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Re: Docket number 00N-0088
March 9,2000 Meeting of the Psychopharmacological Drugs Advisory Committee
Meeting on Psychiatric and Behavioral Disturbances Associated with Dementia.

To whom it may concern:

The following written statement is offered for consideration at the PDAC meeting above. I am not requesting time to speak.

Sincerely,

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Depression Associated with Alzheimer's Disease and Psychosis Associated with Alzheimer's Disease are Definable and Valid Targets for a Medication Treatment Claim

Introduction
In its issues paper (http://www.fda.gov/ohrms/dockets/dockets/00n0088/bkg0001.pdf) the FDA offers three criteria to establish a clinical entity that might be a target for a medication claim: (1) it must be accepted by the clinical and academic community, (2) it must be clinically definable, and (3) it must identify a reasonably distinct and homogenous patient group. Moreover, FDA approval of a drug for any condition, requires that appropriate instruments be used for assessment and measurement, and that appropriately designed clinical trials demonstrate safety and efficacy in the specified population.

One reason that the FDA has not been able to approve medications for behavioral and psychological symptoms associated with dementia is because, from its and many researchers' perspective, it has often been difficult to

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clearly identify the behavioral symptomatology that is the target of treatment. This can be illustrated with the nursing home antipsychotic trials of risperidone and olanzapine, and with several antidepressant trials.

Clinicians, however, use antipsychotic and antidepressant medication to treat symptoms that occur in patients with dementia even without regulatory labeling, and in most cases without adequate and well controlled published studies supporting its use.

This paper is offered to support the position that psychosis of Alzheimer's disease and depression of Alzheimer's disease are clearly identifiable entities and clinically relevant syndromes. Behavioral and Psychological Symptoms of Dementia (BPSD), by contrast, while a useful heuristic concept for teaching students about dementia, is not a useful clinical concept, nor a target for a medication labeling claim.

Agitation Associated with Dementia is Nonspecific
The "agitation" associated with dementia is wholly non specific to it, with the exception that its onset may be after the onset of dementia. Moreover, many behaviors characterized as "agitation" by some experts have been also characterized by others as irritability, lability, disinhibition, aberrant motor behavior, activity disturbances, functional impairment, and aggression. Many examples of "agitated" or "aggressive" behavior could often be better understood as concomitant features of other neuropsychiatric syndromes such as psychosis or depression.

An "agitation syndrome" associated with dementia would have to be operationalized, in part, by defining the agitation or aggression; demonstrating that its onset was subsequent to the onset of dementia; showing that it has a certain critical frequency, duration, and that it is severe enough to cause the patient further distress or disruption; and assessing that it is not better explained by another neuropsychiatric condition such as psychosis, depression, sleep disorder, delirium, or by a medical condition or medication that is itself associated with agitation.

Evidence from the risperidone and olanzapine trials in nursing home residents indicates that only a small proportion of agitated patients would potentially fulfill such criteria. Most patients' agitation in these trials could be better viewed as being associated with psychosis, depression, and medical conditions.

Psychosis associated with Alzheimer's diseae
Psychosis associated with Alzheimer's disease is sufficiently common and clearly identifiable.
For example, in the risperidone trials, patients were selected, not by the presence of psychosis, but primarily by a score on the BEHAVE-AD of greater than or equal to 8 and a global rating indicating that the unspecified behaviors were at least "mildly troubling to the caregiver or dangerous to the patient." It is clinically and methodologically problematical to qualify patients to receive antipsychotic medication, on the basis of a scale score (one that was rather low), not requiring that patients have delusions or hallucinations, and partly defining the consequences of the behaviors by the mild extent to which they "trouble" a caregiver. Nevertheless, inspection of the patients actually entered into

the trial, clearly reveals that a clinically significant psychosis (mostly delusional disorder) of moderate severity could be identified retrospectively in about two-thirds of the patients entered.. Moreover, in about two-thirds, the psychosis was associated with significant aggression or agitation. It is noteworthy that psychosis could be identified even in patients who were on average severely cognitively impaired with MMSE scores less than 7.

