

Cognitive Dysfunction in Major Depressive Disorder: FDA's Perspective, Past and Present

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What is “Pseudospecificity”?

- This term was coined during a January, 2001 Advisory Committee meeting.
 - Is “agitation” an acceptable clinical target for the development of intramuscular antipsychotic drug products?
- Two types of clinical entities are appropriate targets for claims
 - Specific diseases or syndromes (the usual focus of drug claims)
 - Nonspecific signs or symptoms not unique to a single disease or syndrome

Critical to this approach to gaining a new claim is the concept of pseudospecificity. In this context, since the essence of this type of claim is that the symptom is nonspecific, i.e., 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, since such a claim would give the impression that the symptom is specific to that disease.**

Pseudospecificity—Examples

- Demographic subgroup
 - Depression in women, post traumatic stress disorder in men
- Comorbid condition
 - Post-stroke depression
- Non-specific symptom
 - Back pain
- Symptom or symptom cluster of a DSM-5-defined syndrome
 - Hallucinations in schizophrenia
 - ? Cognitive dysfunction in major depressive disorder (MDD) ?

Why would we consider Cognitive Dysfunction in MDD to be pseudospecific?

- Depressed mood most of the day, nearly every day
- Diminished interest or pleasure in most activities
- Significant weight change or change in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive/inappropriate guilt
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death or suicidal ideation

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Progress Happens

- Academic and industry investigators continue to explore this issue.
- Evidence mounts that, perhaps, current treatments do not always adequately address cognitive symptoms in MDD.



American Society of Clinical Psychopharmacology Annual Meeting

- Workshop entitled, “Cognitive deficits in depression: What are they? Are they independent dimensions? Are they targets for treatment?”
 - Clinical characteristics
 - Methods of assessment
 - Effects of treatment
 - Impact on functional outcomes
- FDA participated as a discussant
- End result: FDA’s position moved from “no” to “maybe”

Gathering Information

- Additional workshops:
 - Massachusetts General Hospital Psychiatry Academy
 - Institute of Medicine
- Following the IOM meeting, the Division began a collaboration with NIMH.
 - Expertise without financial conflicts
 - Good fit with RDoCs group
 - Research Domain Criteria
 - Research framework for studying mental disorders



FDA-NIMH Collaboration

- Issues the Division hoped to resolve:
 - What domains of cognition are most relevant to MDD?
 - What are the best tools for assessing those domains?
 - Do changes on objective ratings of cognitive function measure clinically meaningful constructs, or are functional endpoints necessary?
 - Objective and subjective measures of cognitive function can be divergent for a number of reasons—is one or the other more reliable or relevant? If both are necessary, how do we reconcile disparate ratings?
- Goal: Develop a framework for regulatory decision making without being overly prescriptive.

FDA-NIMH Collaboration

- FDA now intends to incorporate information provided by NIMH into its regulatory decision making.
 - What information can be gleaned from different study designs?
 - Add-on study for adjunctive claim.
 - What can a monotherapy study tell us?
 - Is superiority to placebo enough? Or is superiority to an active comparator necessary?
 - Should a functional co-primary or secondary measure be required?
 - The “appropriate” design in any given case will depend on a number of factors, including proposed mechanism of action of new drug.

Today

- The Division was still considering these issues when the first supplemental application seeking a claim for treatment of cognitive dysfunction in MDD was received.
 - Need to understand current state of evidence to inform our decision making on any application
 - If we are going to change our approach to cognitive dysfunction in MDD, we want to have this discussion in a public forum.
- Morning AC is separate from afternoon AC, but will clearly inform the discussion.