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MEMORANDUM

To: Dockets Management Branch
From: Betsy Beckwith
Date: February 16, 2000
Subject: Docket # 00N-0088

Attached is the AAGP testimony for docket number 00N-0088. If you have any questions, please call me at 301-654-7850 ext.107, or email at bbeckwith@aagpgpa.org.

Thank you!

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AAGP POSITION STATEMENT ON THE FDA PROPOSAL FOR THE MARCH 9, 2000 MEETING

The American Association of Geriatric Psychiatry welcomes the invitation to offer testimony regarding the development of specific indications for labeling of psychotropic drugs to treat psychopathology in patients with dementia. The AAGP represents geriatric psychiatrists nationwide, and is dedicated to improving the care of all elderly persons with mental disorders. Among its primary missions is the dissemination of scientific and clinical information to improve clinicians' practice skills. As a large proportion of people treated by geriatric psychiatrists suffer from dementing diseases complicated by psychiatric symptoms, the diagnosis and treatment of dementia-related behavioral and psychiatric symptoms is an issue of great importance to AAGP, whose members are committed to ameliorating the suffering of patients and families across the outpatient, inpatient and long-term care settings. We adhere to the principle that both diagnosis and treatment require good research data to substantiate clinical decision-making.

BPSD. Behavioral and Psychological Symptoms of Dementia, or BPSD, is a generic term useful in focusing attention on the broad range of psychiatric symptoms experienced by patients with dementias of diverse etiologies, and in highlighting their importance in patient management and public health. It also implies that while many of these symptoms resemble those characteristic of other mental disorders such as schizophrenia and major depression, their appearance in the context of dementia poses distinct and, in some instances, unique problems in classification and treatment. As a group, psychiatric symptoms and syndromes in demented patients are common (5,31,33), and they frequently require pharmacologic, behavioral and environmental, or combined therapeutic approaches to alleviate suffering or unsafe behaviors (6,12,16,18,25,30).

However, the AAGP endorses the soundness of the FDA position that "BPSD" does not define a specific clinical entity for purposes of drug development. There is no evidence that drugs used successfully for treatment of a primary psychiatric disorder, such as antipsychotics for schizophrenia, antidepressants for major depression, or anticonvulsants for bipolar disorder, are generically useful for all, or even a majority, of symptoms encompasssed by the term "BPSD." Clear definitions of psychiatric disorders in demented patients are the lynchpin of decisive research on interventions and a prerequisite for appropriate choice of treatment, but have been insufficiently developed for most of these syndromes. Currently, clinicians experienced in the treatment of

dementia make initial therapeutic decisions largely on the basis of the predominant symptom picture, and revise therapy based on treatment outcome. In principle, this practice most closely resembles that employed in the treatment of complex primary psychiatric disorders such as schizoaffective disorder, which contain elements of both psychosis and depression or mania. However, it is recognized that successful treatment of a psychiatric symptom or syndrome with one class of drugs cannot be used to validate a diagnosis unless supported by careful phenomenological study.

DEFINITIONS OF PSYCHOPATHOLOGY IN DEMENTIA

We agree with the FDA that development of reliable and specific criteria for identifying psychiatric syndromes in dementia as potential targets of pharmacologic treatment is an essential goal of research to improve clinical care.

Current Problems in Delineating Psychopathologic Entities in Dementia.

Symptom overlap. The DSM-IV allows for specification of subtypes in making the diagnosis of dementia, i.e., with delirium, with depressed mood, with behavioral disturbances, and with delusions. This approach does not directly address the common problem of overlapping psychiatric symptoms in patients with dementia. In dementing diseases, particularly Alzheimer's disease, many patients have symptoms of both psychosis and agitation, some have symptoms of agitation alone, and occasionally patients have hallucinations or delusions alone without apparent distress, adverse behavioral consequences, or agitation (5,22,31,33). Depressive symptoms and syndromes often occur without psychosis or agitation, but may also co-occur, as can symptoms of anxiety (15,31). These conclusions are drawn from the existing research literature, recognizing that operational criteria that define the boundaries between various psychiatric manifestations of dementia have not been fully clarified by research, and that more needs to be done in this area. However, the presence of overlapping symptoms does not by itself vitiate the definition of a syndrome. There is precedent for this in accepted diagnostic schemes. For example, non-demented patients with major depression often have symptoms of anxiety that could meet diagnostic criteria for an anxiety disorder, based on the type, duration, and course of symptoms. In this instance, DSM-IV recognizes that depression is commonly associated with symptoms of anxiety, but that many patients have an anxiety disorder that occurs outside the timeframe of a depressive episode, and correspondingly allows assignment of a separate anxiety disorder diagnosis only when anxiety occurs during periods when depression is absent. DSM-IV adopts a

