Depression in Alzheimer's Disease and Other Dementias

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Much of our current knowledge about depression in Alzheimer's disease and other dementias is based on the 1991 National Instiute of Health Consensus Development Panel on the Diagnosis and Treatment of Depression in Late Life, and its subsequent 1997 update. However, much research has taken place since these reports. This article summarizes this research, particularly research that has taken place in the past year.

Comorbid depression is common in all types of dementia. It may, however, appear to be different from classic depression. Unlike classic depression, the depression found in dementia may result from anatomic damage to the brain. This is most clearly demonstrated in vascular depression. The implications of this are many. Treatments for depression are designed for classic depression. For those with vascular depression (and other depressions associated with dementia) treatments may not be as efficacious. Newer strategies, including agents not commonly thought of as antidepressants, may be needed.

Introduction

In 1991, the National Institute of Mental Health (NIH) issued the *Consensus Development Panel on the Diagnosis and Treatment of Depression in Late Life* [1]. This document summarized our knowledge, to date, on late-life depression, including depression with dementia. In 1997, an update was published [2], summarizing the significant body of research on geriatric depression that had occurred since the original statement. Much of what we consider the current wisdom on diagnosing and treating depression in our elderly patients with dementia derives from these documents. However, as the documents themselves point out, important research was lacking.

This article examines the significant work that has followed these documents. Findings of the NIH consensus panel are briefly summarized. However, this paper focuses primarily on the research within the past year that has extended, clarified, or shed new light on the consensus recommendations.

Epidemiology

How common is depression in demented individuals?

Clarifying the incidence and prevalence of depression in patients with dementia remains a challenge. Important methodologic dilemmas remain: the problems of case definition, the reliability of scales used in other populations and the proper uses of alternative information sources, for example. Thus, it should not be surprising that epidemiologic data in this population remain wanting. Earlier studies, such as the Epidemiological Catchment Area Study found that major depression seems to be less common in elderly populations than in younger adults. Indirect data, as noted in the NIH consensus panel statement, however, lead one to believe that depression is much more common in individuals with cognitive impairment. For example, the prevalence of major depression in nursing home populations is much higher than in the community. The NIH consensus panel estimated the rate of major depression in nursing homes at 15% to 25%. The update noted that although major depression may be rare subsyndromal depression may be more common. This is particularly true in nursing homes, where rates of depression may be more than 50% if subsyndromal depression is included.

Information on the rates of depression with dementia tends to rely on clinical populations, particularly hospitalized patients. Such data are certainly important in underscoring the often ignored problems inherent in treatment patients with cognitive loss. For example, a recent study of patients in a rehabilitation program (with either strokes or lower extremity fractures) found high rates of both depression and dementia: 28% demented and 25% depressed among fracture patients, 35% demented and 33% depressed among stroke patients [3]. The implications of this on the likelihood of successful rehabilitation are clear.

However, what is needed are community studies of this population. The largest recent epidemiologic study in this country, the National Comorbidity Study, chose not to focus on an elderly population. Several other countries have reported community data. A Spanish study of 1460 subjects older than 69 years showed increasing rates of depression with increasing cognitive impairment [4]. Subjects with no cognitive impairment had only a 5% rate of major depression, whereas subjects with some cognitive impairment but not dementia had a 12% rate. The group with the highest rate of depression (27%) was that with patients who were demented. Thus, the most important

factor in this group predicting depression seemed to be cognitive loss.

Similarly, a Swedish community study of 1101 elderly individuals found dementia to be an important predictor of depression [5]. In their study, only 4% of nondemented patients had major depression, whereas the rate was 12% among individuals with dementia.

Thus, although major depression is though to be less common in the elderly, this appears to not apply to the demented elderly. Earlier indirect data suggesting higher rates of depression among demented individuals are supported by more recent research.

Diagnostic dilemmas

Epidemiologic work in this area remains inhibited by problems with case definition. The design of large community studies would be more feasible if relatively simple diagnostic instruments were available. However, it is not at all clear whether standard instruments used for diagnosing depression among younger patients are useful in elderly populations.

Some recent research is hopeful, however. Radloff [6] and Papassotiropoulos *et al.* [7] investigated the use of the Center for Epidemiologic Studies Depression Scale and the General Health Questionnaire and found them to be valid in elderly populations, including those with dementia. However, both scales yielded a large number of false positives. In the case of the General Health Questionnaire, this problem seemed remedied somewhat by simply increasing the depression cutoff score to some higher level; however, this approach was not as effective for the Center for Epidemiological Studies Depression Scale.

