Published in final edited form as:

Neurodegener Dis Manag. 2013 ; 3(2): 147–155. doi:10.2217/nmt.13.10.

Depressive Symptoms in Clinical and Incipient Alzheimer's Disease

Julia J. Hsiao^{1,3} and Edmond Teng^{1,2,3}

¹Neurobehavior Service, David Geffen School of Medicine at UCLA

²Geriatric Research Education and Clinical Center, Veterans Affairs Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA

³Department of Neurology, David Geffen School of Medicine at UCLA

Summary

The updated diagnostic criteria for Alzheimer's disease (AD) distinguish three stages: dementia, symptomatic pre-dementia [i.e. mild cognitive impairment (MCI)], and asymptomatic pre-dementia. Although AD is primarily associated with cognitive deficits, co-morbid depressive symptoms frequently occur at each stage. Depression in AD dementia is qualitatively different from depression in cognitively intact and/or younger populations, and may be less responsive to established interventions. In MCI, depressive symptoms are associated with higher rates of progression to dementia, and may identify a subset of individuals that are more responsive to acetylcholinesterase inhibitor treatment. Clinical and subsyndromal depressive symptoms in cognitively normal elderly represent a risk factor and/or prodrome for dementia due to AD, but sustained antidepressant therapy may be able to modulate this risk.

Keywords

dementia; Alzheimer's disease; mild cognitive impairment; depression; assessment; treatment

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, and cognitive dysfunction is often considered its hallmark feature. Accordingly, the core features of both the original [1] and updated [2] diagnostic criteria for dementia due to AD primarily focus on the presence of significant cognitive impairment. However, neuropsychiatric symptoms, and in particular, depressive symptoms, are also quite prevalent in clinical AD [3, 4], and are a source of significant morbidity and caregiver distress [5-7]. The recently updated diagnostic criteria for AD place an increased emphasis on imaging and other biomarker evidence of underlying AD neuropathology to identify both symptomatic and asymptomatic pre-dementia stages of the disease [8]. A growing body of work suggests that

depressive symptoms are often present in the predementia stages of AD, and may in some cases serve as a risk factor and/or prodrome that precede the emergence of cognitive symptoms. In this narrative review, we will explore the identification, interpretation, and treatment of depressive symptoms in clinical and incipient AD.

Depressive symptoms in dementia due to AD

Depressive symptoms are commonly reported in patients with AD dementia. In large community-based samples, the prevalence ranges from 20% to 30% and is significantly higher than that reported for cognitive intact elderly cohorts [3, 4]. Depressive symptoms may be both quantitatively and qualitatively different between AD patients and cognitively normal elderly. Depression in AD is more frequently characterized by motivational symptoms, such as fatigue, psychomotor slowing, and apathy, while depression in cognitively normal elderly is more frequently characterized by mood symptoms, such as dysphoria, anxiety, suicidality, sleep disturbances, and appetitive changes [9, 10]. Furthermore, depressive symptoms in AD appear to fluctuate over time and may have high rates of spontaneous remission [11].

Most assessment tools for depression do not account for the characteristic patterns of depressive symptoms in AD and may be less sensitive in AD relative to their target populations, which are often younger and/or cognitively intact. Therefore, the National Institute of Mental Health developed diagnostic criteria that more specifically capture the features of depression in AD (NIMH-dAD) [12] through an adaptation of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depression [13]. The differences between the NIMH-dAD and DSM-IV criteria include: 1) fewer number of symptoms required (3 versus 5); 2) reductions in the duration and frequency of depressive symptoms (they need only be present together in the same 2-week period versus “most of the day, nearly every day” for at least 2 weeks); 3) elimination of the reduced ability to think and concentrate as a symptom; 4) change in the anhedonia criterion to focus on social contacts and activities; and 5) additions of social withdrawal/isolation and irritability as target symptoms [13]. Across multiple countries and clinical settings, the use of the NIMH-dAD criteria has consistently yielded higher prevalence rates for depression in AD (ranging from 27% to 72%) than other common depression assessments [14-18], suggesting that these criteria may indeed be more sensitive for depression in AD. However, some have argued that the lower thresholds for clinical depression established by the NIMH-dAD criteria may result in the overdiagnosis of depression in AD [19]. Nevertheless, in the absence of a “gold standard” diagnosis, it remains difficult to determine the true prevalence of depression in AD dementia.

The high prevalence and high morbidity associated with depression in AD dementia make it an important target for clinical interventions, as mood symptoms appear to be more closely related to declines in quality of life than cognitive deficits [5, 6]. Acetylcholinesterase inhibitors (AChE-Is), which were approved for the treatment of AD based on relative improvements versus placebo on cognitive and global outcome measures, also appear to yield modest benefits for the broad spectrum of behavioral symptoms that are measured by the Neuropsychiatric Inventory (NPI). Some [20-23], though not all [24, 25] studies show

benefits on the NPI in AD after donepezil treatment, and in particular, show relative reductions in depressive and mood symptomatology. A Cochrane meta-analysis of treatment effects of AChE-Is in AD supported a significant reduction in global NPI scores, but included only the earlier studies and did not specifically address depression or other mood disorders [26]. These results suggest that AChE-Is may provide symptomatic improvements in both cognitive and depressive symptoms in dementia due to AD, and reinforce their established role as first-line interventions at this stage of the disease.