different strategy when depression occurs in a patient with clearly diagnosable schizophrenia: since schizophrenia is usually a chronic disorder, there is no period during which the disease is absent, but a separate depression diagnosis is permitted based on syndromal and symptomatic criteria. Moreover, although the depression responds to an atypical antipsychotic agent in many cases, adjunctive use of an antidepressant is necessary in others. Here, DSM-IV permits assignment of a depression diagnosis in addition to schizophrenia, without reference to timing.

These varying rules for diagnostic criteria for overlapping syndromes in DSM-IV indicate that the decision to define specific criteria in such cases cannot be based on a one-size-fits-all approach, and that the specific clinical features and course of overlapping syndromes need to be taken into account in the development of diagnostic criteria.

Heterogeneous combinations and time course of symptoms. Psychopathological and behavioral symptoms in demented patients do not always have a clear onset and offset, fluctuate in character and nature over time, evolve in overlapping and irregular patterns in different patients, and vary considerably as the neurodegenerative disease progresses (5,10). As a result, timing of symptoms as such cannot be used by itself to delineate specific psychopathologic entitities, and phenomenologic criteria are required.

Confounding of diagnostic criteria with symptom severity. In schizophrenia, the criteria used to diagnose the disorder differ in some respects from the symptoms measured as monitors of change with treatment. Diagnostic criteria for schizophrenia currently rely on the DSM-IV scheme, but clinical rating scales, such as the Brief Psychiatric Rating Scale (BPRS), an accepted measure of symptom severity and treatment response, include clinically important symptoms that do not appear in the diagnostic scheme (for example, agitation). Only some of the BPRS items relate to the symptoms required for the diagnosis of schizophrenia, and even these BPRS items do not correspond precisely to the those described in DSM-IV (or SADS or other diagnostic systems). In essence, the definition of a syndrome is primarily qualitative, but the measurement of change with treatment is primarily quantitative and may bear only a modest relationship to defining diagnostic criteria. In dementia, symptom ratings are currently the primary means of identifying the full range of psychopathologic states that may occur, and different scales contain non-overlapping domains; the recent publication of proposed criteria for diagnosing psychosis in dementia (10) is a welcome sign of progress toward formalizing the diagnostic process. We believe that a similar approach should be employed in drug development for the treatment of the several specific syndromes subsumed under the rubric of BPSD. Adoption of this approach might lead, for example, to assignment of a diagnosis of psychosis in dementia, based on a symptom

cluster that may differ from those required to meet diagnostic criteria for a primary mental illness such as schizophrenia; a scale like the BPRS might still be used effectively in both disorders to measure change with treatment. This point is made not to advocate the use of the BPRS but to establish the importance of distinguishing syndromal definitions, using strict criteria, from the application of scales or instruments used for descriptive purposes or to evaluate treatment response.

Heterogeneity in putative etiology and response to different treatments. Clinical observations support the proposition that certain psychopathologic features emerge in some demented patients only under specific environmental conditions and, in others, as a result of individual vulnerabilities. For example, a patient with no history of affective illness may develop a major depressive episode when subjected to abusive care; a change in caregiver may alleviate the syndrome. Others may become depressed despite optimal care and require an antidepressant drug for effective relief. Also, sleep disorder in dementia may respond to treatment for pain in appropriate patients, while in others, properly-timed bright light therapy, an antidepressant, or a sedative-hypnotic may restore relatively normal sleep patterns (14,26).

Inadequately defined thresholds for treating neurobehavioral symptoms in dementia. Careful clinical evaluation of the nature and impact of symptoms, and clinical judgment, are currently the guideposts for choosing what symptoms to treat, particularly when several are present concurrently that may suggest different therapeutic approaches. Similarly, there are no scientifically-based benchmarks that establish a minimum level of severity that justifies drug therapy. While these issues are moot when symptoms are very severe, the threshold for decisions to treat require clearer delineation.

