

# Regulatory Issues on Behavioral and Psychological Symptoms of Dementia in the United States

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The entity, behavioral and psychological symptoms of dementia (BPSD), is a useful concept in that it focuses attention on an aspect of dementia that has long been ignored in both research and treatment. Although it is useful as a broad category that includes a number of more specific clinical entities, BPSD is too broad a target to serve as an indication for a particular drug. Labeling with such a claim would be potentially misleading because it would not be clear what specific patient population would likely benefit from treatment.

One approach for arriving at acceptable indications for the approval of drugs for the treatment of clinical entities falling under the broad umbrella of BPSD would be to identify specific diseases or syndromes that are unique to this popu-

lation. Examples might include subtypes of psychosis, a depression specific to dementia that could be distinguished from major depressive disorder, or a specific manic syndrome. An alternative approach for seeking an indication under the general category of BPSD would be to focus on a nonspecific sign or symptom that cuts across disease categories, e.g., agitation. It would be necessary to establish that such an entity, e.g., agitation, was really nonspecific and represented the same clinical entity, whatever the disease model.

*Dr. Laughren has suggested that the recent Issues Paper from the Food and Drug Administration be included with the brief summary of his presentation. Beginning on the following page is the Issues Paper.*

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**Division of Neuropharmacological  
Drug Products (DNDD) Issues  
Paper for March 9, 2000, Meeting of  
the Psychopharmacological Drugs  
Advisory Committee on  
the Various Psychiatric and  
Behavioral Disturbances  
Associated With Dementia**

There is no question about the importance of Alzheimer's disease (AD) and other dementias to the public health. These illnesses have an increasing prevalence as the U.S. population ages, and there is considerable effort under way to discover effective treatments for the cognitive impairment that is central to these various dementing illnesses. Similarly, it is clear that the various psychiatric and behavioral disturbances that are frequently associated with dementia represent a significant problem for patients with these illnesses and also for their caregivers and the healthcare system generally. Although resources have also been focused on the study of treatments for these associated psychiatric and behavioral disturbances of dementia, one obstacle has been a difficulty in identifying, defining, and naming the different clinical entities that fall under this broad umbrella.

Among the treatments being considered for these various psychiatric and behavioral disturbances that are frequently associated with dementia are pharmacological approaches, and consequently, the Food and Drug Administration (FDA) has a role in the development of such treatment options. FDA approval of a drug treatment for any condition, including those clinical entities associated with dementia, requires that the condition be identified

and defined unambiguously, that appropriate instruments be used for assessment and measurement, and that appropriately designed clinical trials demonstrate safety and effectiveness. The FDA has an interest in all aspects of drug development in this area; however, the important first step would be to identify, define, and name appropriate clinical entities that could be the focus of such development programs. The purpose of the March 9, 2000, meeting of the PDAC is to build consensus on the identification of appropriate clinical entities as targets of drug development in this area.

The FDA's authority to consider the appropriateness of proposed clinical targets for new claims comes from the Food, Drug, and Cosmetic Act (Section 505), in particular, in reference to language pertaining to "labeling proposed to be used for such drug," which must accompany a new drug application. The Secretary may refuse to approve an application if "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular." Labeling recommending a drug as a treatment for a clinical entity that is poorly defined is potentially misleading, because it would not be possible to adequately inform clinicians through labeling as to the appropriate use of the proposed drug treatment. Thus, we consider the evaluation of the appropriateness of proposed clinical targets for new claims in the area of psychiatric/behavioral disturbances associated with dementia as an important regulatory responsibility in drug development in this area.

In general, there are two types of clinical entities that are considered appropriate targets for new claims. Specific diseases or syndromes are the usual

focus of a drug claim, e.g., congestive heart failure or rheumatoid arthritis. Nonspecific signs or symptoms not unique to a single disease or syndrome, e.g., pain or fever, may also be the focus for a claim. Whether a proposed new claim is for a specific disease/syndrome or a nonspecific sign/symptom, similar criteria are used by the FDA to evaluate a proposed clinical entity as an appropriate target for a new claim. The proposed clinical entity must be accepted in the relevant clinical/academic community, it must be operationally definable, and it must identify a reasonably homogeneous patient group. The latter two criteria are important to ensure the validity of the clinical trials supporting the claim and to make it possible to inform clinicians in labeling about the use of the proposed treatment.

