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A multiplicity of approaches to characterize geriatric depression and its outcomes

David C. Steffens

Duke University Medical Center, Durham, NC 27710 USA

Abstract

Purpose of review—Research in geriatric depression has always had a multidisciplinary bent, particularly in methods used to characterize depression. Understanding diagnosis, psychiatric comorbidities, and course continues to be a goal of clinical researchers. Those interested in cognitive neuroscience and basic neuroscience have more recently trained their sights on late life depression. This review identifies recent progress in the characterization of geriatric depression using a variety of methodologies.

Recent findings—Depression in the elderly remains underdetected and underdiagnosed, particularly in non-mental health settings. Studies of the impact of psychiatric comorbidities and of the negative outcomes of depression in older adults demonstrate that geriatric depression is a serious medical condition that not only affects mood, but can lead to functional and cognitive decline. Advances in neuroimaging technology have demonstrated structural and functional changes in the brains of older depressed patients. With the advent of brain banks in neuropsychiatry, we are now seeing post-mortem neuroanatomical studies that seek to replicate findings from clinical practice and from neuroimaging studies.

Summary—Clinicians should become more aware of advances in detection of depression, the effect of psychiatric comorbidities, and the poor mood and cognitive outcomes associated with late life depression, and should keep abreast of recent neuroimaging and neuroanatomical findings.

Introduction

Mood disorders in the elderly are common, adversely affect other medical conditions, and may lead to cognitive and functional decline. Recent studies have focused on finding ways to improve detection of depression, to characterize the impact of psychiatric comorbidities, to examine course of mood and cognitive symptoms. In addition, recent neuroimaging and neuroimaging findings have helped expand our understanding of late life depression, a research direction that was advocated for in a recent consensus meeting (1). Geriatric depression thus remains a fruitful area for clinical, translational and basic science research. This review will focus on several areas that span the diversity of investigations

Correspondence to: David C. Steffens, M.D., M.H.S., Professor of Psychiatry and Medicine, Head, Division of Geriatric Psychiatry, Duke University Medical Center, Box 3903, Durham, NC 27710, Phone: (919)-684-3746, FAX: (919)-681-7668, steff001@mc.duke.edu.

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Screening and diagnosis in geriatric depression

Both clinicians and researchers need tools to help screen and assess for depression in the elderly, and data are lacking on optimal measures to use in a variety of settings (2). For example, visiting nurses providing care to homebound elders is one group on the “front lines” providing care to a population at risk for depression. Marc et al. (3*) studied 526 homebound elderly participants newly admitted to a large visiting nurse service agency over a two-year period. Performance on the Geriatric Depression Scale – 15-item (GDS-15) version was examined in patients diagnosed with major depression. The authors found that the optimal cut-off of 5 on the GDS-15 yielded sensitivity of 71.8% and specificity of 78.2%, but that accuracy of GDS-15 was not influenced by severity of medical burden, functional impairment or a variety of sociodemographic factors. Thus, the GDS-15 may be an excellent tool for screening populations who are very old, medically ill and socially and ethnically diverse.

Methodological studies of depression assessment tools are also important. In a group of subjects with post-stroke depression, Farner et al (4) performed a factor analysis of the Montgomery Asberg Depression Rating Scale (MADRS) investigated whether symptom clusters of depression after stroke are associated with patient characteristics. Among 163 patients, 56.4% scored between 7 and 19 on the MADRS, and 13% had a score above 19. The factor analysis resulted in three factors, called anhedonia (lassitude, inability to feel, suicidal thoughts, loss of appetite), sadness (observed sadness, reported sadness, pessimism) and agitation (inner tension, lack of concentration, disturbed sleep). The anhedonia factor correlated with cognitive impairment, and the sadness factor correlated with sensorimotor and cranial nerve deficits. However, the agitation factor had low internal reliability and did not correlate with any systematic patients characteristics.

Comorbidities in depression

Psychiatric comorbidities in geriatric depression are common, but their effect on course is not well studied. Hybels et al (5**) examined the course of depression symptoms in 250 older depressed patients, 34.8% of whom had comorbid major depression and dysthymia. Compared to those without dysthymia, those with the comorbidity showed longer time to partial remission (median number of days = 175 versus 106) and to full remission (median number of days = 433 versus 244) from major depression. Thus, older depressed patients with comorbid dysthymia may require more intensive treatment, possibly with complex pharmacological approaches and/or multimodel treatment including psychotherapy.

