Antidepressants in Older Adults: Complexities, Confounds and Clinical Effects

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Older adults with depression are often treated with antidepressant medications, but there is only limited evidence from controlled trials to support their efficacy. The high frequency and severity of concurrent illness and medications in older adults with depression often makes the risk-benefit ratio difficult to calculate. Several reports in this issue are relevant to this ongoing dialectic, both in depressed patients without significant cognitive impairment and in patients with dementing illnesses who manifest depressive symptomatology.

REGIONAL BRAIN THINNING AND ANTIDEPRESSANT RESPONSE

Lebedev et al.[1] showed that in patients with Alzheimer disease (AD) and dementia with Lewy bodies, depression was associated with cortical thinning in prefrontal and temporal areas, and antidepressant use was associated with thinning in the parahippocampal region. The cross-sectional study design makes it difficult to infer cause and effect, and it remains unclear if cortical thinning preceded the onset of depression in dementia or whether the use of antidepressants contributed to parahippocampal thinning. The authors suggest that depressive symptoms in mild dementia can develop due to neurodegeneration in the same neural circuits that are compromised in late life depression more broadly. In late-life depression without dementia, antidepressant treatment response has been shown to be lower in patients with smaller hippocampal volumes and impaired cognitive functioning,[2] consistent with the view that neurodegenerative processes underlie depression in many elderly patients and that antidepressant treatment is less effective in these patients. Further, frontal-striatal-limbic circuits have been postulated to be involved in the pathogenesis of late life depression, and cerebrovascular causes have been implicated.[3] Although there is extensive degeneration of catecholaminenergic neurons in the brain in AD,[4] selective serotonin reuptake inhibitors (SSRIs) have shown limited efficacy for depression in AD as discussed in a meta-analysis of antidepressant treatment for depression in dementia.[5]

ANTIDEPRESSANT RESPONSE IN ALZHEIMER DISEASE

As previously reported from the DIADS-2 study, sertraline did not show superior efficacy to placebo in the treatment of depression in patients with AD,[6] consistent with a meta-analysis that showed marginal superiority for antidepressant over placebo across the few trials that have been conducted.[5] In AD, depressive symptoms fluctuate naturalistically over time to a much greater extent than symptoms of agitation that tend to be persistent.[7] These spontaneous fluctuations in depressive symptoms tend to increase the likelihood of placebo response, which is high in nearly all antidepressant treatment trials for

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depression in AD,[5] and reduce the likelihood of observing an antidepressant therapeutic effect.

In this new report from the DIADS-2 study by Longmire et al.,[8] caregivers of patients in both treatment groups had significant reductions in distress scores but with no difference between sertraline and placebo. Caregiver burden and quality of life did not change. Caregiver distress was assessed via the NPI scale that focuses on distress directly due to psychiatric symptoms, although the caregiver burden and quality of life assessments are much broader. Caregiver distress improved concomitant with improvement in depression, emphasizing the importance of improvement in depressive symptoms in these patients. The fact that we have not yet identified a highly efficacious treatment for depression in AD suggests the need for further research efforts in this area, particularly because improvement in depression benefits both the patient and the caregiver.

ANTIDEPRESSANTS AND DECREASED RISK OF SUICIDE

Notwithstanding the difficulty in showing antidepressant efficacy in controlled trials, another approach is to evaluate the effect of treatment on a clinically significant outcome of depressive illness. The Danish national population-based cohort study reported by Erlangsen et al.[9] showed that the use of antidepressants was associated with a decline in the suicide rate in older adults. A weakness in the study is that the suicide rate was lower in people over 80 years old, inconsistent with other reports of high suicide rates in the very old,[10] and this may have minimized the true magnitude of the benefit of antidepressant medication. The sample was dichotomized into subjects 50–59 and 80+ years in age; information about the 60–79 years old group was not presented. The value of detecting and treating depression is highlighted by the lower rate of suicide in subjects who took antidepressant medications with a 2%–3% decline in the suicide rate for each additional year of age. The importance of this finding is further supported by the authors' observation that the suicide rate increased with age, particularly in those above 80 years, in subjects who did not take antidepressants. Antidepressants were associated with a decreased suicide rate in both men and women in both age groups, suggesting that they do indeed have some efficacy in preventing the most adverse of outcomes for patients with depression. A more troubling finding was the limited identification and treatment of depression in older adults with depression, even in this Scandinavian health care system.

ANTIDEPRESSANT EFFICACY IN OLDER ADULTS AND MELACHOLIA

At first glance the reports of Robinson et al.[11] and Sneed et al.[12] in this issue would appear to be examples of the "failed" studies that contribute to the view that antidepressants have limited benefit for patients with late-life depression. Both studies, however, raise the intriguing question of how to evaluate a study where the reported finding of no significant difference in the primary outcome measure occurs in the context of other positive study findings.

The study reported by Robinson et al. is a traditional, industry-sponsored, 24-week (12-week acute and 12-week continuation), randomized, placebo-controlled, double-blind trial of duloxetine compared with placebo in patients with late-life depression. The primary outcome was the change in the Maier subscale of the 17-item Hamilton Depression Rating Scale at week 12. The comparison showed an advantage for duloxetine over placebo at weeks 4, 8, 16, and 20, but there was no significant difference at weeks 12 and 24. The authors correctly report the headline finding but the results appear to be more nuanced and other statistical analyses may have been needed to consider all the data obtained in order to provide a balanced and comprehensive view of the study findings. There was no difference in the remission rate, which is typically an outcome measure of greater importance than change in a scale score.

The Sneed et al. study addresses a long-standing debate since 1994[13] as to whether tricyclic antidepressants (TCAs) are more effective than SSRIs in the treatment of the melancholic subtype of depression. Though the issue may be a topic of continuing discussion at Columbia University more than anywhere

else, nonetheless the results are germane to the treatment of this severe form of depression and the neurobiology of depressive subtypes. The study was a randomized, 12-week trial comparing sertraline to nortriptyline in the treatment of patients with nonpsychotic, unipolar major depression stratified by the presence of melancholia. Though the test of the interaction of medication group and melancholia status on response was not statistically significant, patients with melancholia had response rates of 47% to sertraline and 75% to nortriptyline, whereas nonmelancholic patients had response rates of 51% to sertraline and 42% to nortriptyline. In a multilevel statistical model, the odds of response and remission for patients with melancholia treated with nortriptyline compared with sertraline were 3.46 and 2.80, respectively. The study appears to have been underpowered for the main effect and clearly for the interaction effect. Though the cardiovascular and other side effects of TCAs make their use problematic in elderly patients with heart disease, the clinical conclusion from the study is that in melancholic patients unresponsive to SSRIs a trial of a TCA with therapeutic plasma levels may be worthwhile, particularly in patients without cardiac disease. The serotonin–norepinephrine reuptake inhibitors may be an alternative to TCAs but there is little systematic study of their efficacy in patients with melancholia.[14]

CONCLUSION

The multifactorial etiology of depression in many older patients makes it difficult to draw simple conclusions about the optimal treatment approach, especially when robust differences between active treatment and placebo have proven difficult to establish. The relatively unimpressive response to antidepressants in geriatric depression may be related to a large subgroup having neurodegeneration as in AD or cerebrovascular brain damage or related processes. One possible approach is to exclude these patients or have separate cells for these patients in randomized clinical trials of antidepressant medications, and this approach may provide clarity and help to parse out the clinical meaning of negative or ambiguous trials. Further, the use of clinically significant primary outcomes such as suicide rate and quality of life measures may be more important than depression scale ratings, and may make the findings of randomized trials more clinically relevant.

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