It is important at this point to clarify a significant misunderstanding in psychotropic labeling. Much of the language in the indications sections of psychotropic labeling was developed decades ago and has been carried forward because of precedent and also the complicated effects on other products induced by attempts to change the language for any particular product. The language present in some psychotropic labeling gives the impression that psychotropic drugs have broader, nonspecific indications than is in fact the case. For example, in the Indications and Usage section of labeling for antidepressants, it is stated that the indication is for the "treatment of depression," language that may suggest a general claim for "depression" as manifested by the various depression subtypes and perhaps also for the symptom "depression" in the context of other psychiatric and nonpsychiatric diseases. However, this general statement in

antidepressant labeling is immediately followed by language identifying the specific population in which the antidepressant effect was established, i.e., in every case thus far, major depressive disorder. In fact, antidepressants are approved specifically for major depressive disorder. Any attempt by sponsors of such products to promote these drugs for other depressive subtypes or for depressive symptoms in the context of other disease states would be met with regulatory action.

Similarly, in the Indications and Usage section of labeling for antipsychotics, it is stated that the indication is for the "management of manifestations of psychotic disorders," language that may suggest a general claim for "psychosis" as manifested by the various psychotic syndromes and perhaps also for the symptom "psychosis" in the context of other psychiatric and nonpsychiatric diseases. However, as in antidepressant labeling, this general statement in antipsychotic labeling is immediately followed by language identifying the specific population in which the antipsychotic effect was established, i.e., in every case thus far, schizophrenia. In fact, antipsychotics are approved specifically for schizophrenia. Any attempt by sponsors of such products to promote these drugs for other psychotic subtypes or for psychotic symptoms in the context of other disease states would again be met with regulatory action.

This language in much of psychotropic labeling gives the impression that these drugs have general claims, with the implication that depression, psychosis, and anxiety may be thought of as nonspecific symptoms. Although each of these phenomena may occur in a variety of psychiatric and other disease

entities, the view that they represent non-specific "symptoms" would ideally be supported by evidence that each is universally and identifiably defined, whatever the specific disease with which they are associated, easily measured, well understood from a pathophysiologic standpoint, and equally responsive to treatment, again, regardless of the context in which the symptom occurs. There is little reason to believe that these assertions are true for depression, psychosis, or anxiety.

In fact, over the past decade, the FDA has been moving toward more specific indications for psychotropics. This is particularly true for the anxiety disorders (DSM-IV), where drugs are now specifically approved for panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, social anxiety disorder, and posttraumatic stress disorder. It is our intention with new approvals for other general psychiatric disease areas, for example, depression and psychosis, to focus the indications on the specific entities studied rather than perpetuating the impression of general claims. For example, an antidepressant studied in patients with major depressive disorder would get that as a specific claim, and a drug studied in patients with schizophrenia would get that as a specific claim. The labels antidepressant, antipsychotic, and anxiolytic should be thought of as referring to general drug categories, in the same sense that one considers the terms antibiotic and antiepileptic as general categories for drugs in these therapeutic areas. In neither case would one consider any particular drug given that label as necessarily effective for all the different disease states that might fall under that general category.

As noted, the FDA does, however, provide an alternative approach for new indications, namely, the targeting of non-specific symptoms that may be present in different disease states. Obvious examples of this approach to new indications would be the approach for the symptoms fever and pain. Antipyretics and analgesics are approved for these nonspecific symptoms on the basis of studies involving different "models" for each such symptom, e.g., headache pain and dental pain as different pain models. The basis for accepting this nonspecific approach to indications is the view that, although the disease states leading to these nonspecific symptoms may differ markedly, the symptoms themselves are universally recognized, are readily measured, have a well-understood pathophysiologic basis, and respond similarly to drug treatment for that symptom, quite apart from the diverse disease states that may lead to the nonspecific symptom. Critical to this approach to gaining a new claim is the concept of pseudospecificity. In this context, because the essence of this type of claim is that the symptom is nonspecific to any one disease, it is essential that efficacy be demonstrated in several different disease models. To attempt to obtain a claim for a nonspecific symptom in a single disease model would, by definition, be pseudospecific, because such a claim would give the impression that the symptom is specific to that disease.

