FDA Perspective on the DSM-5 Approach to Classification of "Cognitive" Disorders

Thomas Laughren, M.D.

Primary "cognitive" disorders (e.g., Alzheimer's disease) often have behavioral features, just as primary behavioral disorders (e.g., schizophrenia) often have cognitive features. Drug research in recent years has expanded into targeting the full range of symptoms of both types of disorders. DSM-5 should include these associated features of each type of disorder, because acknowledging the full range of symptoms for each type of disorder has important research and treatment implications.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2011; 23:126–131)

The ongoing revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) that will lead to its next iteration, that is, DSM-5,[1] provides an opportunity to reconsider how the "cognitive disorders" are classified. There are a number of parties with an interest in this process, including patients, clinicians, the academic community, the pharmaceutical industry, healthcare insurers, and various government agencies. The Food and Drug Administration (FDA) has a major interest in how these disorders are classified and characterized, because changes could influence data requirements for new drugs and the design of new clinical studies. This article will discuss current thinking about how to classify and characterize "cognitive" disorders from the perspective of the Division of Psychiatry Products (DPP) at the FDA.

Primary "Cognitive" Disorders Versus Primary "Behavioral" Disorders That Have Cognitive Features

The draft proposal for DSM-5 separates the disorders that are considered primarily "cognitive," for example, Alzheimer's disease, from the rest of the mental disorders, that is, those with primary behavioral or psychiatric features. It is understandable that one might want to group disorders in this way, and, in fact, this ap-

Received August 18, 2010; accepted September 14, 2010. From the Food and Drug Administration, Silver Spring, MD. Send correspondence to Thomas Laughran, M.D., Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993; Thomas.Laughren@fda.hhs.gov (e-mail).

proach to classifying these disorders in DSM-5 does not differ substantially from the DSM-IV and earlier versions. All of these versions of DSM divide "mental disorders" into those with primary cognitive features and those with primary behavioral or psychiatric features. Dichotomizing "cognitive" and "behavioral" disorders, in fact, has been broadly accepted in the field, and has also been the predominant model for dividing these indications at FDA. Until 5 years ago, the Division of Neuropharmacological Drug Products (DNDP) handled both cognitive and behavioral disorders, but an ever-expanding workload led to a division of DNDP into two separate units in 2005; that is, the Division of Neurology Products (DNP) and the Division of Psychiatry Products (DPP). The cognitive disorders, such as Alzheimer's disease, now fall within the purview of DNP, but any psychiatric/behavioral components of those disorders are handled by DPP. Primary behavioral disorders, such as schizophrenia, fall to DPP, but, in this case, any cognitive components of such disorders are also considered by DPP. Thus, the parallelism breaks down somewhat when it comes to cognitive aspects of behavioral illnesses that are not considered primary features of the illness.

DSM-IV-TR[2] has an entire section called "Delirium, Dementia, and Amnestic and Other Cognitive Disorders." For each of the major categories in this section, subtypes of that condition are recognized if an etiology is believed to be known, for example, Dementia of the Alzheimer's Type; if none is known, the category is "Not Otherwise Specified," that is, Dementia, Not Otherwise Specified. Behavioral and psychiatric features of these primary "cognitive" disorders are de-emphasized in this section. For example, for Dementia of the Alzheimer's Type (294.1X), one has the choice of adding a fifth-digit "specifier" to designate whether or not the patient has an accompanying significant "behavioral" disturbance. Thus, a patient would be coded 294.10 if the clinician felt that there was no such accompanying disturbance, or 294.11 if the clinician felt that there was such an accompanying disturbance. There is no possibility within this section to give any greater specificity about the "behavioral" disturbance; that is, the full range of psychopathology would be covered under "behavioral" disturbance, not dementia. There is, however, the possibility of further characterizing the behavioral disturbance by using other sections of the manual, for example, 293.83 (Mood Disorder Due to Alzheimer's Disease With Depressive Features) or 310.1 (Personality Change Due to Alzheimer's Disease, Aggressive Type).

