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In Re: FDA docket Number 00N-0088

This is the response of the American Psychiatric Association Council on Aging to the DNDP Paper for the March 9, 2000 Meeting of the Psychopharmacological Drugs Advisory Committee Meeting on the Various Psychiatric and Behavioral Disturbances Associated with Dementia.

The American Psychiatric Association (APA) is the medical specialty society representing more than 42,000 psychiatric physicians nationwide. The APA Council on Aging (COA) is the APA policy advisory council on issues related to geriatric psychiatry and geriatric patient care. The COA welcomes the opportunity to respond to the FDA initiative challenging the clinical/academic community to define unique psychiatric /behavioral symptoms that exist in dementia patients.

Background: DSM Classification of Alzheimer's Disease

Subtypes of Dementia of the Alzheimer's Type (DAT) and vascular dementia were originally introduced in the DSM-III. These subtypes included with "delirium," with "depressed mood," and with "delusions." As Caine and colleagues¹ point out, the rationale for these subtypes were based on the assumption that these conditions were fundamental manifestations of dementia. A number of questions arose, however. For example did "depressed mood" include a full-blown major depressive disorder? Clarification and refinement of these conditions continued with the DSM-IV. It included a new subtype, e.g., with "behavioral disturbances," although not given a numeric code. DSM-IV also clarified questions about depression; e.g., major depression should be included in the grouping "with depressed mood." Additionally, DSM-IV required that delusions be the principle features in the category "with delusions" subtype.¹

The major problem with the typology used to classify the behavioral conditions in DAT is that the hierarchical scheme implies that these symptoms are subordinate features of the cognitive symptoms of DAT.¹ Data exist that many of these symptoms are caused by the fundamental brain pathophysiology, just as the cognitive symptoms are. In anticipation of the International Classification of Diseases-10 (ICD-10), the DSM-IV text

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revision (DSM-IV-R) will prefer the clinician to use the Axis I diagnostic code for DAT of 294.1 for "Dementia in Diseases Classified Elsewhere," instead of the current 290.xx designation. Alzheimer's Disease should then be recorded on Axis III. Thus the three subtypes captured by the fifth digit of the 290.xx classification will be lost.¹ When DAT patients have symptoms that require psychiatric interventions, clinicians will be asked to record these conditions on Axis I as one of the "mental disorders due to a general medical condition," in addition to the Axis III documentation of Alzheimer's Disease. A fifth digit to indicate whether the dementia is "with behavioral disturbances" (294.11) or "without behavioral disturbances" (290.10) is anticipated for October 2000,¹ but for the time being the recommended classification scheme for a DAT patient with dementia and delusions would be:

Axis I:	294.1, (due to Alzheimer's Disease)
	293.81, (Psychotic disorder due to Alzheimer's Disease)
Axis III:	331.0, Alzheimer's Disease

The changes in the classification system reflect strong scientific evidence supporting the occurrence of clinically important symptoms in patients with DAT. The COA believes that these symptoms such as psychosis, circadian rhythm disturbances, and depression are valid targets for pharmacological interventions. For the above conditions, the existence of these specific entities i.e.: incidence, clinical characteristics and relationship to disease progression, response to treatment and the presence of distinct neuropathological findings, can be found in the scientific literature, and will be briefly reviewed below.

Psychosis in Dementia of the Alzheimer's Type:

Incidence/Prevalence: As outlined in a recent editorial by Jeste and Finkel,² the incidence of psychosis in DAT is reported to be substantially higher than in schizophrenia in the range of 30-50 percent. Patients with DAT rarely have a previous personal or family psychiatric history positive for schizophrenia, or other types of psychosis.

Clinical Characteristics and Relationship to Disease Progression: Symptom presentations are also substantially different than in schizophrenia, with symptoms such as misidentification of caregivers, and visual hallucinations being common in DAT psychosis and rare in patients with schizophrenia. In contrast, patients with schizophrenia usually present Schneiderian first rank symptoms, bizarre complex delusions, and active suicidal ideation. These symptoms, however, are rarely observed in DAT psychosis. We endorse the criteria proposed by Jeste and Finkel for psychosis in DAT.

Disease progression is also reported to be substantially different in DAT. Psychosis in schizophrenia rarely shows remission and the need for antipsychotic treatment is prolonged, psychosis in DAT has a shorter duration and therefore only requires shorter periods of treatment.

Treatment Response: Response to treatment is also different with schizophrenic patients usually responding to higher doses and DAT psychosis responding to lower doses than those used in schizophrenia. Further low doses appear to achieve better results than higher doses of the same compound in the DAT population not only in terms of safety, but also and equally important showing better efficacy at lower rather than higher doses.²

Neuropathological Findings: A number of investigators have reported neuropathological findings that clearly differentiate this population from both schizophrenic and DAT patients without psychosis. In particular, DAT patients with psychosis have increased neurodegenerative changes in the cortex,

increased subcortical norepinephrine, reduced cortical and subcortical serotonin/5-HIAA, and abnormal levels of paired helical filaments (PHF)-tau protein in entorhinal and temporal cortex.^{3,4}

We therefore believe as stated in DSM IV-R that psychosis due to DAT meets the scientific criteria required to be considered a target for pharmacological intervention and labeling. Finally we endorse the specific diagnostic criteria proposed by Jeste and Finkel.

