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Treating depression in older adults with dementia

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Dementia management is a growth industry, as the number of cases in the US is expected to skyrocket from 5 million now to as many as 16 million by 2050¹. Behavioral problems in dementia are extremely common and include agitation, psychosis, anxiety, and depression². Behavioral problems are a leading cause of health care expenditures³, nursing home placement⁴, and caregiver burden⁵ in dementia. Thus, depression and other behavioral problems in dementia are a big problem that is getting bigger; effective means of controlling them are of great importance for clinicians and for the community.

In this issue of the Journal of the American Geriatrics Society, Drs. Nelson and Devanand ask a simple question: do antidepressant medications help depressive symptoms in dementia? To answer this question, they performed a scholarly review and meta-analysis of seven studies that randomized elderly demented persons with depression to antidepressant or placebo (total N=330). They found only marginal evidence of efficacy of antidepressants to bring about response or remission from depression, or to bring about a greater reduction in depressive symptoms than placebo. The studies in the meta-analysis were of good quality but were generally underpowered (only one study randomized more than 50 subjects). Moreover, the studies were heterogeneous in terms of classes of antidepressants tested, depressive symptom measures, levels of severity of depression, and definitions of “depression in dementia.” Among the individual studies, only two of seven found a statistically significant benefit of antidepressant over placebo.

What do these findings mean for clinicians and for researchers? Before addressing these questions, it is important to mention some limitations to the use of meta-analyses in examining mental health treatments. First, a meta-analysis cannot overcome methodological limitations of the studies included in the analysis. Two limitations underlying almost all behavioral treatment research, including antidepressant treatments, are (a) the examination of a “complex phenotype” (a euphemism for “we don’t know what ‘clinical depression’ is on a molecular or systems level”), and (b) the use of crude outcome measures based largely on self-report, which are little-changed since the 1950s. These two limitations are exacerbated in geriatric studies, because of heterogeneity due to medical and cerebrovascular changes⁶ and because of problems with insight and recall which undermine researchers’ ability to accurately measure outcomes. In fact, a meta-analysis may exaggerate methodological limitations, as the weighting favors studies with larger sample sizes, possibly at the expense of smaller but more methodologically sound studies. Finally, the gold standard for validity of a scientific finding is independent confirmation, not meta-analysis; and, the efficacy of antidepressants for depression in dementia has been shown in two independent studies – although, on the other hand, the largest study to date, a multi-center study specifically meant to confirm this efficacy finding, failed to do so⁷. To their credit, Drs. Nelson and Devanand clearly outline the various methodological problems of

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the underlying research as well as the limitations of a meta-analytic approach in this instance.

Clinicians frequently look to meta-analyses for treatment recommendations, but the main finding here is that the question “How do I treat depressive symptoms in my demented patients?” remains incompletely answered. The authors suggest that the marginal findings in this meta-analysis are due to modest efficacy of antidepressants for older adults in general (whether demented or not)⁸. Yet clinicians can achieve excellent outcomes with antidepressant treatment in our older adults. Based on research findings and my own experience as a geriatric psychiatrist who sees such patients and has participated in numerous clinical trials of antidepressant treatment, I would have three points of advice: First, *decide whether initiating antidepressant treatment is appropriate* (vs. watchful waiting). To make this decision, ask the following questions: is depression causing the patient, and/or the caregiver, suffering? Is it recalcitrant to environmental changes (such as increasing physical activity or social and pleasurable events)? Is it frequent? Is it clearly “depression” (including sadness or inability to experience pleasure, excess somatization, core symptoms such as pessimism, guilt, worthlessness and wish to die) or something more non-specific such as apathy or fatigue? Are non-medication options (such as pain relief, medical rehabilitation, or a change in living situation) likely to relieve the depressive symptoms? Second, *follow the patient closely to optimize treatment*. If the treatment is poorly-tolerated, or there is clearly no benefit at an adequate dose, the decision is simple: stop it and try something else. If the treatment is beneficial but incompletely so, try augmentation (if dose is optimized already); the use of dose optimization and medication augmentation and switching approaches will get most depressed older adults to remission.⁹ Also continue to reinforce non-pharmacological approaches¹⁰ which may become more feasible and effective when combined with antidepressants. Close follow-up will also improve adherence and provide a clearer ascertainment of benefits and risks,¹¹ which will mitigate acute risks of antidepressants such as hyponatremia leading to confusion¹² or increased suicidality.¹³ Third, *determine a maintenance strategy*. Here, “the dose that gets you well, keeps you well” has been clearly demonstrated for both cognitively impaired and intact elderly.¹⁴ If an antidepressant medication has been demonstrated to work and is well-tolerated, it should be maintained. In summary, by limiting treatment only to those who are likely to benefit, by discarding treatments that do not work and optimizing those that do, and by using maintenance treatment, astute clinicians usually will get our patients well from depression and keep them well.