This same dichotomized thinking is reflected in the "behavioral" sections of DSM-IV-TR. "Schizophrenia and Other Psychotic Disorders" have their own section, with a strong emphasis in these sections on the "behavioral" aspects of these disorders. Although there is some discussion of cognitive aspects of these disorders, there is no provision for coding for the presence of important cognitive deficits.

Why is this approach to the nomenclature a problem? Consideration of Alzheimer's disease (AD), a primary "cognitive" disorder, illustrates the difficulties that arise in focusing so heavily on the cognitive aspects of a disorder. Unlike primary "behavioral" disorders, AD has a well-recognized neuropathology, and it is certain that its severe impairment in cognitive functioning is related to this neuropathology. It should not be assumed, however, that the various behavioral abnormalities observed in patients with AD are unrelated to the recognized neuropathology; rather, there is good reason to believe that, at least in part, they may be related.[3] Whether or not these very diverse features of AD can be attributed to the observed pathological findings is, however, beside the point. What is important is that the psychiatric and behavioral abnormalities associated with this illness represent an important burden for both patients and their families. This being so, they should not have the second-class status they receive by relegation to "specifiers." To do so discourages investment in how to treat them, and invites inattention to the effect of various treatments for AD on the accompanying psychiatric and behavioral abnormalities, which could surely differ among treatments. In a sense, these aspects of AD have been research orphans.

The situation has until recently been just as problematic regarding primary "behavioral" disorders, as illustrated by the disorder schizophrenia. This is a disorder for which there is no known neuropathology, and the disease covers a wide range of behavioral abnormalities. But it also can include an important cognitive component.[4] Schizophrenic patients often have significant cognitive impairment that, in fact, may precede the onset of the psychotic phase of the illness. The precise profile of deficiencies is unique to schizophrenia, and an important aspect of the illness, particularly during the residual phase when patients are trying to return to a previous level of functional capacity.[5] Despite the importance of cognitive impairment as an aspect of schizo-

phrenia, DSM-IV-TR hardly mentions this as a problem and has no provision for coding its presence or absence. In fact, cognitive impairment in schizophrenia had been largely ignored, at least in drug development, until recent years, when NIMH launched the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative.[6] This program has revived interest in studying and treating this aspect of schizophrenia, and it is now back on the research agenda.

Endorsement by Division of Psychiatry Products (DPP) of New Clinical Entities as Targets for Drug Development

Over the past 20 years, there has been a transition in approved psychiatric indications from fairly broad and general claims to more specific claims, at least in most cases. As an illustration, antipsychotic drugs were previously approved for the "management of the manifestations of psychotic disorders." Although this broad indication was intended to refer to schizophrenia, the condition studied, it was not precise and could easily have been seen as covering schizoaffective disorder, and possibly other psychotic disorders. Recent approvals have been for the "treatment of schizophrenia," the clinical entity actually studied in these development programs, and most psychiatric approvals are now for specific psychiatric syndromes. It is possible, moreover, to obtain an approval for some particular symptom or symptom-cluster of a recognized syndrome if a case can be made for this more narrow focus.

One example of such an approved claim is the approval of clozapine for the treatment of suicidality in patients with schizophrenia. The justification for this more narrow target is that most antipsychotic drugs do not adequately treat suicidality in schizophrenia, and clozapine was clearly shown to do so. Other examples of approved claims for specific symptoms as part of a syndrome include approvals for atypical antipsychotic drugs for the treatment of agitation as part of schizophrenia and bipolar disorder and treatment of irritability as part of autism. Also, DPP has considered studies of more narrow targets for which drugs have not yet been approved, for example, cognitive impairment in schizophrenia. A third possible type of indication is for treatment of a nonspecific symptom, that is, one that is not specific to any particular disorder. Examples of such nonspecific claims in other therapeutic areas are common, for example, the approval of analgesics for pain, of antipyretics for fever, and of diuretics for edema. There are, as yet, no examples of the approval of psychiatric drugs for nonspecific psychiatric symptoms.