Phenommenology

The 1991 NIH statement [1] noted that depression can be heterogenous, and discussed the often-reported adage that the depressed elderly tend to report somatic symptoms more so than affective ones. At the time, however, little was known about how the presentation of depression may differ in elderly patients with dementia.

The 1997 NIH update [2] included then-developing information on the role of vascular pathology in affected depressive symptoms. It suggested that the depressed elderly would be more likely to present with symptoms typical of vascular dementia, such as psychomotor retardation, lack of insight, and impairment of executive functions.

Newer studies also have looked at how depression may influence the symptoms of dementia. Several investigators have found that depression may play an important role in producing or influencing the behavioral disturbances seen in demented patients.

For example, Kunick *et al.* [8], looking at patients with dementia, found that depression was associated with a number of problematic behaviors, such as constant requests for help, complaining, and negativism. Lyketsos *et al.* [9] looked specifically at the link between depression and aggression in 541 demented patients and found that aggressive behaviors were closely associated with moderate to severe depression. Such studies raise the interesting possibility that identification and treatment of depression may play an important role in mitigating those behavioral problems that challenge care givers most acutely.

Pathology

Some of the most exciting developments have been in the area of understanding the pathology behind depression associated with dementia. Little was known in 1991, but by the time of the update, it was already recognized that structural deficits may be important in late-life depression in a manner not found in younger patients. Studies at that time suggested that such findings as ventriculomegaly and white matter changes may be associated with late-life depression.

The availability of newer and better imaging techniques has caused an impressive leap of knowledge in this area, and some of the findings are described here.

Vascular depression

The work of Robinson [10] and others clearly shows that cerebrovascular accidents can cause depression. The question was whether the more heterogenous vascular changes seen in demented patients could also be responsible for depressive symptoms.

This concept of a "vascular depression" was originally proposed by Alexopoulos *et al.* [11]. Noting the association between vascular disease, vascular risk factors, and comorbid depression, they hypothesized that such a depression could be the result of damage to prefrontal systems. Disruption could be direct, or indirect through modulating pathways, such as noradrenergic or serotonergic systems. This damage could be either a single ill-placed lesion or accumulated injury up to a threshold amount.

The symptoms of vascular depression as described by Alexopoulos *et al.* [11] tend to parallel those of vascular dementia. Thus, though still meeting criteria for major depression, there is less emphasis on depressive ideation, and more on subcortical expressions of depression, such as psychomotor retardation, poor motivation, emotional withdrawal, and anhedonia. Unlike the classic depression seen in adults, there is often no family or previous personal history of depression. The cause of the depression seems to be less genetic and more structural. However, unlike dementia alone, the symptoms are more than just apathy or withdrawal.

Subsequent tests of this hypothesis have been largely confirmatory. For example, Simpson *et al.* [12] compared patients with Alzheimer's disease with those with vascular dementia, and found that the latter group was more likely to have severe depression. Hargrave *et al.* [13] did a similar comparison, and found that depressed affect and emotional withdrawal were more common in the patients with vascular dementia.

The advances in neuroimaging have made direct investigations of this hypothesis possible. This is important, for it seems that simply quantifying vascular disease is not sufficient. For example, Lyness *et al.* [14] did not find a direct relationship between the amount of cerebrovascular disease and depression in their sample of depressed psychiatric inpatients over age 50. The damage apparently must be in specific areas

Kramer-Ginsberg *et al.* [15] looked specifically at areas of white matter disease, and found that the relationship between depression and white matter disease was only significant for deep white matter pathology. Others areas of white matter damage, such as periventricular or subcortical areas did not show a significant relationship.

Functional studies have also suggested specific loci. For example, Ritchie *et al.* [16], measuring cerebral blood flow, showed reductions in left temporal regional cerebral blood flow, compared with nondepressed subjects with dementia. Studies using higher resolution techniques, such as positron emission tomography (PET), will hopefully further elucidate this.

Overall, however, data suggest that structural change—specifically those seen in vascular dementia—play an important role in late life depression. There are many clinical implications of this. For example, drugs used in treating cerebrovascular disease may have an important role in the treatment of vascular depression.

Degenerative changes

Cerebral atrophy has been reported to play a role in the pathogenesis of late-life depression. A number of earlier studies supported this. However, most of these studies were in biased populations, such as hospitalized patients, or patients with complicated medical histories.