Not surprisingly, antidepressants are also commonly used for depressive symptoms in dementia due to AD. The initial evidence for antidepressant efficacy comes from studies of major depression in younger populations. Second-generation antidepressants have also been shown to reduce depressive symptoms in cognitively normal geriatric cohorts [27], though effect sizes are relatively smaller and show greater variability. Studies of antidepressants for the treatment of depression associated with AD dementia have yielded more mixed results. Two early trials with small sample sizes demonstrated treatment benefits with clomipramine [28] and sertraline [29]. However, a subsequent larger trial of sertraline failed to show any efficacy relative to placebo [30]. A recent meta-analysis of antidepressants in dementia suggested a trend towards clinical benefit, but failed to conclusively confirm the efficacy of these interventions [31]. This meta-analysis was completed prior to the publication of another large study that also failed to show efficacy of sertraline or mirtazepine versus placebo in depression in participants with dementia [32]. The inclusion of these latest results in the meta-analysis would likely further weaken its findings.

The underlying explanation for the apparently poorer efficacy of antidepressants in patients with dementia due to AD remains uncertain, but the more transient nature of depressive symptoms in AD [11] may lead to the high spontaneous remission rates that are seen in longitudinal studies [15] and reflected in the high response rates for placebo-treated groups in the more recent larger clinical trials [30, 32]. Alternatively, it has been also postulated that the underlying neurobiological substrates for depression in AD may be qualitatively different [32]. However, neuropathological studies have shown neurodegenerative changes in the locus ceruleus and dorsal raphe nucleus in AD brains that are more pronounced in those patients with depressive symptoms, suggesting that depression in AD, much like depression in other clinical contexts, is associated with noradrenergic and/or serotonergic dysfunction [33]. Although some work indicates that depressive symptoms in AD are related to more extensive underlying β -amyloid and tau pathology in the hippocampus [34, 35], another study, which focused on neocortical regions, did not demonstrate this relationship [36]. Alternative explanations for the association between AD and depression have also implicated concurrent cerebrovascular disease, chronically elevated glucocorticoid production, increased neuroinflammation, and decreased nerve growth factor production as possible mechanisms (see [37] for a more comprehensive review).

Depressive symptoms in mild cognitive impairment

Post mortem studies suggest AD neuropathology may be present before patients meet diagnostic criteria for dementia [38]. Given the apparent association between AD pathology and depressive symptomatology, it is likely that mood symptoms may also appear in

incipient stages of AD. One approach to this issue is to look at individuals with mild cognitive impairment (MCI), who have subjective and objective cognitive deficits, but essentially intact functional abilities [39]. MCI often represents an intermediate stage between normal cognitive aging and dementia, as subjects meeting criteria for MCI progress to dementia due to AD at significantly higher rates than cognitively normal elderly controls [39]. Similarly, neuropathological investigations indicate that MCI frequently represents early stage AD [40].

Assessments of community-based MCI cohorts using the NPI reveal that the prevalence of depressive symptoms ranges from 17% to 27% and the prevalence of apathetic symptoms ranges from 9 to 18% [3, 41-43]. These rates are significantly higher than the rates of depressive (7% to 11%) and apathetic (3% to 5%) symptoms reported for comparable cognitively intact elderly cohorts [4, 43], and are most clearly highlighted by a population-based study from Olmsted County [43]. Although depression and apathy may represent distinct nosological entities [44], they frequently co-occur in AD and MCI [45], and many measures of depression, such as the DSM-IV, Hamilton Depression Rating Scale (HDRS), and Beck Depression Inventory (BDI), incorporate items that explicitly assess for the presence of apathy. Although it has been postulated that amnesic MCI is more likely to represent incipient AD than non-amnesic MCI [39], similar rates of depressive and apathetic symptoms have been reported in these MCI subtypes [46, 47]. These findings suggest that depressive symptomatology can emerge prior to a clinical diagnosis of dementia. Although symptoms are less common and less severe in MCI relative to dementia [3], they are already significantly associated with decreased quality of life at this pre-dementia stage of AD [48].

There is a relative paucity of data regarding the optimal approach to treating depressive symptoms in MCI. In contrast to the results seen in clinical AD, donepezil does not appear to ameliorate sub-syndromic symptoms of depression in MCI [49]. Two small open label studies of sertraline in MCI subjects with significant depressive symptoms reported response rates of 65% to 67% [50, 51], but neither study included a placebo group, and others report much lower antidepressant response rates in MCI [52]. Further studies incorporating more rigorous methodology will be needed to clarify the role of antidepressants for the treatment of mood symptoms in MCI.