Although most approved psychiatric drug products are approved for clinical entities that are included in the DSM, presence of an entity in DSM is neither necessary nor sufficient for any particular clinical entity to be considered by DPP as a legitimate target for a drug claim. Examples of such entities that are not explicitly included in the DSM are the more narrow targets listed above (suicidality, agitation, irritability, cognitive impairment) for which DPP has either already approved drugs or has endorsed the entity as one that could be approved. None of these is specifically noted in DSM as a recognized, distinct entity. Such an entity must, however, meet several criteria. First, it would need to be sufficiently defined to allow it to be studied and well-enough described in labeling to allow clinicians to identify patients who are reasonable candidates for the treatment. Second, the entity would need to be reasonably well-accepted in the academic and clinical community, even if it has not yet been included into the DSM. Finally, the entity must be distinguishable from other recognized entities; that is, it would not be acceptable to simply rename an entity that has already been described and recognized.

Regulatory Approach to Targeting Psychosis of Alzheimer's Disease

Alzheimer's disease is a common and very disabling illness that has been the focus of much pharmaceutical research in recent years. The clinical spectrum of illness includes not only the very prominent cognitive impairments but also an array of psychiatric and behavioral symptoms. Both aspects of this illness represent a burden to patients and their families, and the FDA has recognized and acknowledged both as reasonable targets for drug development. An important obstacle in developing drugs for the psychiatric and behavioral disturbances associated with AD has been the difficulty in identifying, defining, and naming the different entities that fall under this broad umbrella. These symptoms cover the full range of behavioral disturbances, including various psychotic symptoms, affective symptoms, anxiety, anger, aggression, sleep and eating disorders, apathy, wandering, pacing, and various stereotypic behaviors. Some years ago, a broad construct was proposed to cover this full range of symptoms in patients with various dementias, that is, Behavioral and Psychological Symptoms of Dementia (BPSD).[7] The

FDA did not accept this construct because it represented too broad a target, referring to multiple, not necessarily consistently-present clinical entities. So it would be potentially misleading; that is, it would be unclear which of these entities was actually responsive to treatment.

To address this problem, a meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) was held on March 9, 2000 to discuss approaches for moving forward.[8] There was reasonable consensus at this meeting that BPSD was too broad a target for an indication. It was agreed that it would be more productive to focus on specific syndromes in AD than on a more diffuse target for all dementias. It was further agreed at this meeting that Psychosis of Alzheimer's Disease could be recognized as a distinct entity and that the criteria for this entity proposed by Finkel et al.[9] were sufficiently clear to define this entity. There was also discussion at this meeting of the symptom "agitation" as a possible target for drug development, but no agreement on how best to characterize this symptom. The committee identified a number of issues for future work, including identifying other psychiatric syndromes of AD and better defining agitation of AD. The FDA has accepted Psychosis of Alzheimer Disease as a reasonable target for drug development.[10]

In the decade since that PDAC meeting, a number of controlled trials have studied atypical antipsychotics for the treatment of Psychosis of Alzheimer Disease or other behavioral symptoms in AD, but none of the development programs for drugs in this class has led to approvals. On the other hand, the substantial database of controlled trials of antipsychotics in this population allowed the FDA to conduct a meta-analysis assessing a signal of excess mortality. This analysis found excess mortality in the patients treated with atypical antipsychotic drugs for psychiatric symptoms in this population, and it led to a box warning regarding this risk for all the drugs in this class.[11] At the present time, there seems to be little interest in targeting Psychosis of Alzheimer disease. There does, however, seem to be renewed interest in trying to properly define agitation or aggression in this population, so that this could become a target for future development programs.