PSYCHOSIS

Prevalence. Psychosis in Alzheimer's disease and other dementias is common, with estimates ranging from 20-50% in systematic large-scale studies (5,22,31). This relatively wide range in estimates may be due to the differing definitions and instruments used to assess psychosis, but may also reflect selection factors and the reality that the prevalence of psychosis changes over time as the disease progresses at different rates in different regions in the brain.

Features. The types of psychotic symptoms prevalent in patients with dementia have been relatively well characterized. For example, the delusion that someone is stealing the patient's possessions is commonly reported (23), and this symptom is rare in

schizophrenia. Delusional misidentification is also common, which some have argued is a primary result of cognitive deficits and not a delusion according to standard psychiatric definitions (20). Visual hallucinations are not uncommon in dementia but rare in schizophrenia where auditory hallucinations predominate. These and other distinctions between psychosis in Alzheimer's disease and psychosis in schizophrenia have been well summarized by Jeste and Finkel (10). Although the boundaries of psychosis in dementia, i.e., which symptoms should and should not be included in the definition, are still the subject of academic debate, the relative uniqueness of psychotic symptoms compared to those seen in schizophenia strongly support the classification of psychosis in dementia, or psychosis in Alzheimer's disease, as a distinct entity. The criteria proposed by Jeste and Finkel represent a sound approach to developing such a definition.

Validity and reliability. There is evidence for the construct validity of psychosis using rating instruments developed specifically to evaluate dementia-associated symptoms of psychopathology (1,4,7,22,31). From a psychometric perspective, strong inter-rater reliability has been established for several different instruments used to evaluate symptoms of psychosis in dementia (1,4,7,22,31). There is now considerable agreement, across a range of studies using different scales, as to the existence of a core group of psychotic symptoms, their clinical features, and their prevalence in patients with dementia (1,5,22,31). Predictive validity, including treatment response, has also been established in a number of studies (6,12,28,29).

Pathophysiology. The pathophysiology of psychosis in dementia is not fully understood, as is the case for psychopathology in most psychiatric disorders. The FDA position paper outlines a model of pain, and states that "the pathophysiology of pain is well understood." The peripheral pathophysiology of pain is indeed well understood, but its central nervous system pathophysiology continues to be a subject of active research and is not yet fully understood. The brain is the site of action of many effective analgesics, yet the mechanism of action of analgesics in the brain was poorly understood during the several decades when most analgesics were approved for human use. Therefore, it is not necessary to insist upon consensus on the pathophysiology of psychosis in dementia as a prerequisite for approving drugs that demonstrably treat it. However, there is evidence of dopaminergic and noradrenergic abnormalities in psychotic dementia patients that differ from those of non-psychotic demented patients (9,34). These and other data from biological studies support the validity of the construct.

OTHER PSYCHOPATHOLOGIC FEATURES OF DEMENTIA

Agitation. Conceptually, agitation may be a final common pathway for the expression of of symptoms of depression, anxiety, psychosis, and even pain in dementia; alternatively, it may reflect a specific internal state change that may ultimately be defined by studies of brain function, and it can clearly be a behavioral response to environmental stressors, unskillful caregiving, or unmet psychosocial needs in patients with cognitive and verbal communication deficits. This theoretical model is accepted and used by many clinicians in making therapeutic recommendations, and multiple simultaneous interventions involving drug therapies, caregiver-based, and environmental interventions are frequently used in managing agitated patients in clinical practice. However, insufficient research data currently exist to make definitive statements about the specificity of agitation as a diagnostic entity in and of itself. Nevertheless, a case can be made that agitation in dementia may represent a distinct entity, although this has been better demonstrated for psychosis. There is some empirical evidence supporting the uniqueness of agitation as a phenomenon in demented persons, but sufficient specificity has not yet been established relative to agitation in other disorders to justify delineating it as a clearly definable and distinct syndrome of dementia. Part of the problem may be quantitative. If only severe forms of agitation in dementia are defined as the target, it may be easier to identify and delineate as a separate entity. Since agitation has rarely been a primary focus of either phenomenological classification or therapeutic intervention in other psychiatric disorders, its definitions and boundaries have not been elucidated with the precision accorded to delusions and hallucinations (and psychosis) in the psychiatric nomenclature. Although this weakness has existed historically, the extant database on evaluation of agitation, aggression, and related symptoms in dementia is large enough that rapid progress should be possible in defining the parameters of psychomotor agitation (and related symptoms/syndromes) in dementia more specifically than has occurred to date. Another problem in defining agitation in demented patients is confusion emanating from its multiple potential sources. For example, clinicians and families may observe that agitation occurs only in the context of caregiving by one but not by another individual. In such instances, agitation is best construed as a response that has specificity for another person, rather than for a unique psychopathological state. The delineation of the issues related to competing causes has been insufficiently addressed in research thus far.