Depressive symptoms in MCI may have greater portent beyond their association with poorer quality of life. A number of longitudinal studies of MCI cohorts have suggested that symptoms of depression [49, 52-56] or apathy [57-59] increase the likelihood of subsequent progression to dementia, although other conflicting findings have also been reported [60-63]. A number of factors may contribute to the heterogeneity of these results, including differences in operationalization of diagnostic criteria for MCI, assessment of mood symptoms, and length of follow-up. However, when taken as a whole, these findings raise the possibility that depressive and/or apathetic symptoms may serve as early markers of underlying neurodegenerative disease. This conclusion is further bolstered by an analysis of brain magnetic resonance imaging data from MCI subjects enrolled in the Alzheimer's Disease Neuroimaging Initiative. Participants with sub-syndromal depressive symptoms at baseline (i.e. scores < 6 on the 15 item Geriatric Depression Scale and > 0 on the dysphoria/

depression domain of the NPI-Q) demonstrated significantly greater white matter atrophy over the next two years than those without depressive symptoms [64]. Furthermore, some evidence suggests that depressive symptoms in MCI may help identify individuals that are more likely to respond to therapeutic interventions. While global analyses of the Alzheimer's Disease Cooperative Study of donepezil treatment for MCI failed to demonstrate a sustained benefit in delaying progression to AD [65], a subsequent subgroup analysis focused on subjects with clinically significant sub-syndromic depressive symptoms at baseline (i.e. HDRS scores ≥ 12 and BDI scores ≥ 10) [49]. Donepezil treatment decreased progression to AD among subjects with depressive symptoms, but had no effect for those without depressive symptoms (BDI scores < 10), suggesting that depression in MCI may be a marker for more pronounced cholinergic hypofunction. Notably, the effect of donepezil on reducing progression from MCI to AD in the depressed group was achieved without a concomitant reduction in depressive symptomatology. Taken together, although these findings require further confirmation, they indicate that depressive symptoms in MCI may have utility in predicting both prognosis and response to therapeutic interventions.

Clinicians are often faced with the challenge of distinguishing incipient AD (i.e. MCI) with depressive symptoms from cognitive symptoms associated with geriatric depression. In geriatric depression, impaired neuropsychological performance can be seen across multiple cognitive domains [66], but cognitive impairment related to depression (also known as pseudodementia) has often been considered reversible. However, a number of studies suggest that even after successful antidepressant treatment for mood symptoms, cognitive deficits do not improve beyond that expected from practice effects alone [67, 68]. Furthermore, a significant proportion of patients diagnosed with geriatric depression fulfill criteria for MCI even after successful antidepressant treatment [69]. These results reflect that cognitive symptoms in geriatric depression and depressive symptoms in MCI likely represent an overlapping continuum rather than two discrete conditions. Therefore, suboptimal cognitive responses to antidepressant treatment in geriatric depression should prompt clinicians to consider a diagnosis of MCI and the possibility of underlying neurodegenerative disease.

Depressive symptoms prior to cognitive impairment in incipient AD

Both neuropathological [70, 71] and β -amyloid positron emission tomography (PET) [72] studies indicate that early stages of AD pathology may even be present in individuals with normal cognition. The increased prevalence of depressive symptoms in MCI suggests that they may be an early manifestation of neurodegenerative changes associated with AD. These findings raise the question of whether mood symptoms may emerge at even earlier stages of incipient AD, and in some individuals, precede the onset of cognitive symptoms.

Several epidemiological studies have examined the association between depression and dementia risk but only a subset has specifically focused on dementia due to AD (as opposed to other etiologies). A comprehensive systematic review indicates that many, but not all of the more recent studies have found that late-life depression, defined as onset after age 60, is associated with subsequent AD dementia [37]. One interpretation of these cumulative findings is that even in cognitively normal elderly, depressive symptoms may represent a

prodromal syndrome of underlying AD neuropathology, despite the aforementioned qualitative differences between geriatric depression and depression in AD dementia [9, 10]. This conclusion is supported by recent work demonstrating increased β -amyloid/tau PET binding (suggesting increased AD-related neuropathology) in depressed versus non-depressed cognitively normal elderly [73]. However, cerebrospinal fluid levels of β -amyloid 1-42, which are decreased in AD, have been shown to be decreased [74], unchanged [75], or increased [76] in patients meeting criteria for major depression relative to non-depressed controls. These conflicting data, which have been tentatively attributed to underlying differences in study cohorts [74], highlight the heterogeneity of potential etiologies for geriatric depression.