Regulatory Approach to Targeting Cognitive Impairment Associated With Schizophrenia

Schizophrenia is a well-recognized psychiatric syndrome for which many drug products have been approved. The schizophrenic syndrome includes an array of symptoms; however, until recently, the emphasis in drug development programs has been on positive symptoms. Although it has long been acknowledged that cognitive impairment is part of this syndrome, this aspect has not received much attention until recently. Typical registration trials have utilized a broad symptom scale, for example, BPRS or PANSS, as the primary efficacy measure, and change in total score has been the primary endpoint. Indeed, as noted, DSM-IV-TR barely acknowledges cognitive impairment as a feature of schizophrenia and has no provision for coding on this aspect of the illness. This is an important omission because an abundance of data shows substantial cognitive impairment in schizophrenia; that is, these patients on average fall 1–2 standard deviations below normal scores on cognitive functioning. Moreover, cognitive impairment is a strong predictor of poor functional outcome in this population, and it is well-recognized that currently approved antipsychotic drugs do not effectively treat the cognitive impairment of schizophrenia. Several years ago, NIMH initiated the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) program to develop an assessment battery and facilitate drug research for this aspect of schizophrenia. The MATRICS program has yielded a standard assessment battery, the MCCB (MATRICS Consensus Cognitive Battery), and this instrument is now in widespread use. A regulatory pathway for developing drug products for cognitive impairment associated with schizophrenia has now been established.[12]

DSM-5 Proposal for Neurocognitive Disorders

The initial draft of DSM-5 (February, 2010) includes a section on "Neurocognitive Disorders" as a replacement for the current section in DSM-IV-TR titled "Delirium, Dementia, and Amnestic and Other Cognitive Disorders." This new section maintains the distinction between delirium and dementia, with three subsections, that is, "delirium," "major neurocognitive disorder," and "minor neurocognitive disorder." The term "dementia" has been replaced with a presumably more neutral and less stigmatizing term, "major neurocognitive disorder." If there is a strongly predictive clinical picture or objective evidence supporting a known pathology, a more specific subtype diagnosis is given; for example, Alzheimer's disease subtype of major neurocognitive disorder. It is unclear as yet how behavioral features of these disorders will be addressed. One possi-

bility would be to continue to use the fifth-digit specifier for such conditions, but to expand this to designate the specific type of associated disturbance, for example, psychosis, depression, or agitation, among others. Another proposal would be to have separate criteria for each specific type of behavioral disturbance. Criteria are included in the appendix of the draft DSM-5 document for both psychosis and depression of Alzheimer's disease.

Is this an improvement? It is not clear that the term "major neurocognitive disorder" is better than dementia, as they both mean serious cognitive impairment, however one labels it. The major-versus-minor distinction, however, seems potentially useful, particularly since this distinction may have some predictive value for patients and clinicians. The annual conversion rate from MCI (mild cognitive impairment) to progressive dementia appears to be about 5%–10%, and, even after 10 years, many people with MCI will not progress.[13] A major concern continues to be that this approach still focuses almost entirely on the cognitive aspects of these disorders, with little attention to the psychiatric and behavioral aspects, despite their clinical importance. This deficiency could be addressed by fleshing out diagnostic criteria for the various specific behavioral syndromes, then including these syndromes in this section of the manual so that they will get the same level of attention as the cognitive impairments. Using single fifth-digit specifiers does little to improve the problems of the current nomenclature, and would not allow for having more than one associated syndrome, even though patients may clearly have a variety of behavioral problems and usually do have more than one. It is also not clear how the revised DSM-5 will address cognitive disturbances that are part of primary "psychiatric" disorders, for example, schizophrenia. Cognitive and behavioral disorders are both important, can coexist, and can vary in severity; and both deserve attention.

Years ago, cognitive disorders were classified as either "acute organic brain syndrome;" that is, what is now considered delirium, or "chronic organic brain syndrome," what now generally falls under the heading of dementia. The qualifier "organic" has no value, since it implies that other cognitive and behavioral disorders are somehow not "organic," when, in fact, they all must reside in the brain. It may be useful to think more broadly in terms of what represents a brain disease. Clearly-defined gross anatomic or histopathological changes would certainly qualify, but it is also reasonable to consider altered neurochemistry, receptor sensitivity, or brain circuits as "organic" changes.