Circadian Rhythm (Sleep-Wake) Disturbance in Dementia of the Alzheimer's Type:

Incidence/Prevalence: Circadian rhythm disturbances among DAT patients, which we will term sleep-wake rhythm disturbances, make a strong demand on caregivers and are among the most important reasons for institutionalization. The prevalence of sleep abnormalities may range from 20-40% in dementia.^{5,6}

Clinical Characteristics and Relationship to Disease Progression: Circadian rhythms are important regulators of sleep in humans. Sleep disturbances in patients with DAT have been strongly associated with behavioral disturbances such as wandering, daytime agitation, and "sundowning."⁷ Sleep wake cycles among patients with DAT have been shown to degenerate and be replaced by arrhythmic polyphasic patterns of sleep.⁸ Additionally, nocturnal sleep has been shown to be fragmented and associated with a 10-fold increase in daytime sleep.⁹

Treatment Response: Standard pharmacological treatment with benzodiazepine and antipsychotic medications have limited or even adverse effects in demented elderly people, including excessive sedation, confusion, impaired cognition, and personality changes.¹⁰ Non-pharmacological treatments such as bright light therapy have been studied.^{11,12,13,14} The efficacy of these treatments remains unclear. Without a specific labeling indication, the pharmaceutical industry has little incentive to pursue specific studies in DAT patients.

Neuropathological Findings: It has been suggested that degeneration of the hypothalamic suprachiasmatic nucleus (SCN), the 'biological clock' of the brain that imposes 24-hour rhythms in physiology and behavior, plays a key role in disturbed sleep-wake pattern.¹⁵ Degeneration of suprachiasmatic vasopressin cells has indeed been demonstrated in a post-mortem study on brain tissue of patients with DAT.¹⁶

Depression and Dementia:

The relationship between late-life depression and dementia has been a major focus of clinical and epidemiological research over the last two decades. The relationships are complicated, and for purposes of this review we will just examine the evidence for depression complicating DAT.

Incidence/Prevalence: Depression has long been recognized as a major co-morbidity of dementia syndromes.¹⁷ Most studies report the prevalence of clinically significant depression in DAT between 17-29%.¹⁸ For vascular dementia the prevalence rates are roughly comparable, e.g., 19-27%.¹⁹ Dementia patients with depression may have a genetic vulnerability to depression. In one study depressed DAT patients were more likely to have a positive family history for depression than DAT patients without depression, even if the patient did not have a personal history of depression prior to the dementing illness.²⁰

The relationship between depression and the development of dementia has been extensively studied in clinical populations. Patients with "reversible dementia" may not achieve complete cognitive recovery following remission of depression. During follow-up, an average of 11-23% of patients with an initially reversible dementia become irreversibly demented every year.^{21, 22, 23, 24, 25} Irreversible dementia begins to be diagnosed approximately two years after the initial recovery from depression.²⁵ Conclusions from clinical studies must be tempered because of potential problems with selection and case ascertainment biases, e.g., patients with cognitive impairment associated with depression may seek help because of the cognitive difficulties more than patients who are depressed but are not suffering from cognitive difficulties.

Clinical Characteristics and Relationship to Disease Progression: Depressive symptoms in dementia patients often fluctuate and are difficult to identify in those patients with advance dementia because of language impairments. Behavioral manifestations of depression (psychomotor slowing, emotional lability, crying spells, insomnia, weight loss, alexythymia, and nihilism) can occur in dementia patients without depression.²⁶ Depressed patients with DAT exhibited more self-pity, rejection sensitivity, anhedonia and fewer neurovegetative signs than depressed older patients without dementia.²⁷ Research based depression rating scales for dementia patients have been developed to help discriminate between depressed and non-depressed dementia patients,^{28, 29} and while useful in research settings, widespread clinical application have yet to be adopted.

The natural history of major depressive disorder in DAT patients is somewhat unclear. Most evidence suggests that major depression tends to first emerge in patients in the mild to moderate stage of cognitive impairment. Some studies have suggested that the emergence of major depression in DAT is associated with an increased mortality rate, but no acceleration of cognitive decline.³⁰

Treatment Response: Dementia patients with co-existing depression can be effectively treated with antidepressants.^{31, 32, 33} Experts recommend avoiding tricyclic antidepressants secondary to anticholinergic side effects that may significantly impair cognition.¹⁷ Major depression in DAT patients typically recur.

Neuropathological Findings: Major depression in DAT patients has been associated with increased degeneration of brainstem aminergic nuclei, particularly the locus coeruleus, and relative preservation of the cholinergic nucleus basalis of Meynert. Associated increase in the numbers of senile plaques or neurofibrillary tangles in the neocortex or allocortex has not been found.³⁰ Modest decreases in the levels of serotonin and 5-HIAA are also found in DAT patients. A paradoxical increase in dopamine levels was observed in the entorhinal cortex of depressed, demented patients, but this pattern has not been consistently found in different brain regions.

Conclusions:

The COA also understands the need of the FDA to have a widely accepted and clear defined set of diagnostic criteria in order to develop indications for psychotropic medications. We believe that urgent action should be taken on this issue. Psychoactive drugs are among the most commonly prescribed medication for this population. The "off-label" use of conventional antipsychotics, for example, carries a high risk for side effects including 25% risk for the development of tardive dyskinesia. We believe that appropriate labeling will provide physicians with needed guidelines to improve prescribing practices. In addition, such labeling will provide the physician with specific, desperately needed safety information that will permit a more accurate risk-benefit assessment when a prescription is written. Finally, the existence of a path for seeking specific labeling will provide the

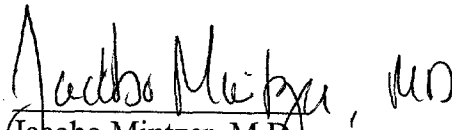
pharmaceutical industry with a strong incentive to develop more effective and safe compounds to treat these difficult psychiatric syndromes.

We congratulate the FDA for this important step. Given the urgency of this matter this council will welcome the opportunity to assist your agency in any way that will speed the resolution of this important issue.

Sincerely,



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