This meta-analysis has important implications for researchers. Drs. Nelson and Devanand suggest that additional research is needed to establish the efficacy of antidepressants in depressed patients with dementia, focusing on patients most likely to be drug-responsive; i.e., those with more severe levels of depressive symptoms, and those with a more chronic or recurrent illness. Additionally, the authors point out the challenges in accurately assessing outcomes of depression using standard rating scales. Taking this point further, it is unlikely that we will be able to clarify the benefits of antidepressants (or any behavioral treatment) in older adults, or to personalize treatment based on clinical trial findings, until we greatly improve assay sensitivity of our outcome measures. Experience sampling¹⁵ and objective measures of physical and social functioning¹⁶ are well known and validated methods to overcome insight and recall biases and might greatly increase the precision of depression outcome measurement. Finally, observational studies have recently raised a host of potential long-term risks of antidepressants in older adults, including suicide¹⁷, gastrointestinal bleed¹⁸, and falls and bone loss leading to increased fracture risk¹⁹. The suicide risk seems unlikely in the aggregate, as a large FDA meta-analysis specifically examining suicide in antidepressant clinical trials found a protective effect of antidepressants versus placebo in those aged 65+.²⁰ Likewise gastrointestinal bleed is a rare event, so its potential risk would

not preclude antidepressant use in most older adults. But the growing concern of falls, bone loss, and fractures with serotonergic antidepressants could and should be determined definitively by an appropriate randomized clinical trial; until then, the causality of these risks will remain unclear. It would be helpful to know whether in treating depression we are contributing to the \$19 billion-plus annual US cost of treating fall-related injuries in older adults.²¹

In conclusion, Nelson and Devanand show us not only what we have learned in treating depression in dementia, but how much we still need to learn. Improved methods to measure outcomes, and a greater focus on risks as well as benefits of treatment should be the focus of future clinical trials in this field. Until then, clinicians should continue to use a trial-and-error approach, often frustrating but (with adequate skill and time) still producing good clinical outcomes in the treatment of late-life depression.

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References

1. Attea P, Johns H. Confronting Alzheimer's disease and other dementias. *J Am Geriatr Soc.* 58:1587–1590. [PubMed: 20942873]
2. Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry.* 2008; 23:170–177. [PubMed: 17607801]
3. Jonsson L, Eriksdotter Jonhagen M, Kilander L, et al. Determinants of costs of care for patients with Alzheimer's disease. *Int J Geriatr Psychiatry.* 2006; 21:449–459. [PubMed: 16676288]
4. Gaugler JE, Yu F, Krichbaum K, Wyman JF. Predictors of nursing home admission for persons with dementia. *Med Care.* 2009; 47:191–198. [PubMed: 19169120]
5. Mohamed S, Rosenheck R, Lyketsos CG, Schneider LS. Caregiver burden in Alzheimer disease: cross-sectional and longitudinal patient correlates. *Am J Geriatr Psychiatry.* 18:917–927. [PubMed: 20808108]
6. Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry.* 67:277–285. [PubMed: 20194828]
7. Rosenberg PB, Drye LT, Martin BK, et al. Sertraline for the treatment of depression in Alzheimer disease. *Am J Geriatr Psychiatry.* 18:136–145. [PubMed: 20087081]
8. 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; 16:558–567. [PubMed: 18591576]
9. Dew MA, Whyte EM, Lenze EJ, et al. Recovery from major depression in older adults receiving augmentation of antidepressant pharmacotherapy. *Am J Psychiatry.* 2007; 164:892–899. [PubMed: 17541048]
10. Gitlin LN, Winter L, Dennis MP, Hodgson N, Hauck WW. Targeting and managing behavioral symptoms in individuals with dementia: a randomized trial of a nonpharmacological intervention. *J Am Geriatr Soc.* 58:1465–1474. [PubMed: 20662955]
11. Zivin K, Kales HC. Adherence to depression treatment in older adults: a narrative review. *Drugs Aging.* 2008; 25:559–571. [PubMed: 18582145]
12. Fabian TJ, Amico JA, Kroboth PD, et al. Paroxetine-induced hyponatremia in older adults: a 12-week prospective study. *Arch Intern Med.* 2004; 164:327–332. [PubMed: 14769630]

13. Kales HC, Kim HM, Austin KL, Valenstein M. Who receives outpatient monitoring during high-risk depression treatment periods? *J Am Geriatr Soc.* 58:908–913. [PubMed: 20406321]
14. Reynolds CF 3rd, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med.* 2006; 354:1130–1138. [PubMed: 16540613]
15. Ben-Zeev D, Young MA. Accuracy of hospitalized depressed patients' and healthy controls' retrospective symptom reports: an experience sampling study. *J Nerv Ment Dis.* 198:280–285. [PubMed: 20386257]
16. Friedman L, Zeitzer JM, Kushida C, et al. Scheduled bright light for treatment of insomnia in older adults. *J Am Geriatr Soc.* 2009; 57:441–452. [PubMed: 19187411]
17. Juurlink DN, Mamdani MM, Kopp A, Redelmeier DA. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. *Am J Psychiatry.* 2006; 163:813–821. [PubMed: 16648321]
18. de Abajo FJ, Garcia-Rodriguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. *Arch Gen Psychiatry.* 2008; 65:795–803. [PubMed: 18606952]
19. Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med.* 2007; 167:188–194. [PubMed: 17242321]
20. Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ.* 2009; 339:b2880. [PubMed: 19671933]
21. Stevens JA, Baldwin GT, Ballesteros MF, Noonan RK, Sleet DA. An older adult falls research agenda from a public health perspective. *Clin Geriatr Med.* 26:767–779. [PubMed: 20934621]