Do the frequency and/or severity of mood symptoms modulate the association between depression and subsequent dementia in cognitively normal cohorts? Data from the Baltimore Longitudinal Study of Aging indicate that although participants with clinically significant depressive symptoms on even a single longitudinal assessment had an increased risk of subsequent AD relative to those without depressive symptoms, the risk was even greater amongst those with depressive symptoms on two or more longitudinal assessments [77]. Multiple reports have indicated that the link between depression and subsequent dementia due to AD is stronger among individuals with greater depressive symptomatology [78, 79]. However, another study suggests elevations in dementia risk among individuals diagnosed with either clinical depression or dysthymia and emphasizes the prognostic importance of even less severe depressive symptoms [80]. Overall, these data suggest that in cognitively normal elderly, recurrent and/or persistent late-life depressive symptoms, particularly those of greater severity, may more likely represent prodromal AD.

Another view is that depression in cognitively normal individuals represents a risk factor rather than a prodromal symptom for subsequent AD. This hypothesis is supported by a meta-regression analysis that indicated a stronger correlation across multiple studies between depressive symptoms and AD amongst individuals reporting longer intervals between the onset of depressive symptoms and a diagnosis of AD [81]. Additionally, data from the Rotterdam study revealed a stronger relationship between subsequent AD and earlier-life depression (onset before age 60) relative to later-life depression (onset after age 60) [82]. However, other work suggests that mid-life depression may be more robustly associated with vascular rather than AD dementia [83]. Given these conflicting findings, it remains difficult to definitively determine whether depressive symptoms in cognitively normal elderly represent a risk factor or a prodrome for subsequent AD dementia and a reasonable conclusion is that they may represent both. Alternatively, differences in study type (cohort vs. case-control, prospective vs. retrospective), assessments of depression, and length of follow-up may additionally contribute to these divergent reports [81].

Although antidepressant therapy appears to be efficacious for mood symptoms in geriatric depression [27], few studies have investigated whether such interventions modulate the risk of developing dementia in this population. Studies from transgenic mouse models of AD suggest that chronic antidepressant administration can delay AD-related cognitive and neuropathological changes [84, 85], raising the possibility of potential neuroprotective effects. This question has not been systematically addressed in longitudinal epidemiological

studies of aging, but two registry studies conducted in Denmark that incorporate detailed medical and pharmacy records have suggested that sustained treatment with antidepressants (particularly tricyclic antidepressants) was associated with lower rates of dementia due to AD or other causes than transient or short-term treatment with antidepressants in both the general population [86] and in psychiatric patients specifically diagnosed with depression [87]. These registry findings may have methodological limitations, but their conclusions are bolstered by a report demonstrating that, in cognitive normal elderly participants, chronic antidepressant use was associated with decreased cortical β -amyloid PET signaling [85]. Although more rigorous prevention studies have yet to be done, and may prove to be impractical, this constellation of preliminary results poses the intriguing hypothesis that depressive symptoms may be a modifiable risk factor and/or prodrome for AD in a subset of cognitive normal individuals. However, further studies are needed to establish the relationship between antidepressant use and AD neuropathology, as other work has suggested that antidepressant use is associated with smaller hippocampal volumes in non-demented elderly individuals [88]. Nevertheless, it remains unclear whether this effect was specifically linked to antidepressant use since individuals with greater cognitive impairment may be more likely to be prescribed antidepressants.

Conclusion and future perspective

Depressive symptoms are frequently associated with AD at various stages of disease progression, and their presence may have significant clinical implications for morbidity, prognosis, and treatment. Depression in dementia due to AD is qualitatively different from that seen in the cognitively normal elderly, but it remains uncertain why antidepressant therapy, which has demonstrated efficacy for depressive symptoms in other clinical contexts, is less effective in this population. Future studies of this issue will need to focus on the distinctive features of depression in dementia due to AD (i.e. greater prominence of motivational symptoms), as interventions that target apathetic rather than affective disturbances may prove to be more successful.

At earlier stages of disease progression, such as MCI, the presence of depressive and/or apathetic symptomatology signals not only a poorer prognosis, but also the potential for more robust responses to AChE-I treatment [49]. Results indicating that cognitive deficits in geriatric depression often represent more than just secondary manifestations of presenting mood symptoms [69] provide a compelling argument that the emergence of depressive symptoms in elderly patients warrants further investigation for underlying neurodegenerative etiologies through the use of neuroimaging or other biomarker studies. Additional research is needed to determine the both the role of and approach to treatment of depressive symptoms in MCI.

Moreover, even in elderly individuals with intact cognition, depression appears to be a risk factor and/or prodromal symptom for subsequent dementia due to AD or other etiologies [37], and may be associated with early stages of underlying AD neuropathology [73]. Although preliminary evidence raises the possibility that sustained antidepressant treatment in depressed older patients plays a neuroprotective role against AD [85-87], it is difficult to draw firm conclusions from the limited available data. However, given the increasing

emphasis on interventions at earlier stages of disease progression in AD, additional longitudinal studies of the long-term effects of treatment of geriatric depression are needed to provide further insight into whether mood symptoms represent a modifiable risk factor for AD dementia.