Anxiety is commonly seen in older depressed patients (6), and it may represent a modifiable target to improve depression outcome (7). Several recent studies have attempted to characterize anxiety symptoms. In a Canadian population of 12,792 older community-dwelling adults aged 55 and older, Cairney et al (8) examined psychiatric comorbidity and associated impairment of four disorders (major depression, panic disorder, social phobia, and agoraphobia). Social phobia was the most common comorbid disorder among respondents with depression, and depression was the most common comorbid disorder among respondents with any of the anxiety disorders.

In an interesting cross-sectional study, van Haastregt et al (9) began with the construct of fear of falling and activity avoidance to examine presence of anxiety and depressive symptoms. Among 540 community-living person age 70 and older who reported fear of falling, 28.2% and 26.1% had feelings of anxiety and symptoms of depression, respectively. The rates were 28.5% and 22.6% among those with severe fear-related activity avoidance. As those with the most severe fear of falling and highest activity avoidance most likely to experience depression and anxiety, this group should be targeted for assessment of anxiety and depression and for specific interventions to relieve anxiety and depression symptoms.

Course and Outcome of Depression

In a two-year observational cohort study, Cui et al (10*) followed 316 older primary care patients with weekly telephone interviews to track depressive symptoms. Applying cluster analysis the authors identified six distinct trajectory clusters that followed clinically predictable patterns. Individuals who were nondepressed or in the subsyndromal to minor depression range at baseline had a range of possible outcomes over two years. Those initially near the major depression level remained at that level over time. Predictors of depression trajectory included baseline depressive symptom severity, medical burden, and psychiatric functional status. In some clusters depression trajectory was predicted by previous history of depression and perceived social support.

The Vienna Transdanube Aging (VITA) study is one of several large community-based European cohort studies that have provided important insights into geriatric mood and cognitive disorders (11). Individuals living in an area on the left shore of the river Danube, in Vienna, Austria, born between May 1925 and June 1926 have been followed over time with a comprehensive assessment including a thorough neurologic, psychiatric, and neuropsychological battery. Follow-up assessment after 30 months was obtained in 331 of the 406 initially enrolled participants. Among those who were not depressed at baseline, 31.4% had developed a subsyndromal, minor, or major depressive episode at the 30-month follow-up; 14.2% were diagnosed with mild cognitive impairment at follow-up, 42.5% of whom were also diagnosed with new-onset depression. Significant predictors of depression were “troubles with relatives” and summative scores on the Fuld Object Memory Evaluation. This study is important in its finding that the prevalence of late-onset depression increases with age.

Depression and cognitive decline

Cognitive impairment and cognitive decline in late life depression has become an active area of research (12). Han et al (13**) studied 12-month cognitive outcomes of major and minor depression among 281 acutely hospitalized medical patients aged 65 and older without cognitive impairment at baseline. At study entry, 121 (43.1%) and 51 (18.1%) patients, respectively, met DSM-IV criteria for major or minor depression. Based on a mixed effects regression model, depression diagnoses were associated with poorer cognitive function, independent of age, education, baseline cognitive and physical function, cardiovascular diseases and other comorbidities, previous history of depression and antidepressant treatment, and fluctuation in the severity of depression symptoms over time. That a diagnosis of major or minor depression at hospital admission was shown to be an independent risk factor for poorer cognitive function during a relatively short follow-up period has clear implications for treatment planning for outpatient follow-up.

