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Dockets Management Branch
Food and Drug Administration
Room 1093
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Subject: Docket Number 00N-0088
Response to Call for Written Statements for March 9, 2000 Meeting of
Psychopharmacological Drugs Advisory Committee

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To Whom It May Concern:

In accordance with the procedures described in the February 9, 2000 Federal Register Notice, Janssen Research Foundation is responding to the call for written statements reacting to FDA's issues paper, entitled *Division of Neuropharmacological Drug Products (DNDP) Issues Paper for March 9, 2000 Meeting of Psychopharmacological Drugs Advisory Committee Meeting on the Various Psychiatric and Behavioral Disturbances Associated with Dementia*. This paper was posted on FDA's website (www.fda.gov/ohrms/dockets/dockets/00N-0088/00N-0088.htm) on January 24, 2000.

The enclosed written statement summarizes data derived from two large Janssen databases containing information on the characteristics of patients with dementia. This information is used to support the validity of the FDA's proposed criteria for a clinical entity of a psychosis syndrome in dementia.

If you have any questions regarding this document, I can be reached by e-mail at eturek@janus.inj.com or by telephone at (609) 730-3328. You may also contact Ms. Victoria Wagner-Weber at (609) 730-3068 or by e-mail at vweber@janus.inj.com.

Sincerely,


Elizabeth M. Turek
Director, Regulatory Affairs

Enclosure

Desk copy: S. Titus, Ph.D., Executive Secretary, PDAC
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00N-0088

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Janssen Research Foundation Issues Paper on Psychosis of Alzheimer Disease for March 9, 2000 Meeting with the FDA Psychopharmacology Advisory Committee

INTRODUCTION

In a recent Issues Paper,¹ the FDA has proposed that it might be possible to “define a unique psychotic syndrome in the population of patients with Alzheimer’s disease or, perhaps, dementia more generally.”

The FDA Issues Paper recognizes *diseases, syndromes, and nonspecific signs or symptoms* as “clinical entities” appropriate for treatment development. The entity must meet three validity criteria: (1) be “accepted in the relevant clinical/academic community,” (2) be “operationally definable,” and (3) identify “a reasonably homogeneous patient group.” The purpose of this issues paper is to share Janssen’s knowledge about the characteristics of patients with dementia derived from two large databases.

Characteristics of Psychosis of Dementia

In an important recent editorial, Jeste and Finkel² described diagnostic criteria for a psychosis of Alzheimer’s disease (AD) and differentiated the syndrome from the phenomenology and biology of schizophrenia. The incidence of psychosis among elderly patients with AD is higher than that of schizophrenia; psychosis in AD also presents with different patterns of symptoms and remission rates, and the treatment strategies are dissimilar. Diagnostic criteria for psychosis of AD include visual or auditory hallucinations or delusions, onset of psychosis after the onset of symptoms of dementia, presence of psychotic symptoms for 1 month or longer, and symptom severity sufficient to disrupt functioning, and that the disturbance is not better accounted for by another condition or effects of a drug of abuse or medication. Moreover, psychosis of AD often occurs with other phenomena, including aggression, agitation, irritability, apathy, and depression, further diminishing cognition and overall patient function and placing patients at imminent risk for hospitalization or the need for skilled nursing care.

Data on Psychosis of Dementia

The Janssen Research Foundation has a well-defined set of data from 1,603 subjects enrolled in two randomized controlled trials (RCT). The 5-month cumulative database of patients with mild to moderate dementia was derived from a mostly community-dwelling population. The 3-month database of patients with severe dementia was derived from a mostly nursing home population.