In the olanzapine trial, the inclusion criteria required mainly that nursing home residents score greater than or equal to "3" on any of the three NPI/NH agitation, delusions, or hallucinations items. (A "3" on this scale means one of the following: (1) very disruptive hallucinations, delusions, or agitation occurring less than once per week, (2) hallucinations or delusions that are harmless, produce little distress and occur several times per week, or (3) mild agitation that can be managed with redirection or reassurance that occurs several times per week). Again, it is not apparent that these are sufficiently severe enough criteria for a patient to qualify as having clinically significant psychosis, or as a clinically acceptable indication for antipsychotic treatment. Nevertheless, on this basis, 56% of patients fulfilled this trial's criteria for delusions, and an overlapping 23% for hallucinations, while well over 70% of patients with hallucinations or delusions also had significant agitation.

Recently there has been a proposal to define a psychosis of Alzheimer's disease (Jeste and Finkel, 2000) based in part on observing differences with it and other psychotic disorders. For example, the incidences of psychosis in Alzheimer's disease is fairly high, complex delusions are rare, misidentification syndromes are frequent, visual hallucinations are more common than the auditory hallucinations occurring in schizophrenia, suicidal ideation is uncommon. Moreover, patients with Alzheimer's disease who have a subsequent psychosis uncommonly have a past history of psychosis, show a clinical course in which remission of the psychosis is frequent, and don't usually require indefinite antipsychotic medication in the way schizophrenics require this. Lastly, the effective doses of antipsychotic medications seem to be less.

These authors proposed diagnostic criteria for a psychosis of Alzheimer's disease in order to differentiate it from psychosis occurring in other contexts. In their criteria, modeled in the style of DSM-IV, patients must have delusions or hallucinations that are characteristic of dementia, a diagnosis of Alzheimer's disease, psychotic symptoms occurring after symptoms of dementia, a duration at least intermittently of one month, with symptoms severe enough to cause disruption,and the psychosis can not be caused by other neuropsychiatric disorders, medical causes, drugs, or deliria.

Depression Associated with Alzheimer's Disease

The relationship between late-life depression and dementia is complex. At least three conditions can be contemplated: (1) Depression occurring prior to AD and as a risk factor for it. (2) Depression occurring prior to AD and continuing throughout the onset, diagnosis, and early course of the dementia. (3) Depression occurring after the onset of cognitive signs and symptoms of AD or its diagnosis.

In the latter condition, patients may have had a prior history of major or minor depression and the depression in dementia can be conceptualized as a recurrent episode of primary mood disorder; or the depression may represent the first episode of depression occurring in late-life and subsequent to the dementia. Regardless, depression occurring after the onset of AD can be readily identified, has clear and different characteristics and clinicalcourse from depression occurring in elderly people without dementia, and thus is an identifiable target for a medication claim.

[In passing, it should be mentioned that depression occurring in late-life is different from depression occurring earlier in life in many important clinical ways (Schneider et al 1994). With respect to dementia, depressed mood among the elderly is associated with a three fold increase in risk for developing it (Devanand et al, 1996), and patients presenting with depression and cognitive impairment whose cognitive impairment reverses with treatment of depression have a four-fold increased risk for developing progressive and irreversible dementia (Alexopoulos et al, 1993)].

Prevalence
When the published evidence is taken as a whole, there is a higher prevalence of clinically significant depression in patients with Alzheimer's dementia than would otherwise be expected, overall about a 25% prevalance. The prevalance estimates are highly variable depending on population and threshold for identifying depression.

Evidence for a genetic contribution to depression associated with Alzheimer's dementia, is that even in the absence of a history of depression earlier in life and before the onset of dementia, dementia patients who subsequently developed depression are more likely to have a positive family history for depression than Alzheimer patients without depression, suggesting an exacerbating role for the dementia (Pearlson et al 1991).