In another study of depression and cognitive decline, Ravaglia et al (14*) examined the association between depressive symptoms and prevalent and incident mild cognitive impairment (MCI) in elderly individuals in a longitudinal cohort study. Among adults 65 years and older, at baseline, 595 had no cognitive impairment (NCI), and 72 subjects had prevalent MCI; those with NCI underwent four-year follow-up for incident MCI. Baseline depressive symptoms were measured using the 30-item Geriatric Depression Scale (GDS), and baseline use of antidepressants was also recorded. Baseline depressive symptoms ($GDS \geq 10$) were more frequent in prevalent MCI cases (44.4%) than in NCI participants (18.3%). The association was independent of MCI subtype, antidepressant use, and sociodemographic and vascular risk factors. At follow-up, among NCI subjects, baseline depressive symptoms were also associated with increased risk of MCI, but only for subjects on antidepressant drugs at baseline (incident cases = 72.7%) compared with those without depressive symptoms and not on antidepressant therapy (incident cases = 24.0%).

In another large population study, Corsentino et al (15) followed 1,992 community dwelling older adults, comparing the effects of depression and apolipoprotein E (*APOE*) genotype on cognitive decline. The $\epsilon 4$ allele of *APOE* has been shown to be a risk factor for later development of AD (16), and prior studies have shown that depression and *APOE* independently predict development of AD (17). In the Corsentino study, the authors examined two waves of assessment conducted six years apart and found that depressive symptoms and the *APOE* $\epsilon 4$ allele independently predicted cognitive decline. Interestingly, they also found that the influence of depressive symptoms on cognitive decline was greater for individuals with the *APOE* $\epsilon 4$ allele compared with those without the allele.

Depression and Mortality

Previous studies have reported a link between depression and increased mortality risk (18, 19), and recent studies have sought to extend this finding. In a representative sample of 7,381 community-dwelling adults age 70 and older, Reynolds et al. (20) reported that depressive symptoms reduced average life expectancy (ALE) by 6.5 years for young-old men (age 70), 3.2 years for old-old men (age 85), 4.2 years for young-old women, and 2.2 years for old-old women, and these effects remained significant at all ages and across gender even after controlling for chronic disease, the one exception being depressive symptoms and cancer in old-old women. Depressive symptoms also reduced total life expectancy significantly, although controlling for some chronic diseases (particularly cancer and stroke) eliminated the effect of depressive symptoms across age and gender groups.

Similarly, Rapp et al (21) examined the relationship between depression and mortality among 497 participants of the Berlin, Germany, Aging Study (mean age: 85.16 years; range: 70-103 years), a population based, age-stratified, longitudinal (up to 15 years) study. They found strong predictive effects of depression diagnoses for mortality among the young old (Relative Risk = 1.60, 95% Confidence Interval = 1.13-2.26) that were not due to the effects of other mortality predictors (Relative Risk = 1.56, 95% Confidence Interval = 1.09-2.22), including age, gender, education, dementia, cardiovascular risk factors, and other somatic diseases. Among the oldest old, they found no depression-mortality associations. Taken together, these studies identify depression as a risk factor among the younger cohort of elderly.

Neuroimaging studies

Geriatric mental health researchers have sought to take advantage of technological advances in neuroimaging in order to study structural and functional changes in late life depression. For example, Gunning-Dixon et al (22) used magnetization transfer ratio (MTR) imaging, a technique that is thought primarily to reflect myelin integrity, to white matter abnormalities in frontostriatal and limbic regions in geriatric depression. Relative to 24 non-depressed elderly subjects, 55 older depressed patients demonstrated lower MTR in multiple left hemisphere frontostriatal and limbic regions, including white matter lateral to the lentiform nuclei, dorsolateral and dorsomedial prefrontal, dorsal anterior cingulate, subcallosal, periamygdalar, insular, and posterior cingulate regions. Depressed patients had lower MTR in additional left hemisphere structures including the thalamus, splenium of the corpus callosum, inferior parietal, precuneus, and middle occipital white matter regions.

In a study combining neuroimaging and genetic data, Taylor et al (23*) used a semi-automated method to determine white matter lesion volume and compared volumes based on genotypic differences for the gene coding for brain-derived neurotrophic factor (BDNF), which may protect against cerebral ischemia. In a sample consisting of 199 depressed and 113 nondepressed subjects aged 60 years or older, the authors examined whether the *BDNF* Val66Met polymorphism, which affects BDNF distribution, was associated with greater volumes of hyperintense lesions as detected on magnetic resonance imaging. After controlling

for covariates, Met66 allele carriers exhibited significantly greater white matter hyperintensity volumes. This effect was independent of a diagnosis of depression or report of hypertension.