In the spirit of the Jeste and Finkel criteria, we identified psychosis of AD by reviewing our data through the lens of the FDA’s three validity criteria. We evaluated data from the Neuropsychiatric Inventory (NPI) and the Behavioral Pathology in Alzheimer’s Rating Scale (BEHAVE-AD) in the community-dwelling and nursing home populations, respectively. Advice was provided by several experts in geriatric mental health and dementia (Alistair Burns, MD, The University of Manchester, England; Jeffrey L. Cummings, MD, UCLA School of Medicine, Los Angeles, California; Sanford I. Finkel, MD, Northwestern University, Chicago, Illinois; Ira R. Katz, MD, University of Pennsylvania, Philadelphia; and Lon S. Schneider, MD, University

of Southern California School of Medicine, Los Angeles). In our data review, the underlying construct for clinically meaningful symptoms of psychosis was this group's endorsement of items from the scales (characteristic delusions and hallucinations of AD) that were associated with *significant* disruptions to the system of care (e.g., violence or threats of violence).

Using this approach, we reviewed patient assessments from the 447 subjects (285 community-dwelling outpatients and 162 residents of nursing homes) randomized to the placebo arm of each RCT. This is a database from which information on the prevalence, incidence, and persistence of psychosis of dementia and its severity can be measured. We reviewed our data to identify and describe persons with a psychosis of dementia and thus to contribute to the understanding of the syndrome.

METHODS

Mild to Moderate AD in Community-Dwelling Patients. NPI data on the placebo-treated patients with mild to moderate AD were reviewed with respect to psychosis at baseline and over time. Clinically meaningful psychosis was defined as distressing and disruptive hallucinations and delusions that had been present for the 4 weeks before baseline assessment (NPI score of 4 or greater).

Severe Dementia in Nursing Home Patients. Individual items of the BEHAVE-AD scale are evaluated in order to identify a group of patients with clinically meaningful psychosis over a 2-week period. Clinically meaningful psychosis in the nursing home study was determined from the BEHAVE-AD scores on the items that measure the severity of paranoid and delusional ideations (7 items) or hallucinations (5 items). Each item is scored from 0–3; 0 = not present; 1–3 = increasing severity of symptom. Clinically meaningful psychosis was defined as a score of 2 or 3 (clear verbal or physical symptoms) on any one of 12 items at both screening and baseline. A score of 3 indicates presence of verbal or physical violence on most items.

RESULTS

Of the 285 mild to moderately impaired community-dwelling patients who received placebo, all had AD; 62% were women; mean age was 77.1 years; and the mean Mini-Mental State Examination (MMSE) score was 18 (range, 10 to 22). Of the 162 severely impaired patients receiving placebo in the nursing home study, 84% had AD, 16% other dementia; 67% were women; mean age was 83 years; and the mean MMSE score was 7 (range, 0 to 23). According to the patients' Functional Assessment Staging (FAST) rating in the nursing home study, 96% had cognitive and functional deficits that were sufficiently severe to interfere with basic daily

Mild to Moderate AD in Community-Dwelling Patients

The subjects were selected, in part, on the basis of having mild to moderately severe dementia (MMSE scores 10–22). Two hundred eighty-six patients were randomized to placebo and the others to one of the three doses of galantamine. They were in reasonably good health at study entry. Delusions and hallucinations were not explicit exclusion criteria; however, patients with moderate to severe or uncontrolled behavioral disturbances were excluded from the study since a requirement was that patients had to be able to cooperate with the cognitive testing procedures. Delusions and hallucinations were assessed by means of the NPI in 285 placebo patients at baseline and in 272, 249, and 238 at months 1, 3, and 5, respectively.

Prevalence of Psychosis in Placebo Patients at Baseline. Of the 272 patients with at least one post-treatment assessment, 12% (33/272) showed clinically meaningful psychosis during the 4 weeks before the baseline assessment.

Persistence of Psychosis in Placebo Patients. Of the 33 patients with clinically significant psychosis at baseline, 64% (21/33) had a persistent psychosis for at least 1 month, 39% (13/33) for 3 months, and 33% (11/33) for 5 months. Six of the 33 patients no longer fulfilled criteria for psychosis after baseline.