The "acute" versus "chronic" distinction has some value, since it addresses the issue of reversibility, an important clinical distinction. Additional distinctions are needed, however, for example, "progressive" versus "stable," and "continuous" versus "episodic." Having a relentlessly progressive cognitive decline, as is the case for Alzheimer's disease, is clearly worth distinguishing from cognitive impairment with traumatic brain injury that, although chronic and disabling, may not progress. The cognitive impairment observed with schizophrenia is clearly disabling for many patients, but tends to be stable and continuous over time. Cognitive impairment is also seen with affective disorder, but, here, it tends to be episodic over time, with return to a relatively normal baseline between episodes, in keeping with the periodicity of these disorders. All of these distinctions are useful both to clinicians and to patients. A diagnostic nomenclature should provide a balanced perspective and appreciation for the full range of clinical phenomenology in the various mental disorders, and should also recognize important distinctions having to do with the pattern of symptomatology over time.

CONCLUSIONS

As the classification of "cognitive" disorders is reconsidered in the development of DSM-5, it may be useful to rethink the long-standing distinction made between primary "cognitive" disorders and primary "behavioral" disorders. Although this distinction may be worth preserving, it would be useful to recognize that there is considerable overlap in symptoms across these disorders, with "cognitive" disorders having behavioral features and "behavioral" disorders having cognitive features. Minimizing these features is a disservice to patients and their families and may discourage research and drug development into these important aspects of each. In recent years, drug research has expanded into targeting both the behavioral features of Alzheimer's disease, a primary "cognitive" disorder, and the cognitive features of schizophrenia, a primary "behavioral" disorder. As DSM-5 is developed, it will be important to acknowledge the full range of symptoms in each of these cognitive and behavioral subgroups, as well as other useful distinctions characterizing patterns of symptoms, for example, "acute" versus "chronic,"

"progressive" versus "stable," and "continuous" versus "episodic." These distinctions have both research and treatment implications.

Previous presentation: American Neuropsychiatric Association, 21st Annual Meeting, Tampa, FL, March 17–20, 2010.

Dr. Laughren is affiliated with the Food and Drug Administration, Silver Spring, MD. However, Dr. Laughren's contribution to the paper was made in his private capacity. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

References

1. *http://dsm5.org/pp/Default.aspx*
2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, D.C, American Psychiatric Association, 2000
3. Paulsen JS, Ready RE, Stout JE, et al: Neurobehaviors and psychotic symptoms in Alzheimer's disease. J Int Neuropsychol Soc 2000; 6:815–820
4. Heinrichs RW, Zakzanis KK: Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 1998; 12:426–445
5. Green MF: What are the functional consequencesof neurocognitive deficits in schizophrenia? Am J Psychiatry 1996; 153: 321–330
6. *http://www.matrics.ucla.edu*
7. *http://www.ipa-online.orgipaonlinev3/ipaprograms/taskforces/bpsd/intro.asp*
8. *http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Psychopharmacologic*
9. Finkel SI, Burns A, Cohen G: Overview, in Behavioral and psychological symptoms of dementia (BPSD): a clinical and research update. Int J Psychogeriatr 2000; 12(suppl1):13–18
10. Laughren TP: A regulatory perspective on psychiatric syndromes in Alzheimer's disease. Am J Geriatr Psychiatry 2001; 9:340–345
11. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm*
12. Buchanan HW, Davis M, Goff D, et al: A summary of the FDA-NIMH-MATRICS Workshop on Clinical Trial Design for Neurocognitive Drugs for Schizophrenia. Schizophr Bull 2005; 31:1–15
13. Mitchell AJ, Shiri-Feshki M: Rate of progression of mild cognitive impairment to dementia: meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 2009; 119:252–265

Note of Attribution

In the article "Within-Session Mood Changes From TMS in Depressed Patients," by Tobias Dang, David H. Avery, and Joan Russo (*J Neuropsychiatry Clin Neurosci* 2007; 19:458–463), the name of a co-author/contributor, Walid Fawaz, M.D., was inadvertently omitted. The journal and co-authors regret this omission.