Several research groups are now using functional MRI (fMRI) to examine brain function in late life depression, particularly the relationship between cognition and mood. Woo et al (24) used 4-Tesla fMRI to determine with older individuals with subsyndromal depressive symptoms show impaired deactivation of the posteromedial cortex (PMC), a process that underlies normal memory. In 62 non-demented subjects aged 55-85, the authors found that a PMC cluster confined to the dorsal posterior cingulate cortex whose activity correlated significantly with score on the Beck-II Depression Inventory (BDI).

Aizenstein et al (25) used fMRI to examine 13 elderly depressed patients and 13 non-depressed older controls in an executive control task. Both depressed and comparison participants performed the task as expected, with greater response latency during high versus low-load trials. In contrast to the null findings for behavioral data, pretreatment, depressed patients showed diminished activity in the dorsolateral prefrontal cortex (dLPFC) and diminished functional connectivity between the dLPFC and dorsal anterior cingulate cortex compared with controls. Right dLPFC showed increased activity after treatment.

Another imaging innovation is shape analysis of brain structures, a technique that moves beyond a more simple volume measurement to examine local shape changes. Zhao et al (26) examined 61 elderly subjects with major depression and 43 non-depressed elderly subjects. Shape analysis showed significant differences in the mid-body of the left (but not the right) hippocampus between depressed and controls. When the depressed group was dichotomized into remitted versus unremitted at time of imaging, the shape comparison showed remitted subjects to be indistinguishable from controls (both sides) while the unremitted subjects differed in the midbody and the lateral side near the head. In a subsequent study, Qiu et al (27*) examined the effect of *APOE* genotype on hippocampal shape among 38 depressed patients without the *APOE* ϵ 4 allele, 14 depressed patients with one *APOE* ϵ 4 allele, and 31 healthy comparison subjects without *APOE* ϵ 4. The depressed patients with one *APOE* ϵ 4 allele show more pronounced shape inward-compression in the anterior CA1 than the depressed patients without *APOE* ϵ 4 when compared with the healthy controls without *APOE* ϵ 4.

Vascular depression is a construct linking cerebrovascular disease and development of depressive symptoms. Neuroimaging studies have been key to testing this hypothesis, and recent work has leveraged technological advances in structural magnetic resonance imaging (MRI) to characterize integrity of white matter tracks in geriatric depression. One such modality is diffusion tensor imaging (DTI). Shimony et al (28) studied 73 depressed elderly subjects and 23 nondepressed control subjects matched for age and cerebrovascular risk factors using DTI and including a comprehensive neuropsychological assessment. The depressed group showed widespread abnormalities in DTI parameters, particularly in prefrontal regions. From the cognitive test battery, the investigators found the correlations between cognitive processing speed and DTI abnormalities.

Neuroanatomical studies

There are very few reported human neuroanatomical studies in the literature. Van Otterloo et al (29) examined postmortem tissue from the dLPFC of 10 older (> 60 years) depressed subjects 10 age-matched non-psychiatric controls. The majority of the subjects were the same as those used for our previous study on neuronal reductions in the orbital frontal cortex (OFC) (30). Neither the overall nor laminar density of dLPFC pyramidal or non-pyramidal neurons were significantly different between groups. The cortical and laminar widths were also not affected. In the prior study, prominent reductions in the density of pyramidal glutamatergic neurons were observed previously in the OFC.

Conclusion

Depression in the elderly is a serious medical condition that can be challenging to detect and diagnose. Yet proper diagnosis and careful follow-up are essential, as late-life depression is associated with psychiatric comorbidity, and severe depression may have a profoundly negative course. Beyond mood symptoms, geriatric depression is associated with cognitive decline and higher mortality risk. Technological advances in neuroimaging have identified key brain structures implicated in geriatric depression, including the hippocampus, prefrontal cortex and cingulate cortex. Newer studies combining genetics and neuroimaging data, such as BDNF and vascular brain lesions, allow better understanding of the pathophysiology of late-life depression. Finally, neuroanatomical studies, so common in dementing illnesses, are now being reported in affective illness and serve to identify microstructural changes in brain regions linked to depression.

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