Patients with dementia may have a variety of associated signs and symptoms, including but not limited to: delusions, hallucinations, suspiciousness/paranoia, depression, mania, anxiety, anger, aggression, labile mood, abnormal sleep, eating disorders, wandering, pacing, and stereotypic behaviors. As

noted, these associated signs and symptoms represent an important area for further drug development. Two approaches have emerged external to the regulatory environment for addressing this problem.

The position is held by some experts in the field that the overall concept, behavioral and psychological symptoms of dementia (BPSD), fully captures this clinical condition. The FDA has not to date accepted this concept as defining an indication for treatment. Although the concept BPSD acknowledges and focuses attention on this important aspect of dementia, and identifies dementia as a population with possibly unique psychiatric disturbances, the FDA has considered this too broad a target. It refers to multiple clinical entities. It contains unique and heterogeneous psychiatric disturbances, some of which remain to be defined. Because it is unclear which of these many clinical entities would be responsive to treatment, the FDA has considered the use of BPSD in labeling potentially misleading.

A second approach has been taken by several sponsors of antipsychotic drug products in attempting to establish claims in this area of psychiatric/behavioral disturbances in association with dementia. Since these products are already approved for schizophrenia, it seemed to these sponsors reasonable to, in a sense, borrow from this claim in that psychotic disorder in establishing an "antipsychotic" claim in patients who have psychotic symptoms in the context of AD on the basis of a single study. We firmly believe that it is reasonable to work toward establishing claims for antipsychotics and possibly other drugs in the population of patients with AD and other dementias, and we acknowledge

that the issue of whether one or two studies might be needed in any particular situation is open to debate. Our concern has been with the approach suggested for defining the clinical entity that is the target for the claim. In fact, the approach used in these development programs has been to define a target population in terms of a minimal quantitative rating on "psychotic" symptoms from a rating instrument intended to measure a broad group of psychiatric symptoms in this population. To date, we have questioned this approach, given that the population targeted may not be sufficiently defined for clinicians to know what is meant by "psychosis associated with AD." Similar problems arise in attempting to establish claims for antidepressants and anxiolytics in this population using this approach.

The general question to address at the March 9, 2000, meeting is how one might develop drugs for treating the various psychiatric/behavioral disturbances that occur in patients with dementia. If the two approaches described in the previous two paragraphs are problematic, and we acknowledge that this is a matter for debate, what approaches would be acceptable from a regulatory standpoint?

We would propose, as one approach for discussion at this meeting, that the clinical/academic community attempt to identify and define unique psychiatric/behavioral syndromes that may exist in this population. For example, an approach to establish a claim for an "antipsychotic" drug in patients with dementia would be to attempt to define a unique psychotic syndrome in the population of patients with AD, or perhaps dementia more generally. This is clearly a challenging task, and one that would require considerable work to accomplish.

However, we find this approach more consistent with our current views on the very different nature of the "psychosis" that one finds in schizophrenic patients compared to that seen in patients with dementia. If a unique psychosis of dementia could be defined and developed to the point of having general recognition in the academic/clinical community, that entity would be an appropriate target for a new claim. The support for such a new claim would probably require two independent studies supporting the claim, but as noted, whether one or two trials might be needed is a matter for debate. But if accomplished, such a claim would warrant independent recognition in the Indications and Usage section. In fact, this is the accepted approach for establishing new claims in most therapeutic areas, both psychiatric and nonpsychiatric, i.e., the development of specific diagnostic criteria for recruiting patients with a specific disease or syndrome for studies to support a new claim for that entity.

An alternative approach that would be acceptable from a regulatory standpoint would be to target nonspecific

signs and symptoms. For reasons discussed above, we have to this point felt that psychosis, anxiety, and depression do not meet the requirements for non-specific signs and symptoms. One possibility might be the clinical entity "agitation." There would need to be agreement on a definition and diagnostic criteria for agitation, and it would need to be a broad enough definition that it could be considered an entity not specific to the dementias. It would be necessary to establish that this entity occurs across disease states, e.g., dementia, mental retardation, schizophrenia, delirium, etc., and, ideally, to establish that it has a common pathophysiologic mechanism wherever it happens to occur. In order to demonstrate efficacy for this entity, a drug would need to be studied in several different disease models.

In summary, the FDA recognizes the need for better treatments of behavioral and psychiatric disturbances associated with dementia and looks forward to working with the different groups interested in facilitating the development of possible drug treatments in this area.