Regulatory Challenges in Targeting Cognitive Impairment in Depression

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Current & Past Consulting Relationships

- Part time employee of MGH CTNI
- Consultant to NIMH
- Consultant to AbbVie, Acadia, Alcobra, Astra Zeneca, Camurus, Cerecor, Corcept, Curemark, Dart NeuroScience, Delpor, Edgemont, EnVivo, Fabre Kramer, Gedeon Richter, Janssen, JDS Therapeutics, Lilly, MAPS, Medgenics, Naurex, Neuren, Neurocrine Biosciences, Noven, Omeros, Pfizer, Retrophin, Reviva, Roche, Shire, Spinifex, Sunovion, Taisho, Targacept, Teva, Theravance, Tonics, Transition, Zogenix
- Consultant to ERT, MedAvante, Salamandra
- Consultant to Quinn Emanuel, Ulmer & Berne, King & Spalding

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

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

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

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)

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?