

Regulatory Challenges in Targeting Cognitive Impairment in Depression

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Current & Past Consulting Relationships

- Part time employee of MGH CTNI
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- Consultant to ERT, MedAvante, Salamandra
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Regulatory Challenges in Targeting Cognitive Impairment in Depression

- Defining cognitive impairment in depression
- Developing approaches to measurement
- Pseudo-specificity
- Models for drug development targeting cognitive impairment in depression

What is cognitive impairment in depression?

- Cognitive impairment is not prominently included among the symptoms defining MDD in DSM-V
 - Except for “diminished ability to think or concentrate, or indecisiveness...”
- Is there a consensus definition of “cognitive impairment in depression”?
- What aspect of cognitive impairment would be the target of a treatment development program (cognitive impairment broadly or more specific domains)?

Primary Regulatory Challenge in Targeting
a Domain or Symptom Considered Part
of a DSM-Defined Syndrome:
Pseudo-Specificity

- What is pseudo-specificity?
- Do regulatory agencies ever accept targeting domains or subgroups of defined syndromes?
- Approaches to overcoming regulatory concern that claim is pseudo-specific

What is pseudo-specificity?

- Potentially artificially narrow claim
- Examples:
 - Demographic subgroup, e.g., depression in women, or in elderly
 - Symptom, or symptom cluster, of defined DSM syndrome, e.g., hallucinations in schizophrenia
 - Comorbid condition, e.g., depression with cardiovascular disease, post-stroke, Parkinson's disease, dementia
 - Specific example of non-specific symptom, e.g., dental pain

Regulatory agencies initial rejection of claim as
“pseudo-specific” might be considered
a “straw man” position

- Objection may be overcome with arguments and data to show validity and value of targeting a particular domain or subgroup of an established syndrome

CIAS: Example of successful establishment of domain within schizophrenic syndrome

- CI is a well-established aspect of schizophrenia
- CI is not well addressed by available treatments
- CI has different time course than positive symptoms of schizophrenia
 - Present even before onset of psychosis
 - Still present in “residual” phase of illness
- Regulatory agencies have endorsed CIAS as legitimate target for drug development

Other Domains Within DSM Defined Syndromes that FDA has Accepted as Legitimate Targets for Drug Development

- Negative symptoms of schizophrenia
- Suicidal ideation and behavior in schizophrenia
- Agitation in schizophrenia and bipolar disorder
- Irritability of autism
- Impulsive aggression in ADHD
- Agitation/aggression in dementia

Domains Within DSM Defined Depression that are Under Consideration as Possible Legitimate Targets for Drug Development

- Cognitive impairment associated with depression
- Irritability associated with depression
- Fatigue associated with depression
- Amotivation, apathy

Approaches to overcoming regulatory concern that claim is pseudo-specific

- Provide evidence that available drug treatments in the class (e.g., antidepressants) do not address the domain in question
 - Little to no effect of available drugs on this domain
 - Residual phase of illness with persistence of symptoms in this domain
 - Evidence for subtype of disorder, with prominence of symptoms in this domain, and that is not responsive to antidepressants
- Is this type of evidence available for cognitive impairment in depression?

Possible Models for Demonstrating Specificity of a Particular Drug for Treating this Domain

- Adjunctive study targeting cognitive impairment in residual phase depression
- Acute phase study comparing 2 antidepressants on cognitive impairment
- Switching study in residual phase depression showing benefit on cognition in switching to another antidepressant

Adjunctive design targeting cognitive impairment in residual phase depression

- Must show that new drug adjunctively treats only this domain
 - If the added drug improves depression overall, it is likely to be considered an adjunctive antidepressant
 - Recent example: adjunctive lisdexamfetamine improved BRIEF-A GEC T score, but also MADRS

Acute phase study comparing 2 antidepressants on cognitive impairment

- Must show that new antidepressant superior to standard antidepressant on this domain alone
 - Both drugs would need to be shown to be active as antidepressants (i.e., superior to placebo on broad depression scale)
 - Superiority on cognition could mean new drug beats placebo on cognition and active control does not
 - Recent example: CONNECT Study for Vortioxetine; differential benefit on cognition vs duloxetine

Switching study in residual phase depression showing benefit on cognition in switching to another antidepressant

- Would involve patients in residual phase of depression but having clinically important residual cognitive impairment
- Would need to show that antidepressant response is maintained during switch, but cognition improves once patients are switched to new antidepressant
- Potential problem: interpretation of superiority on cognition still not clear, since new drug may simply have a lesser effect on impairing cognition

Likely Additional Regulatory Challenge: Must Show Benefit on Functional Co-Primary Measure

- A carry-over from Alzheimer's disease requirements
- Regulatory concern is clinical relevance of small benefit on cognitive measure
- CIAS trials programs all required to have co-primary functional measure (proxy measure considered acceptable)

Other Questions

- To what extent is cognitive impairment in depression a result of antidepressant treatment?
 - Bolling, et al (2004): SSRI emergent cognitive Sx in MDD patients (loss of memory-14%; loss of concentration-16%)
- Does cognitive impairment in depression diminish responsiveness to antidepressants?

Summary

- Regulatory agencies are not fundamentally opposed to considering targeting domains of defined DSM syndromes, including cognitive impairment in depression
- But there is a need to come prepared with strong arguments and data to support narrowly targeting such domains

Questions for Panel

- Question: Are regulatory agencies ready to recognize CI in MDD as a legitimate target for drug and device development?
- If so,
 - What are the pathways going forward?
 - What domains of CI should be targeted?
 - What assessments are optimal for measuring these impairments?
 - What populations would be optimal for studies?
 - Enrichment for cognitive impairment?
 - What study designs would be useful in showing benefits of treatments in a way that addresses regulatory concerns about pseudo-specificity?
 - What specific claims would be supported by such studies?
- Can cognitive impairment (or specific domains of cognitive impairment) be considered as legitimate clinical targets across DSM syndromes?