Acknowledgments

This research was supported by grants from the National Institute on Aging (P50 AG 16570), the Alzheimer's Disease Research Centers of California, and the Sidell-Kagan Foundation. ET receives additional support from K08 AG 34628 (jointly sponsored by NIA, AFAR, the John A. Hartford Foundation, the Atlantic Philanthropies, the Starr Foundation and an anonymous donor).

References

1. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34(7):939–944. [PubMed: 6610841]
2. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3):263–269. [PubMed: 21514250]
3. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, Dekosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the Cardiovascular Health Study. *JAMA*. 2002; 288(12):1475–1483. [PubMed: 12243634]
4. Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry*. 2000; 157(5):708–714. [PubMed: 10784462]
5. Naglie G, Hogan DB, Krahn M, et al. Predictors of family caregiver ratings of patient quality of life in Alzheimer disease: cross-sectional results from the Canadian Alzheimer's Disease Quality of Life Study. *Am J Geriatr Psychiatry*. 2011; 19(10):891–901. [PubMed: 21946805]
6. Naglie G, Hogan DB, Krahn M, et al. Predictors of patient self-ratings of quality of life in Alzheimer disease: cross-sectional results from the Canadian Alzheimer's Disease Quality of Life Study. *Am J Geriatr Psychiatry*. 2011; 19(10):881–890. [PubMed: 21946804]
7. Porta-Etessam J, Tobaruela-Gonzalez JL, Rabes-Berendes C. Depression in patients with moderate Alzheimer disease: a prospective observational cohort study. *Alzheimer Dis Assoc Disord*. 2011; 25(4):317–325. [PubMed: 21346516]
8. Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3):257–262. [PubMed: 21514247]
9. Chmerinski E, Petracca G, Sabe L, Kremer J, Starkstein SE. The specificity of depressive symptoms in patients with Alzheimer's disease. *Am J Psychiatry*. 2001; 158(1):68–72. [PubMed: 11136635]
10. Janzing JG, Hooijer C, Van 't Hof Ma, Zitman FG. Depression in subjects with and without dementia: a comparison using GMS-AGECAT. *Int J Geriatr Psychiatry*. 2002; 17(1):1–5. [PubMed: 11802223]
11. Lee HB, Lyketsos CG. Depression in Alzheimer's disease: heterogeneity and related issues. *Biol Psychiatry*. 2003; 54(3):353–362. [PubMed: 12893110]
12. Olin JT, Schneider LS, Katz IR, et al. Provisional diagnostic criteria for depression of Alzheimer disease. *Am J Geriatr Psychiatry*. 2002; 10(2):125–128. [PubMed: 11925273]
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th edition. APA; Washington: 1994.

14. Vilalta-Franch J, Garre-Olmo J, Lopez-Pousa S, et al. Comparison of different clinical diagnostic criteria for depression in Alzheimer disease. *Am J Geriatr Psychiatry*. 2006; 14(7):589–597. [PubMed: 16816012]
15. Teng E, Ringman JM, Ross LK, et al. Diagnosing depression in Alzheimer disease with the National Institute of Mental Health provisional criteria. *Am J Geriatr Psychiatry*. 2008; 16(6):469–477. [PubMed: 18515691]
16. Engedal K, Barca ML, Laks J, Selbaek G. Depression in Alzheimer's disease: specificity of depressive symptoms using three different clinical criteria. *Int J Geriatr Psychiatry*. 2011; 26(9): 944–951. [PubMed: 21845597]
17. Chiu PY, Steffens D, Chen PK, Hsu YC, Huang HT, Lai TJ. Depression in Taiwanese patients with Alzheimer's disease determined by the National Institutes of Mental Health Provisional Criteria. *Int Psychogeriatr*. 2012; 24(8):1299–1305. [PubMed: 22333495]
18. Portugal Mda G, Coutinho ES, Almeida C, et al. Validation of Montgomery-Asberg Rating Scale and Cornell Scale for Depression in Dementia in Brazilian elderly patients. *Int Psychogeriatr*. 2012; 24(8):1291–1298. [PubMed: 22185723]
19. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. The construct of minor and major depression in Alzheimer's disease. *Am J Psychiatry*. 2005; 162(11):2086–2093. [PubMed: 16263848]
20. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology*. 2001; 57(4):613–620. [PubMed: 11524468]
21. Gauthier S, Feldman H, Hecker J, et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *Int Psychogeriatr*. 2002; 14(4):389–404. [PubMed: 12670060]
22. Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology*. 2004; 63(2):214–219. [PubMed: 15277611]
23. Cummings JL, McRae T, Zhang R. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. *Am J Geriatr Psychiatry*. 2006; 14(7):605–612. [PubMed: 16816014]
24. Black SE, Doody R, Li H, et al. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. *Neurology*. 2007; 69(5):459–469. [PubMed: 17664405]
25. Howard RJ, Juszcak E, Ballard CG, et al. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med*. 2007; 357(14):1382–1392. [PubMed: 17914039]
26. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*. 2006; (1):CD005593. [PubMed: 16437532]
27. Nelson JC, Delucchi K, Schneider LS. Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. *Am J Geriatr Psychiatry*. 2008; 16(7):558–567. [PubMed: 18591576]
28. Petracca G, Teson A, Chemerinski E, Leiguarda R, Starkstein SE. A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 1996; 8(3):270–275. [PubMed: 8854297]
29. Lyketsos CG, Delcampo L, Steinberg M, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Arch Gen Psychiatry*. 2003; 60(7):737–746. [PubMed: 12860778]
30. Rosenberg PB, Drye LT, Martin BK, et al. Sertraline for the treatment of depression in Alzheimer disease. *Am J Geriatr Psychiatry*. 2010; 18(2):136–145. [PubMed: 20087081]
- 31••. Nelson JC, Devanand DP. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *J Am Geriatr Soc*. 2011; 59(4): 577–585. [PubMed: 21453380] [Comprehensive reviews the results of clinical trials of antidepressants in AD and indicates that overall, they have not conclusively demonstrated efficacy in this population.]
32. Banerjee S, Hellier J, Dewey M, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet*. 2011; 378(9789):403–411. [PubMed: 21764118]