Incidence of Psychosis in Placebo Patients. Among the 239 patients without clinically meaningful psychosis at baseline, 12% (29/239) developed psychosis during the 5-month period. Psychosis at months 1, 3, and 5 was noted in 4% (9/239), 6% (14/220), and 9% (19/209) of the patients, respectively. Of the 9 patients with a psychosis at month 1, the psychosis persisted to month 3 in 5 patients and to month 5 in 2 patients. New-onset psychosis was noted in 9 patients at month 3; in 5 patients this persisted to month 5.

Severe Dementia in Nursing Home Patients

The subjects were nursing home patients with dementia and behavioral disturbances (BEHAVE-AD scores ≥ 8); 163 patients were randomized to placebo (of whom 162 had at least one BEHAVE-AD assessment) and the others to one of three doses of risperidone.

Prevalence of Psychosis in Placebo Patients at Baseline. Of the 162 placebo-treated patients, 63% (102/162) had a clinically meaningful psychosis at baseline (BEHAVE-AD score 2 or 3 on any one delusion or hallucination). In approximately two thirds of these patients (66 patients, 41% overall), psychosis was accompanied by violence or physical aggression.

Persistence of Psychosis in Placebo Patients. Of the 102 patients with clinically meaningful psychosis at baseline, the psychosis persisted for at least 2 weeks in 75% (76/102), for at least 4 weeks in 51% (52/102), and for at least 6 weeks in 37% (35/102). A persistent or continuous psychosis was present in 29% (30/102) of the patients for 12 weeks.

Incidence of Psychosis in Placebo Patients. Among the 37% of patients (60/163) who did not fulfill criteria for psychosis in dementia at baseline, 17% (10/60) developed a psychosis lasting at least 2 weeks during the subsequent 12 weeks, with 7% (4/60) developing a persisting psychosis for 6 weeks or more.

CONCLUSIONS

Psychosis of AD has been described since the recognition of AD nearly a century ago. In an effort to define a unique psychotic syndrome in the population of patients with AD, data from two trials are presented that meet the validity criteria of the FDA: acceptance in the clinical/academic community; identification of a clinically definable entity; and identification of a homogeneous patient group.

The psychosis in AD has long been recognized and characterized by delusions that are different from those of schizophrenia or mood-related psychosis, and by a higher incidence of hallucinations. The clinical course of the psychosis is different as well, and the psychosis is associated with a high frequency of other behavioral symptoms, including depression, agitation, aggression, and apathy. This long-standing recognition by clinicians and academicians constitutes acceptance in this community.

The data support the concept that psychosis of dementia is a clinically definable entity, across the spectrum of AD from mild to severely impaired patients. Psychosis was identified by eliciting the presence of the types of delusions and hallucinations characteristic of AD, ensuring that they were sufficiently severe to compromise function and cause distress, and showing that the psychosis persisted for a substantial duration. Notably, the characteristic psychosis could be identified independent of the severity of patients' cognitive or functional deficits.

Finally, this database also supports the similarity or homogeneity of psychosis between the mildly and severely impaired groups of patients. Both the NPI and the BEHAVE-AD assess for the presence of delusions of AD and the characteristics of the delusional items overlap significantly. For example, NPI paranoid delusions, including beliefs that others "are stealing . . . , spouse is having an affair . . . , others are not who they claim," etc., are matched by BEHAVE-AD delusional items that "people [are] hiding or stealing objects . . . , violence for supposed infidelity . . . , and violence for being an impostor." In addition, both scales capture the extent of distress and disruption within patients, albeit by different means.

The large number of patient assessments in this database builds upon the concept of psychosis of AD in a useful manner. It helps demonstrate that it is possible to define a unique psychotic syndrome in the population of patients with Alzheimer's disease.

References

1. Division of Neuropharmacological Drug Products (DNDP) issues paper for March 9, 2000 meeting of the Psychopharmacological Drugs Advisory Committee Meeting on the various psychiatric and behavioral disturbances associated with dementia. Food & Drug Administration, January, 2000.
2. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. *Am J Geriatr Psychiatry* 2000;8:29-34.

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