



# AGITATION IN DEMENTIA

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

20<sup>TH</sup> 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

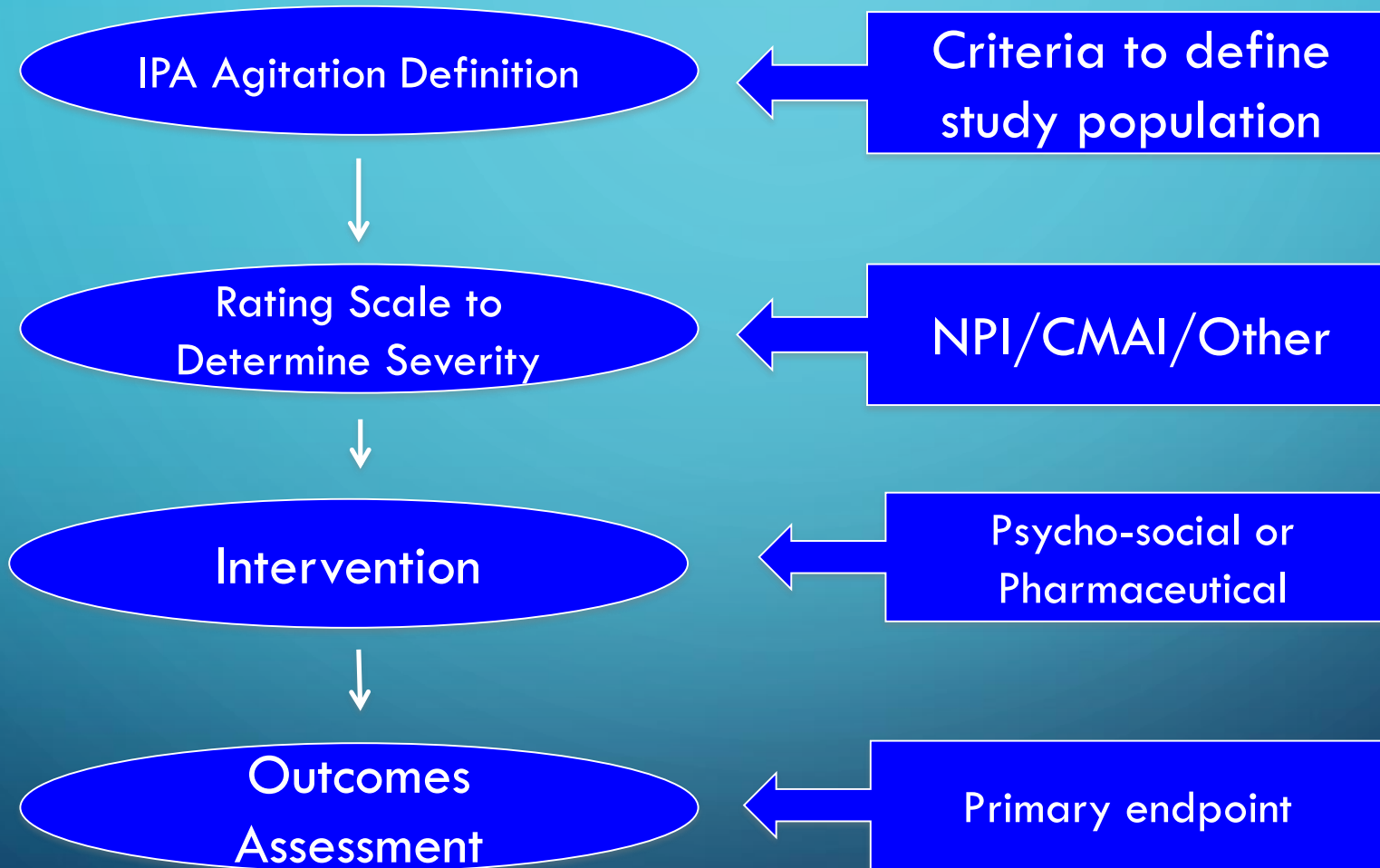
# AGITATION TREATMENT: UNMET NEED

- 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

Agent	Sponsor
AXS-05 (dextromethorphan/bupropion)	Axsome Therapeutics
ITI-007 (lumateperone)	Intracellular Therapies
AVP-786 (DM/Q)	Avanir
Escitalopram	Hopkins/NIH
Brexpiprazole	Otsuka
ORM-12741	Orion/Janssen
Drobaninol	Hopkins/McLean
Prazosin	ADCS
Lithium	NY State Psychiatric Institute
Mirtazipine or carbamazepine	U Sussex; UK
Nabilone	Sunnybrook Health Science Center, CA

# CONSENSUS IS NEEDED TO FACILITATE DRUG DISCOVERY



# 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	LEADS ASSIGNED	TIMELINES/DELIVERABLES
1. Intro/Unmet Need/Disease State/Prevalence & Burden/ Current Treatment issues (off-label, box warning etc.)	NANCO HEFTING/TOM SHIOVITZ/ANNA ERAMO/HANS MOEBIUS	2018 (JULY 1)
2. Clinical Development Experience to date (what have we learned?/why no drugs approved to date?)	CEDRIC O’GORMAN/SANJAY DUBE	2018 (JULY 1)
3. Scales, Assessments and Outcomes	PAUL ROSENBERG/ARIANA ANDERSON	2018 (JULY 1)
4. Clinical Trial design features (patient pop; durations; maintenance of effect, symptoms; inclusion / exclusion; length of study, arms, placebo)	SANJAY DUBE/FRANCO DICESARE/CEDRIC O’GORMAN	2018 (JULY 1)
5. Novel approaches/ biomarkers	GEORGE GROSSBERG/RITA KHOURY/LARRY ERESHEFSKY	2018 (JULY 1)
6. US & Global Regulator Perspective	SAIMA KHAN/MONIQUE CARTER	2018 (JULY 1)



# 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 8<sup>th</sup>
- NIMH 3.0 – Neurocircuitry underlying AD agitation? Biomarkers?
  - High P-Tau/Tau Ratio is Associated with Agitation<sup>1</sup>
  - Agitated Patients Have More Neurofibrillary Tangles in the Frontal Cortex<sup>2</sup>
- *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?

1. Guadagna S, et al. *Neurobiol Aging* 2012; 33: 2798-2806.

2. Tekin et al, *Ann Neurol* 2001; 49: 355-361.