33. Zweig RM, Ross CA, Hedreen JC, et al. The neuropathology of aminergic nuclei in Alzheimer's disease. *Ann Neurol.* 1988; 24(2):233–242. [PubMed: 3178178]
34. Rapp MA, Schnaider-Beeri M, Grossman HT, et al. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Arch Gen Psychiatry.* 2006; 63(2):161–167. [PubMed: 16461859]
35. Rapp MA, Schnaider-Beeri M, Purohit DP, Perl DP, Haroutunian V, Sano M. Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression. *Am J Geriatr Psychiatry.* 2008; 16(2):168–174. [PubMed: 18239198]
36. Wilson RS, Schneider JA, Bienias JL, Arnold SE, Evans DA, Bennett DA. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. *Neurology.* 2003; 61(8):1102–1107. [PubMed: 14581672]
- 37•. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol.* 2011; 7(6): 323–331. [PubMed: 21537355] [Comprehensive review of recent epidemiological studies examining the link between depression and dementia.]
38. Price JL, McKeel DW Jr, Buckles VD, et al. Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. *Neurobiol Aging.* 2009; 30(7):1026–1036. [PubMed: 19376612]
39. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med.* 2004; 256(3):183–194. [PubMed: 15324362]
40. Markesbery WR. Neuropathologic alterations in mild cognitive impairment: a review. *J Alzheimers Dis.* 2010; 19(1):221–228. [PubMed: 20061641]
41. Chan WC, Lam LC, Tam CW, et al. Neuropsychiatric symptoms are associated with increased risks of progression to dementia: a 2-year prospective study of 321 Chinese older persons with mild cognitive impairment. *Age Ageing.* 2011; 40(1):30–35. [PubMed: 21106558]
42. Peters ME, Rosenberg PB, Steinberg M, et al. Neuropsychiatric symptoms as risk factors for progression From CIND to dementia: The Cache County Study. *Am J Geriatr Psychiatry.* 2012 e-pub ahead of print, doi: 10.1097/JGP.0b013e318267014b.
43. Geda YE, Roberts RO, Knopman DS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Arch Gen Psychiatry.* 2008; 65(10):1193–1198. [PubMed: 18838636]
44. Tagariello P, Girardi P, Amore M. Depression and apathy in dementia: same syndrome or different constructs? A critical review. *Arch Gerontol Geriatr.* 2009; 49(2):246–249. [PubMed: 19022508]
45. Benoit M, Berrut G, Doussaint J, et al. Apathy and depression in mild Alzheimer's disease: a cross-sectional study using diagnostic criteria. *J Alzheimers Dis.* 2012; 31(2):325–334. [PubMed: 22543849]
46. Lee KS, Cho HS, Hong CH, Kim DG, Oh BH. Differences in neuropsychiatric symptoms according to mild cognitive impairment subtypes in the community. *Dement Geriatr Cogn Disord.* 2008; 26(3):212–217. [PubMed: 18781071]
47. Rozzini L, Vicini Chilovi B, Conti M, et al. Neuropsychiatric symptoms in amnesic and nonamnesic mild cognitive impairment. *Dement Geriatr Cogn Disord.* 2008; 25(1):32–36. [PubMed: 18025827]
48. Teng E, Tassniyom K, Lu PH. Reduced Quality-of-Life Ratings in Mild Cognitive Impairment: Analyses of Subject and Informant Responses. *Am J Geriatr Psychiatry.* 2012; 20(12):1016–1025. [PubMed: 23018474]
- 49•. Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL. Donepezil delays progression to AD in MCI subjects with depressive symptoms. *Neurology.* 2009; 72(24):2115–2121. [PubMed: 19528519] [Demonstrates that depressive symptoms in MCI are associated with higher rates of progression to dementia, but also better responses to donepezil treatment.]
50. Devanand DP, Pelton GH, Marston K, et al. Sertraline treatment of elderly patients with depression and cognitive impairment. *Int J Geriatr Psychiatry.* 2003; 18(2):123–130. [PubMed: 12571820]
51. Pelton GH, Harper OL, Tabert MH, et al. Randomized double-blind placebo-controlled donepezil augmentation in antidepressant-treated elderly patients with depression and cognitive impairment: a pilot study. *Int J Geriatr Psychiatry.* 2008; 23(7):670–676. [PubMed: 18088076]