Recent studies in community populations have not supported this relationship. For example, Palsson *et al.* [17] looked at the relationship between depression and dementia and cerebral atrophy in a Swedish sample of almost 300 elderly patients. They found no relationship between depression and cerebral atrophy in their sample.

Specific areas and pathologies

Previous data, relying mainly on limited data, have suggested a number of associations between late life depression and certain specific structural pathologies. Most of these studies had importance methodologic limitations, however, and have not always survived detailed scrutiny.

Frontotemporal dementia

Some clinical and theoretic observations have suggested that frontotemporal dementia may be a source of depressive symptoms. Earlier retrospective studies lent some support to this theory. A recent prospective study [18], however, did not find significant associations between frontotemporal dementia and neuropsychiatric symptoms. Some patients did show affective symptoms that could be misconstrued as depression, but such symptoms tended to be shallow, poorly elaborated, and did not progress to a full spectrum of depressive symptoms.

Hippocampus

Some studies have found associations between hippocampal pathology and depression. For example, Sheline *et al.* [19] found that elderly women with histories of recurrent depression tended to have smaller hippocampal volumes when compared with normal subjects. They proposed a "neurotoxicity hypothesis" in which the frequent elevated cortisol caused by recurrent depression might cause neuronal loss. Though an interesting theory, some recent studies have not supported this. One such study, looking at a more heterogenous sample of depressed elderly patients, found no such association when using high-resolution magnetic resonance imaging volumetric techniques [20]. It is possible, however, that the second study is not comparable to the first, as the second tended not to have recurrent depression, thus they may not have had a sufficient duration of neurotoxicity.

Locus ceruleus

Damage to the locus ceruleus has also been suggested as a cause of depression in Alzheimer's disease. Support for this has been mainly theoretical, with some anecdotal support. Using magnetic resonance imaging data, however, Hoogendijk *et al.* [21] found no relationship between depression and neuronal loss in the locus ceruleus in their sample of patients with Alzheimer's disease.

Lewy body disease

Some studies have reported a higher association of depression (and a number of other neuropsychiatric symptoms) and dementia in patients with Lewy body disease than those with Alzheimer's disease [22].

Receptor pathologies

Advances in functional imaging, using such techniques as PET, has allowed us to look at receptor dysfunction. The serotonin receptor subtype 5-HT_{2A} has previously been implicated both in symptoms of depression as well as Alzheimer's disease. It would be reasonable, therefore, to postulate a common mechanism involving the serotonin receptor. However, a recent PET study [23] found no such relationship. The complicated techniques employed, however, as well as the relatively small sample sized used in such studies leave open the possibility that more subtle receptor relationships may eventually be found.

Course

When the NIH consensus statement was published, little really was known about the course of depression in the elderly; even less about those with comorbid dementia. By the time the update was released, there was an appreciation

of the fact that late-life depression may be more chronic than earlier-onset depression. Also of interest in the update was some preliminary data that suggested that late-onset depression predicted the onset of dementia.

Recent data have further clarified both the predictive and modifying roles that depression and dementia have both on each other and on overall mortality and morbidity.

The effect of depression on outcome

There may be instances in which the presence of comorbid depression in patients with cognitive deficits may have a positive influence on outcome. Akin to concepts of pseudodementia, the treatment of a depression may produce some cognitive improvements. The assumption is that depression magnifies cognitive deficits. Most examples of this hypothesis are in primary psychiatric populations. For example, Benedict *et al.* [24] looked at a sample of geriatric psychiatry inpatients, with various degrees of cognitive impairment. Patients whose mood improved as a result of treatment also improved significantly on cognitive tests, particularly tests of spatial processing and learning. However, the changes were modest.

More often, the presence of depression in patients with dementia has negative consequences. Geerlings *et al.* [25] looked at demented patients with higher education, examining the effects of education (cognitive reserve) on the course of dementia. Generally, true to their hypothesis, they did find that patients with higher cognitive reserve had lower mortality rates. However, there was one important exception to this rule: patients with comorbid depression fared more poorly, apparently negating the potential benefits of cognitive reserve. Similar results were reported by Janzing *et al.* [26], who looked at 12-month mortality in a group of 73 patients with dementia, and found that depressive symptoms were a significant predictor of mortality.