Depression. The definition of major depression in dementia is relatively less problematic than the definition of agitation, i.e., the DSM-IV symptom criteria for major depression can be applied directly to patients with dementia. While some symptoms of depression do overlap with those that are common in dementia per se, e.g., apathy and loss of interest, the symptom criteria for major depression in DSM-IV cover a large enough range of severe depressive symptoms that an erroneous diagnosis of major depression in patients with dementia (when depression does not "truly" exist) is unlikely in the hands of skilled clinicians. Nevertheless, to avoid the potential pitfalls posed by non-specific symptoms that are common to both depression and dementia, the presence of depressed mood (and not the non-specific symptom of apathy alone) should be required for the diagnosis of major depression in dementia.

Anxiety. Anxiety has received relatively less attention than other forms of psychopathology in dementia, and there is no current consensus as to its treatment. While recent paper suggests that symptoms of anxiety are both common and frequently associated with other neurobehavioral symptoms (31,32), diagnostic criteria have not been tested.

TREATMENT OF PSYCHIATRIC SYNDROMES IN DEMENTIA

Several published studies document moderate efficacy of both typical and atypical antipsychotic drugs for psychosis and behavioral dyscontrol (primarily psychomotor agitation and aggressive behavior) in dementia (3,6,8,12,27,28,29) and the anticonvulsant carbamazepine (30). The evidence regarding antidepressant drug treatment for symptoms of major depression in dementia is suggestive but not conclusive of efficacy (11,17,18,19,21,24).

Antipsychotics have been studied far more systematically than any other class of psychotropic medication in demented patients. For the use of antipsychotics to treat target syndromes of psychosis or behavioral dyscontrol, the therapeutic window for both atypical and atypical agents is narrow, emphasizing the importance of systematic controlled studies to help guide clinical practice in other neuropsychiatric symptoms of dementia as well. Before the 1990s, it was not uncommon for physicians to prescribe relatively high doses of typical antipsychotics, e.g., haloperidol 5-15 mg daily or chlorpromazine 400-800 mg daily, to treat psychosis and behavioral dyscontrol in demented patients, resulting in severe short- and long-term neurologic side effects

including extrapyramidal signs and tardive dyskinesia. Recent clinical trials with an emphasis on low-dose treatment strategies have helped to define the safe and effective dose range for several typical and atypical antipsychotics (6,12,28,29), and led to improved standards of clinical practice for those physicians who have become aware of these findings. Given the widespread clinical applicability of such studies, it is unwise to ignore their utility, and it is of great importance to extend the conceptual and methodologic framework employed therein to studies of other classes of psychotropic drugs.

CONCLUSION

A large number of physicians currently prescribe psychotropic medications, off-label, at fairly high frequency, to treat a variety of psychiatric symptoms in patients with dementia (2,13). This use will only increase as a result of the rapid rise in prevalence of dementia due to the aging of the population. The need is pressing to establish reliable criteria for diagnosing specific syndromes within the domain of BPSD, in order to facilitate the development of optimal treatment strategies. If the FDA cannot establish clear guidelines that permit approval of labeling based on appropriate clinical trials for the treatment of psychosis and other syndromes in demented patients, opportunities to establish treatment efficacy and safety, and the impetus for industry support of these efforts, will greatly diminish in the future. With respect to specific antipsychotic drugs, efficacy has been satisfactorily established, the parameters of safety have been satisfactorily defined, and clinical practice in geriatric psychiatry has been improved independent of the FDA labeling process. Any diminution of research efforts is likely to have a detrimental impact on the treatment of patients with dementia who develop significant psychopathology. The AAGP strongly supports all efforts to avoid this adverse result of unwarranted hesitancy in the regulatory process.

Respectfully submitted for the Board of the American Association for Geriatric Psychiatry.

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