AGITATION IN DEMENTIA

BEHAVIORAL AND PSYCHIATRIC SYMPTOMS IN DEMENTIA (BPSD)
AGITATION SUBGROUP SESSION

20TH FEBRUARY 2018.
BRIEF OVERVIEW: AGITATION ASSOCIATED WITH ALZHEIMER’S DISEASE (AD)

• AD afflicts an estimated 50 million people worldwide, a number that is expected to double in 20 years.

• Agitation and aggression seen in approximately 45% of AD patients during 5-year period.

• Characterized by emotional distress, aggressive behaviors, disruptive irritability, disinhibition, and caregiver burden.

• Associated with:
  • Accelerated cognitive decline
  • Earlier nursing home placement
  • Increased mortality

• No approved medication = unmet medical need.
SEVERAL PERSPECTIVES ON AGITATION

• Several Perspectives on Agitation
  • Physician
  • Caregiver
  • Nursing
  • Researchers
  • Regulatory Bodies

• Lack of consensus on definition of agitation and how to measure it

• Must be able to define clinical condition in order to construct clinical population
AGITATION TREATMENT: UNMET NEED

• No approved treatments for agitation in AD
• Commonly used agents pose management challenges
  • Antipsychotics
    • Impaired cognition
    • Stroke, death
    • Metabolic syndrome
  • SSRIs
    • Impaired cognition
    • QTc prolongation
## DRUG DEVELOPMENT IN AD AGITATION

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sponsor</th>
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</thead>
<tbody>
<tr>
<td>AXS-05 (dextromethorphan/bupropion)</td>
<td>Axsome Therapeutics</td>
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<tr>
<td>ITI-007 (lumateperone)</td>
<td>Intracellular Therapies</td>
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<tr>
<td>AVP-786 (DM/Q)</td>
<td>Avanir</td>
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<tr>
<td>Escitalopram</td>
<td>Hopkins/NIH</td>
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<tr>
<td>Brexpiprazole</td>
<td>Otsuka</td>
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<tr>
<td>ORM-12741</td>
<td>Orion/Janssen</td>
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<td>Drobaninol</td>
<td>Hopkins/McLean</td>
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<tr>
<td>Prazosin</td>
<td>ADCS</td>
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<tr>
<td>Lithium</td>
<td>NY State Psychiatric Institute</td>
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<tr>
<td>Mirtazapine or carbamazepine</td>
<td>U Sussex; UK</td>
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<tr>
<td>Nabilone</td>
<td>Sunnybrook Health Science Center, CA</td>
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CONSENSUS IS NEEDED TO FACILITATE DRUG DISCOVERY

- IPA Agitation Definition
- Rating Scale to Determine Severity
- Intervention
- Outcomes Assessment

Criteria to define study population
NPI/CMAI/Other
Psycho-social or Pharmaceutical
Primary endpoint
THE OBJECTIVES OF THE WORKING GROUP

• Develop a plan to gain consensus on drug development in AD agitation

• Confirming our points of agreement

• Identifying the gaps in the white paper
  • What are the areas of disagreement with regard to agitation associated with AD

• Use the white paper as an initial approach to gain consensus across stakeholders

• Build on from the white paper to plan a consensus meeting

• The white paper and the consensus meeting, in composite, can provide a roadmap for drug development
## Status of the White Paper

### Key Sections Identified

<table>
<thead>
<tr>
<th>Key Sections</th>
<th>Leads Assigned</th>
<th>Timelines/Deliverables</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intro/Unmet Need/Disease State/Prevalence &amp; Burden/Current Treatment issues (off-label, box warning etc.)</td>
<td>Nanco Hefting/Tom Shiovitz/Anna Eramo/Hans Moebius</td>
<td>2018 (July 1)</td>
</tr>
<tr>
<td>2. Clinical Development Experience to date (what have we learned?/why no drugs approved to date?)</td>
<td>Cedric O’Gorman/Sanjay Dube</td>
<td>2018 (July 1)</td>
</tr>
<tr>
<td>3. Scales, Assessments and Outcomes</td>
<td>Paul Rosenberg/Ariana Anderson</td>
<td>2018 (July 1)</td>
</tr>
<tr>
<td>4. Clinical Trial design features (patient pop; durations; maintenance of effect, symptoms; inclusion / exclusion; length of study, arms, placebo)</td>
<td>Sanjay Dube/Franco Dicesare/Cedric O’Gorman</td>
<td>2018 (July 1)</td>
</tr>
<tr>
<td>5. Novel approaches/biomarkers</td>
<td>George Grossberg/Rita Khoury/Larry Ereshefsky</td>
<td>2018 (July 1)</td>
</tr>
<tr>
<td>6. US &amp; Global Regulator Perspective</td>
<td>Saima Khan/Monique Carter</td>
<td>2018 (July 1)</td>
</tr>
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NEXT STEPS FOR THE WORKING GROUP

• Consider bringing more members from academia into the working group

• Complete drafting of the different sections under the guidance of identified leads

• Combine the sections into a white paper

• Publication Plan including publication of white paper
  • Consider target journals (and potential conference presence)

• Plan potential consensus meeting
  • Late 2018 – Early 2019?

• Position Paper/Guidance stemming from consensus meeting
RECENT EVENTS & POINTS FOR DISCUSSION

• FDA Mini-Symposium on BPSD February 8th

• NIMH 3.0 – Neurocircuitry underlying AD agitation? Biomarkers?
  • High P-Tau/Tau Ratio is Associated with Agitation
  • Agitated Patients Have More Neurofibrillary Tangles in the Frontal Cortex

• *Early Alzheimer’s Disease: Developing Drugs for Treatment – Draft FDA Guidance for Industry*

• PIA ISTAART initiatives (Neuropsychiatric Symptoms)

• European Perspective, European Survey and New Alzheimer’s Disease Guidance

• Engagement/Participation: Who else? And how?

• Other issues that the Agitation in Dementia BPSD sub-group should tackle?