52. Modrego PJ, Ferrandez J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. *Arch Neurol.* 2004; 61(8): 1290–1293. [PubMed: 15313849]
53. Gabryelewicz T, Styczynska M, Luczywek E, et al. The rate of conversion of mild cognitive impairment to dementia: predictive role of depression. *Int J Geriatr Psychiatry.* 2007; 22(6):563–567. [PubMed: 17136705]
54. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *Am J Geriatr Psychiatry.* 2012 e-pub ahead of print, doi: 10.1097/JGP.0b013e318252e41a.
55. Teng E, Lu PH, Cummings JL. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2007; 24(4):253–259. [PubMed: 17700021]
56. Houde M, Bergman H, Whitehead V, Chertkow H. A predictive depression pattern in mild cognitive impairment. *Int J Geriatr Psychiatry.* 2008; 23(10):1028–1033. [PubMed: 18651723]
57. Palmer K, Di Iulio F, Varsi AE, et al. Neuropsychiatric predictors of progression from amnesic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. *J Alzheimers Dis.* 2010; 20(1):175–183. [PubMed: 20164594]
58. Vicini Chilovi B, Conti M, Zanetti M, Mazzu I, Rozzini L, Padovani A. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dement Geriatr Cogn Disord.* 2009; 27(4):390–398. [PubMed: 19339777]
59. Robert PH, Berr C, Volteau M, et al. Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease A one-year follow-up study. *Clin Neurol Neurosurg.* 2006; 108(8):733–736. [PubMed: 16567037]
60. Rozzini L, Chilovi BV, Trabucchi M, Padovani A. Depression is unrelated to conversion to dementia in patients with mild cognitive impairment. *Arch Neurol.* 2005; 62(3):505. [PubMed: 15767521]
61. Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology.* 2007; 68(19):1596–1602. [PubMed: 17485646]
62. Panza F, Capurso C, D'introno A, et al. Impact of depressive symptoms on the rate of progression to dementia in patients affected by mild cognitive impairment. The Italian Longitudinal Study on Aging. *Int J Geriatr Psychiatry.* 2008; 23(7):726–734. [PubMed: 18188869]
63. Mackin RS, Insel P, Aisen PS, Geda YE, Weiner MW. Longitudinal stability of subsyndromal symptoms of depression in individuals with mild cognitive impairment: relationship to conversion to dementia after 3 years. *Int J Geriatr Psychiatry.* 2012; 27(4):355–363. [PubMed: 21744390]
64. Lee GJ, Lu PH, Hua X, et al. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. *Biol Psychiatry.* 2012; 71(9):814–821. [PubMed: 22322105] [Indicates that depressive symptoms are associated with greater longitudinal white matter atrophy in MCI, and suggests that such symptoms may be a marker for more aggressive underlying neurodegenerative disease.]
65. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med.* 2005; 352(23):2379–2388. [PubMed: 15829527]
66. Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry.* 2004; 61(6):587–595. [PubMed: 15184238]
67. Nebes RD, Pollock BG, Houck PR, et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. *J Psychiatr Res.* 2003; 37(2):99–108. [PubMed: 12842163]
68. Portella MJ, Marcos T, Rami L, Navarro V, Gasto C, Salamero M. Residual cognitive impairment in late-life depression after a 12-month period follow-up. *Int J Geriatr Psychiatry.* 2003; 18(7): 571–576. [PubMed: 12833300]
69. Bhalla RK, Butters MA, Becker JT, et al. Patterns of mild cognitive impairment after treatment of depression in the elderly. *Am J Geriatr Psychiatry.* 2009; 17(4):308–316. [PubMed: 19307859] [Reports that a significant proportion of individuals with successfully treated geriatric depression

continue to meet criteria for MCI. Demonstrates that geriatric depression with cognitive dysfunction and MCI with depressive symptoms likely lie on a diagnostic continuum.]