The effect of dementia on outcomes

Generally, dementia is thought to have a negative effect on the course of depression. Previous data were confounded somewhat by the fact that age itself may have a negative effect on the course of depression [27•]. However, a recent study by Tuma [28] on elderly patients hospitalized for depression found that concurrent dementia predicted a poorer outcome for depression, independent of age.

The effect of dementia and depression on overall course

Both dementia and depression have negative influences on mortality from medical illness. This was demonstrated recently in a study by Afken *et al.* [29], who reported that both depression and cognitive deficits predict mortality from medical illness. They appeared to be independent predictors, thus producing additive deficits.

Both can also have important implications for overall well-being. A large Veteran's Administration study [30], looking at more than seven thousand patients found that patients with coexistent depression and dementia had higher utilization of both psychiatric and medical inpatient services. However, they also used fewer outpatient services. This appears to underscore the problems with early identification and treatment of patients with comorbid depression and dementia.

Depression as a predictor of dementia

As discussed in the update, there are data to suggest that late-onset depression is a predictor of subsequent dementia. Some have gone as far as to suggest a cause and effect relationship, with depression somehow predisposing an individual to dementia.

More recent data have been mixed. Overall, recent studies tend to support the association between depression and subsequent dementia, but not the cause and effect relationship. Devanand *et al.* [31] found a small but significant relationship between depression and dementia in a community sample of elderly patients (1070 patients), with depression predicting dementia. Similarly, Berger *et al.* [32] found on 3-year evaluation that patients with Alzheimer's disease had more depressive symptoms at baseline. However, not all studies have agreed. For example, Henderson *et al.* [33] did not find such a relationship in examining a community sample of elderly patients in Australia. They found no correlation between depressive symptoms and cognitive decline three to four years following initial evaluation.

To examine this question in more detail, Chen *et al.* [34] conducted a prospective study designed to examine the temporal relationship between depression and dementia. In their study, they found that when patients were examined closely, their depressive symptoms tended to follow the onset of cognitive symptoms. It seems likely that, for patients that develop dementia, the depressive symptoms were actually an early manifestation of the dementia.

One can imagine a variety of reasons why depression may accompany early dementia. It could be a psychologic reaction to the awareness of cognitive loss. Alternatively, it could have a direct neurobiologic cause. Furthermore, the problem may be one of diagnostic specificity, as many of the symptoms of dementia can overlap with depression. In the Chen study [34], patients tended to have depressive symptoms regardless of whether they were aware of cognitive loss, thus arguing against psychologic reactions as the sole explanation.

Influence on caregivers

Depression comorbid with dementia has implications beyond the patient. A number of recent studies have demonstrated how comorbid depression has important ramifications for those caring for patients with dementia. Donaldson *et al.* [35] found that the noncognitive features of Alzheimer's disease, particularly depressive symptoms, are a significant predictor of caretaker burden and perceived stress. They may even cause caretaker psychiatric morbidity; Brodaty [36] found among families attending a

memory disorder clinic that patient depressive symptoms were significantly associated with psychologic morbidity among the caretakers.

The negative effects of depression on the patient-caretaker relationship may be even more serious. Dyer *et al.* [37] found a higher incidence of elder abuse and neglect in elderly patients with dementia or depression. The effects of dementia and depression were independent and additive.

Treatment

The NIH consensus statement noted the paucity of data on treatment for depression in the elderly. Particularly lacking was data on treatment of the "old-old" (80 or more years of age). This is unfortunate, as these octogenarians are one the most rapidly growing segments of the population.

At the time of the consensus statement, tricyclic antidepressants (TCAs) were still the most commonly used antidepressants in the United States. nortriptyline and desipramine were generally recommended in the elderly given their improved tolerability (compared with tertiary amines), and some data existed on the use of these agents in the elderly. Recommendations for ongoing treatment at that point followed emerging data on the need for continuation treatment in depression, and a period of 6 to 12 months following recovery from an initial episode of major depression was recommended.

The efficacy of alternative treatments was acknowledged, though little data existed to support this. Monoamine oxidase inhibitors (MAOIs), earlier feared to be dangerous in the elderly, were found to be relatively safe, and were suggested as a reasonable (though rarely used) treatment option. The selective serotonin reuptake inhibitors (SSRIs) were just emerging and the NIH consensus statement discusses their potential. Again, data were lacking. The efficacy of electroconvulsive therapy was noted, though the consensus statement raised some concerns about the potential greater confusion and memory loss in a vulnerable population. Little could be said regarding psychotherapy in the elderly. Virtually no data existed on the use of any of these treatments in depressed patients with comorbid dementia.

