Regulatory Issues in Targeting Cognitive Impairment in Depression

Thomas Laughren, M.D.
Director, Regulatory Affairs
MGH CTNI

Current Financial Relationships

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

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”?
- Does the profile of impairment differ from that seen in other disorders, e.g., schizophrenia?

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?

Demonstrating Response 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 showing 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
- But there is a need to come prepared with strong arguments and data to support narrowly targeting such domains
- Question for today: Is cognitive impairment in depression a legitimate target for drug development?