70. Schmitt FA, Davis DG, Wekstein DR, Smith CD, Ashford JW, Markesbery WR. "Preclinical" AD revisited: neuropathology of cognitively normal older adults. *Neurology*. 2000; 55(3):370–376. [PubMed: 10932270]
71. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*. 2006; 66(12):1837–1844. [PubMed: 16801647]
72. Mielke MM, Wiste HJ, Weigand SD, et al. Indicators of amyloid burden in a population-based study of cognitively normal elderly. *Neurology*. 2012; 79(15):1570–1577. [PubMed: 22972644]
73. Kumar A, Kepe V, Barrio JR, et al. Protein binding in patients with late-life depression. *Arch Gen Psychiatry*. 2011; 68(11):1143–1150. [PubMed: 22065530] [Demonstrates increased cortical F18FDDNP PET signal in cognitively normal depressed elderly patients. Suggests that geriatric depression is associated with increased underlying AD neuropathology.]
74. Pomara N, Bruno D, Sarreal AS, et al. Lower CSF amyloid beta peptides and higher F2-isoprostanes in cognitively intact elderly individuals with major depressive disorder. *Am J Psychiatry*. 2012; 169(5):523–530. [PubMed: 22764362]
75. Reis T, Brandao CO, Freire Coutinho ES, Engelhardt E, Laks J. Cerebrospinal fluid biomarkers in Alzheimer's disease and geriatric depression: preliminary findings from Brazil. *CNS Neurosci Ther*. 2012; 18(7):524–529. [PubMed: 22530600]
76. Gudmundsson P, Skoog I, Waern M, et al. The relationship between cerebrospinal fluid biomarkers and depression in elderly women. *Am J Geriatr Psychiatry*. 2007; 15(10):832–838. [PubMed: 17911361]
77. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology*. 2010; 75(1):27–34. [PubMed: 20603482]
78. Wilson RS, Barnes LL, Mendes De Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*. 2002; 59(3):364–370. [PubMed: 12177369]
79. Gatz JL, Tyas SL, St John P, Montgomery P. Do depressive symptoms predict Alzheimer's disease and dementia? *J Gerontol A Biol Sci Med Sci*. 2005; 60(6):744–747. [PubMed: 15983177]
80. Byers AL, Covinsky KE, Barnes DE, Yaffe K. Dysthymia and depression increase risk of dementia and mortality among older veterans. *Am J Geriatr Psychiatry*. 2012; 20(8):664–672. [PubMed: 21597358]
81. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry*. 2006; 63(5):530–538. [PubMed: 16651510]
82. Geerlings MI, Den Heijer T, Koudstaal PJ, Hofman A, Breteler MM. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. *Neurology*. 2008; 70(15):1258–1264. [PubMed: 18391157]
83. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry*. 2012; 69(5):493–498. [PubMed: 22566581]
84. Nelson RL, Guo Z, Halagappa VM, et al. Prophylactic treatment with paroxetine ameliorates behavioral deficits and retards the development of amyloid and tau pathologies in 3xTgAD mice. *Exp Neurol*. 2007; 205(1):166–176. [PubMed: 17368447]
85. Cirrito JR, Disabato BM, Restivo JL, et al. Serotonin signaling is associated with lower amyloid-beta levels and plaques in transgenic mice and humans. *Proc Natl Acad Sci U S A*. 2011; 108(36):14968–14973. [PubMed: 21873225] [Shows that chronic antidepressant treatment reduces β -amyloid deposition in a transgenic mouse model of AD and is associated with lower cortical β -amyloid PET signal in cognitively normal elderly human subjects.]
86. Kessing LV, Sondergard L, Forman JL, Andersen PK. Antidepressants and dementia. *J Affect Disord*. 2009; 117(1-2):24–29. [PubMed: 19138799]
87. Kessing LV, Forman JL, Andersen PK. Do continued antidepressants protect against dementia in patients with severe depressive disorder? *Int Clin Psychopharmacol*. 2011; 26(6):316–322. [PubMed: 21876440]

88. Geerlings MI, Brickman AM, Schupf N, et al. Depressive symptoms, antidepressant use, and brain volumes on MRI in a population-based cohort of old persons without dementia. *J Alzheimers Dis*. 2012; 30(1):75–82. [PubMed: 22377782]

Practice Points

- Depressive symptoms should be assessed in patients with clinical or incipient Alzheimer's disease (AD) given their prevalence, associated morbidity, and prognostic implications.
- Depression in dementia due to AD may have more prominent motivational symptoms and less prominent affective symptoms than depression in younger and/or cognitively intact populations.
- Acetylcholinesterase inhibitors appear to decrease depressive symptoms in AD, but the efficacy of antidepressant medications in these patients has yet to be conclusively established.
- Patients meeting criteria for mild cognitive impairment (MCI) with depressive and/or apathetic symptoms are more likely to progress to dementia than those without depressive symptoms, but may also potentially derive greater treatment benefits from acetylcholinesterase inhibitors.
- Depressive symptoms in cognitively normal elderly individuals represent a risk factor and/or prodrome of incipient AD.
- Preliminary data raise the possibility that sustained antidepressant treatment of mid-life or late-life depression may modulate the risk for subsequent AD dementia, but require additional confirmation.