Clinical Characteristics and Course
Behavioral manifestations of depression (e.g., psychomotor slowing, emotional lability, crying spells, insomnia, negativism, or nihilism) occur in dementia patients, and are sometimes not ascribed to depression . Depressed patients with Alzheimer's disease show anhedonia and fewer vegetative signs than depressed older patients. Depressive symptoms in dementia patients often fluctuate. Depression can manifest itself in patients at any stage of dementia..

The course of depression associated with dementia appears different from that of depression in late-life (without dementia). Remission or improvement of symptoms occur more frequently and over a shorter period of time (see below). But there is also evidence that depression in dementia is associated with an increase mortality rate compared to non-depressed dementia patients.

The use of scales to identify depression associated with dementia has been unsatisfactory, and leads to variances in estimates of depressive syndromes. At best, scales only compile the presence of individual symptoms and rate on the basis of frequency or severity. At worst, the scales are

arbitrary and of unclear metric or clinical meaning.

Research-based depression rating scales for dementia patients have been useful to discriminate symptoms between depressed and non_depressed dementia patients, but have been unhelpful for identifying depression syndromes.

The above characteristics, alone, justify the recognition of depression of Alzheimer's disease, even though more work can be done on its precise criteria.

Treatment Response

Although patients in antidepressant treatment trials often have not been effectively characterized with respect to depression criteria or to the relationship to the onset of their dementia, treatment response provides information on the distinctness of depression associated with Alzheimer's disease.

The very few treatment trials have limitations. Nevertheless, treatment response appears to be different in depressed patients with dementia. Compared to the literature on patients with late-life major depression (without dementia) there appears to be a greater placebo response (Reifler et al Roth et al 1996), over a shorter period of time (6 weeks), with improvements in cognitive function, irritability and anxiety, but little on no observed drug-placebo differences with the antidepressants and outcomes used.

These findings stand in marked contrast to the outcomes in late-middle-aged and elderly people with major depression and no dementia where antidepressants are clearly effective and become more so over longer initial treatment periods (Schneider et al 1994; Tollefson et al 1995, Schneider et al 2000).

In one randomized clinical trial that included patients with primary dementia and major depression, both imipramine and placebo-treated patients improved considerably compared to baseline, but there was no significant difference in response between the medication treatments (Reifler et al 1990). Similarly in a randomized trial comparing clomipramine with placebo both groups improved considerably, without a drug-placebo difference over the first 6 weeks (Petracca et al. 1996). In the crossover phase, the placebo group, now switched to medication, did not improve significantly more than they had previously, and the medication group maintained their improvement and did not worsen when they were switched to placebo.

In another trial, over 4 weeks there was modest improvement with citalopram compared to placebo in confusion, irritability, restlessness, fear_panic, and mood in a mixed group of 98 dementia patients with both vascular and primary dementia with only 62 having depressive symptoms (Nyth and Gottfries, 1990). A problem with this trial of course is that patients cannot be easily characterized having been selected not on the basis of depression but because they had "emotional disturbances" and dementia.

One trial offers a direct comparison between primary dementia (DSM-III) plus depression and major depression (DSM-III) (Roth et al 1996). Moclobemide and placebo both improved Hamilton Depression Rating

Scale scores. But the placebo improvement was greater in patients with both depression and primary dementia than it was in patients with major depression without cognitive impairment. In addition, cognitive improvement was observed as well.

In brief, the efficacy and effectiveness of pharmacological therapy for depression associated with dementia is not known. It is not clear that patients with dementia and co_existing depression can be effectively treated for their depression with antidepressants. This alone argues for depression of dementia to be recognized.

Conclusion

As with psychosis of AD, there is sufficient evidence to recognize a depression associated with Alzheimer's disease (and possibly other dementia) as a therapeutic target for a medication claim. The depression is characterized by mild to moderate persistent or persistently intermittent depressive symptoms, not necessarily as severe as in major depression, but severe enough to further impair function and/or quality of life, with its onset after the onset of other signs and symptoms of dementia. Usually this is a first onset of depression and there has been no previous personal or family history. As with other depression there may be an amount of associated and heterogeneous signs and symptoms such as anxiety, irritability, anger, agitation, aggression in later stages, decreased initiative and interests.

References

Available on request