Special Challenges: Bipolar and Epilepsy

Challenges in Study Design:
What Needs to be Done to Move Things Along

Industry Perspective Discussants

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Disclosures

• Discussants are employees of Sunovion Pharmaceuticals
Cognitive endpoints are infrequent in bipolar disorder trials

**ClinicalTrials.gov**

*Condition = “bipolar”*

*Sponsor = “Industry”*

*Phase = 2 or 3*

188 clinical trials

- only 7 trials reported with neurocognitive endpoints (asenapine, ziprasidone, and EPO)
  - only as secondary endpoints

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trials</th>
</tr>
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<tbody>
<tr>
<td>quetiapine</td>
<td>27</td>
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<tr>
<td>aripiprazole</td>
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<td>ziprasidone</td>
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<td>asenapine</td>
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<td>risperidone</td>
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<td>lurasidone</td>
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<td>lamotrigamine</td>
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<tr>
<td>licarbazepine</td>
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</tbody>
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Number of clinical trials (cumulative)

Year initiated

- 2000
- 2002
- 2004
- 2006
- 2008
- 2010
- 2012
- 2014
The magnitudes of cognitive improvements are small relative to impairment, regardless of disorder or treatment.

- Magnitude of effect sizes reported for cognitive improvements is always small.
- Attempts to improve cognition are much smaller than the impairments.
- The consequences of small and uncertain effect sizes is evident in the (large) scale and (high) risk of industry-sponsored clinical development.
Replication is a challenge for registering cognition drugs – confidence around underlying effect size

- hyperbolic relationship Enrollment vs. Effect Size
- curve is punishingly steep at the low effect sizes
- size of effect uncertain after a Phase 2 result
- if the true effect size is poorly estimated in Phase 2 studies, the subsequent replication studies are at risk

**Lurasidone 160mg vs. placebo 6-weeks**

*Eur Neuropsychopharm, 2013*
Industry perspective on challenges – developing treatments for cognitive impairment

• Very large investments have failed even in the face of
  – plausible mechanism or evidence for preclinical behavioral effects, preclinical validation in animal models
  – favorable clinical checkpoints of target engagement confirmation in man, modulation of cognitive impairment biomarkers/neuroimaging
  – safety demonstrated in Phase I studies
  – positive initial POCs

• Replication is a unique challenge to industry
  – uncertainty around small effect sizes elevates statistical risk
  – economic consequences of all-or-nothing investments

• Regulatory pathway/requirements for cognitive endpoints and indication in bipolar disorder need to be better defined

• HCP and payer acceptance is somewhat unclear
Searching For New Procognitive Agents In Bipolar Disorder: What Are We Looking For?

• Preclinical requirements (2-4 years)
  – good discovery science/MOA
  – drug-like characteristics attuned to CNS
  – safety toxicology
  – preclinical biomarkers of target engagement

• Phase 1 approach (1-2 years)
  – early tolerability/safety demonstrated in NHV/patients
  – preliminary therapeutic dose range (including min/max dose)
  – translational biomarkers (qEEG, ERPs, fMRI, PET, PSG)

• Phase 2 transitions (~2.5 years)
  – initial open-label study demonstrating "signal" (2a)
  – POC study – fairly rigorous demonstration of effect vs control (2b)
  – dose ranging studies (2b/3)
Searching For New Procognitive Agents In Bipolar Disorder: What Are We Looking For?

• Phase 3 and beyond (3+ years)
  – confirmatory trials to clearly and consistently demonstrate both statistically and clinically relevant effects
  – secondary endpoints showing effects on multiple domains of outcome (eg employment, educational, interpersonal), quality of life, cost-effectiveness

• Cognitive remediation approaches

• Will payers support such an agent based on clinical trial evidence and “real world” effectiveness?
  – restrictions on use (eg ”fail first”/eligible populations/duration of therapy etc)

• Assessment of response to treatment/clinical dilemmas
Searching for New Procognitive Agents in Bipolar Disorder

• Registration study design?
  – guidance document/academic consensus publication
  – cognitive test battery; pencil and paper vs electronic
    • cognitive endpoints-- composite or specific domain(s)
  – functional co-primary assessment
  – validated translations for international use
  – study duration

• Cognitive/functional impairment at baseline?
  – Change from premorbid level of cognitive functioning
  – severity cut-off
  – how to control practice effects

• Stable vs symptomatic patients?
  – criteria for stability (eg time since stabilized; severity thresholds for depressive/manic sx)
    • can acutely symptomatic (depressed/manic) populations be utilized?
    • treatment-resistant patients
What Are The Implications of This Statement?

- “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”.