By the time of the NIH update [2], the landscape had greatly changed. SSRIs had supplanted TCAs as the first line treatment for depression. The panel judged SSRIs to be equally effective as TCAs, but noted that in some studies SSRIs were barely more effective than placebo. They also raise concerns about the potential for drug-drug interactions with SSRIs. Regarding even newer antidepressants, they noted that no data existed in the elderly.

The NIH update also expanded recommendations for ongoing treatment. Acknowledging data suggesting that depression is more chronic in the elderly, they suggest that the earlier recommendations of 6 to 12 months of continuation therapy should be a minimum duration, and that older patients may need longer, or even indefinite treatment.

At the time of the NIH update several psychotherapies known to be efficacious for depression, including cognitive behavioral therapy and interpersonal therapy, now had data in the elderly.

Again, most of the data presented were from relatively healthy elderly patients, and only scant data existed on the treatment of depression in patients with dementia.

Since the update, data continue to accumulate on the treatment of depression in the elderly, with some studies including or even focusing on elderly patients with dementia. Some of the data are of great concern. Simpson *et al.* [38] found that patients with subcortical disease (diagnosed by magnetic resonance imaging and neuropsychological testing) showed poorer responses to treatment for depression than other patients.

There is a growing number of studies that report the efficacy of antidepressants for elderly patients, including those with dementia. TCAs continue to present data on their usefulness in the elderly However, most of the studies on TCAs are in elderly patients without dementia. There remains some hope for the MAOIs, particularly the reversible MAOIs, which may also have some efficacy for cognitive enhancement in patients with dementia [39].

The SSRIs have replaced earlier agents as the mainstay of treatment. In clinical practice they have become the first-line agents for depression in the demented, both for their presumed equal efficacy with other agents, and their apparent superior safety and tolerability. Though the support for these assumptions is based more on experience than accumulated data, what data exists do back these assumptions. For example, Katona *et al.* [40•] compared imipramine with paroxetine for treating depression in patients with dementia. In this 8-week double-blind study, both agents were equally effective. Paroxetine, however, had a trend toward greater tolerability.

Novel approaches to treating depression in patients with dementia may contain new hope. Agents used primarily for the treatment of dementia may also have psychotropic effects. The use of reversible MAOIs, mentioned above, may represent this crossover approach of using agents that have been shown helpful for "cognitive enhancement" as well as depression. Donepezil, the most common anti-Alzheimer's disease agent, may also have a role in treating depression. In a retrospective study of 86 patients with Alzheimer's disease, it was found that a number of patients (41%) have improvement of behavioral symptoms as well as cognitive ones while on donepezil [41•]. Symptoms that seemed most effected by donepezil were depression and agitation, and this effect was dose-dependent. Interestingly, these improvements were independent of any improvements in cognition. Unfortunately, if donepezil does have psychotropic effects, these effects may be unpredictable; 28% of patients had behavioral worsening when treated with the drug. All the same, the results hint at promising future approaches, and as more agents for the treatment of Alzheimer's disease are

made available, it will be interesting to see whether these findings will be replicated.

Conclusions

Sometimes research gives new understanding to that which we do not understand. Just as often, it questions what we thought was already understood. Much of the research presented seems to confound the consensus recommendations. However, some patterns are emerging.

It appears that the commonly held belief that depression is less common in the elderly is not true for those elderly who suffer from dementia. In fact, depression is likely to be found in all types of dementia. It may, however, appear to be different from classic depression. This difference may owe a great deal to different etiologies. Whereas classic depression represents a presumed physiologic rather than structural pathology, the depression found in dementia may result from anatomical damage to the brain. This is most clearly demonstrated in vascular depression. The implications of this are many. Treatments for depression are designed for classic depression. For those with vascular depression (and other depressions associated with dementia) treatments may not be as efficacious. Newer strategies, including agents not commonly thought of as antidepressants, may be needed.

The need to treat depression in these groups cannot be emphasized. There is no cure for the most common causes of dementia. The available treatments for Alzheimer's disease, vascular dementia, and other common dementias are, at best, approaches to improving a patient's quality of life for as long as possible. Clearly, comorbid depression causes significant morbidity, and perhaps even mortality for these patients. The recognition and treatment of depression in dementia remains our most promising approach for improving the quality of life for these patients.

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