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The interface between depression and dementia: Where are we with this important frontier?

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The most recent report of Alzheimer Disease International[i], released on World Alzheimer Day 2009, is a grim reminder that the dementia epidemic is now upon us. Worldwide, over 35 million people are estimated to be living with dementia today. This number will double roughly every 20 years exceeding 115 million by the year 2050. In North America, the estimates suggest that in 2010 4.38 million people will be living with dementia; the number will grow to about 11 million by the year 2050. Geriatric psychiatrists are confronted ***daily*** with issues surrounding the care of people with cognitive disorders, especially depression, and their caregiver. Given that between one third and one half of older people with depression also have dementia, this is a defining discussion for our field. Further, it is well established that over the course of dementia as many as two thirds of patients develop depression[ii].

We struggle with multiple issues surrounding the interface between depression and dementia. For example, is depression is a risk factor for dementia? Is depression in Mild Cognitive Impairment (MCI), the putative prodrome of Alzheimer's dementia, associated with a higher risk of dementia conversion? What are the best approaches to the management of cognitive impairment and depressed older adults? How about the management of depression in patients with dementia, and their caregivers?

This issue of the *American Journal of Geriatric Psychiatry* (AJGP) contains several papers that advance our understanding in this important area. In a sophisticated review, Panza et aliii follow-up on the report of a 2003 NIMH panel on this topiciv with a summary of knowledge almost a decade later. They emphasize that, across hospital- and population-based studies, about 34% of MCI patients have depressive symptoms, at the median. Far fewer date exist regarding the prevalence of MCI in patients with late life depression (LLD) although existing data indicate that one third to one half meet criteria for this condition. Further, they confirm that, on balance, evidence indicates that the presence of depressive symptoms, perhaps affective symptoms more broadly, confers a higher risk of conversion both to MCI and to dementia. Their conclusion is that this reflects a common underlying pathophysiology and that targeting LLD continues to hold promise as a way of reducing dementia incidence.

An important issue raised implicitly by Panza et al relates to the measurement of depressive symptoms in patients with cognitive impairment. As the 2003 NIMH panel revealed, the LLD and MCI fields have traditionally use different measurement approaches for depression. For example, researchers in LLD have typically quantified its severity using clinician rated or self-report questionnaires designed for depression such as the Hamilton Depression Rating Scale and the Geriatric Depression Scale. In contrast, those studying MCI and dementia have traditionally used dementia tailored measures such as the Neuropsychiatric Inventory (NPI) in the Cornell Scale for Depression in Dementia. These differences in measurement likely underlie differences in estimates of prevalence, incidence, and reviewed by Panza et al. The field continues to need a single approach to measurement at this interface. The recent development of the clinician rated version of the NPI, or NPI-C[v], is in part an attempt to marry

these approaches into a single measure that would allow both the assessment of depressive symptoms as well as the assessment and quantification of associated affective of symptoms (i.e., irritability, anxiety, and apathy), using the same approach used to quantify other neuropsychiatric symptoms that are prevalent in patients with cognitive disorders (e.g., disinhibition, delusions). Wide adoption of the NPI-C should reduce measurement variability and greatly improve comparability of studies in this interface area.

What about the treatment of patients with LLD and cognitive symptoms? It's already widely accepted that the treatment of late life depression with antidepressants does not always lead to remission of cognitive symptoms. In fact the persistence of cognitive symptoms is often an indicator of emerging MCI or dementia. In an important paper in this issue of AJGP, Sneed et al[vi] follow-up on their earlier work to indicate that one aspect of executive dyscontrol, "deficient response inhibition (DRI)," may be a predictor of poor antidepressant response to the SSRI antidepressant citalopram. Their critical finding is that the presence of DRI in patients with LLD might not simply predict failure to respond to treatment, but might be a marker for patients who should not be treated with SSRI antidepressants. Follow-up on this study, and ones like it, is urgently needed since it has direct implications for daily treatment practices in our field.

Interestingly enough, in this issue of AJGP Rosenberg et al[vii] report results from the *Depression in Alzheimer's Disease Study-2* (DIADS-2) a multicenter, randomized, placebo-controlled trial to treat "Depression of Alzheimer's Disease" following up on preliminary data developed by our group at Johns Hopkins. The findings are a reminder that what is learned in general psychiatry does not necessarily apply to neuropsychiatry[viii] since the study failed to show an antidepressant advantage for sertraline, at a median dose of one about 100 mg/day, over placebo for this group of patients. Since almost all depressed patients in the study improved considerably over the first 12 weeks, this result can in part be explained by the use of a psychosocial intervention targeted at their caregivers. As with CATIE-ADix tolerability concerns were raised. As a result, the treatment of neuropsychiatric symptoms in patients with Alzheimer's and related dementias using psychotropic medications continues to be problematic. While psychotropics are not necessarily contraindicated, the bar for their use has been raised higher again. Research further defining the comparative effectiveness of psychosocial treatments and psychotropic medications for these highly prevalent conditions in dementia patients is urgently needed.

Two other papers in this issue relate to depression in the caregivers of dementia patients. In a unique and highly innovative study, Joling et al[x] attempt to estimate the frequency of depression, and its treatment, among dementia caregivers at the population level. This is very important because the vast majority of studies of dementia caregivers come from referral settings. It is likely that depression in caregivers leads to selection bias, such that more depressed caregivers are more likely to seek care for their care recipients.

Not unexpectedly, Joling et al found that general practitioners diagnose depression in about half the caregivers of dementia patients they see. This apparently low rate might reflect under-diagnosis by general practitioners; it could also indicate that dementia caregivers at the population level have lower rates of depression than in clinical settings. The same study emphasizes how general practitioners diagnose depression and dementia caregivers four times more commonly than in the spouses of their non-demented elderly patients. It's reassuring that, at least in the Netherlands, general practitioners also frequently prescribed antidepressant medications to these caregivers which indicates that they take their condition seriously and attempt to alleviate it.

The latter is especially important in light of the report by Lavretzky et al[xi] whose randomized placebo-controlled trial, one of the first of its kind, demonstrates preliminarily that treating major or minor depression in the caregivers of dementia patients with the SSRI antidepressants escitalopram is superior to placebo. A most remarkable and encouraging finding was that antidepressant treatment also was superior to placebo in improving distress, resilience, burden, and quality of life for caregivers. If replicated this study has huge implications for dementia care. It emphasizes the critical importance a pharmacologic therapies for caregivers and reminds us that even though the major objective indicators of burden and stress in their lives if anything get worse, it is possible through an antidepressant to help them and improve their life quality.

In summary, the field that lives at the interface between depression and dementia has a long way to go. Since the 2003 NIMH panel that summarized the agenda for the field there have been important advances. Nevertheless we need to redouble our efforts in this area not in the least because of the fact that the dementia epidemic is upon us and that as geriatric psychiatrists we urgently need answers to many of the questions we face in our daily practices.

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