treatment practices are still being established.

Several challenges still await further study. First, a better understanding of the etiology of late life depression is developing. Already, several factors have been identified to elucidate the heterogeneity of this disease. Research findings support a genetic association interacting with environmental events throughout the life cycle that may increase vulnerabilities and resiliencies to the development of depression. However, there may also be specific genetic associations that relate more to the development of depression in late life. These include vascular disease vulnerabilities that are either causative or comorbid with depression. Future neuroimaging studies (especially with DTI and PET techniques) and genetic studies will assist in our understanding of these observations.

Secondly, this past decade has seen a great improvement in clinical trials of antidepressants focusing on the elderly

depressed. Also, clinical based trials such as the IMPACT study have continued to guide our understanding of best practice. However, even the largest trials to date have demonstrated a large placebo response, and a significant number of patients still either do not respond, or continue to struggle with marked residual symptoms (151). Moreover, the newer antidepressant agents do not yet have adequate data about efficacy, and augmentation and combination studies are lacking. Complicating this is the problem of comorbidity in late life depression. More research is required to assess interventions in the depressed elderly with comorbid medical, psychiatric, or neurologic illnesses.

Finally, the experience of being an elderly member of our society needs to be carefully reviewed. Concern has been expressed by multiple voices (1) that trends such as the erosion of retirement plans, difficulty in accessing health care, and the changes in core family and social ties during late life may place additional burden on older adults, causing increased vulnerability to problems like depression.

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