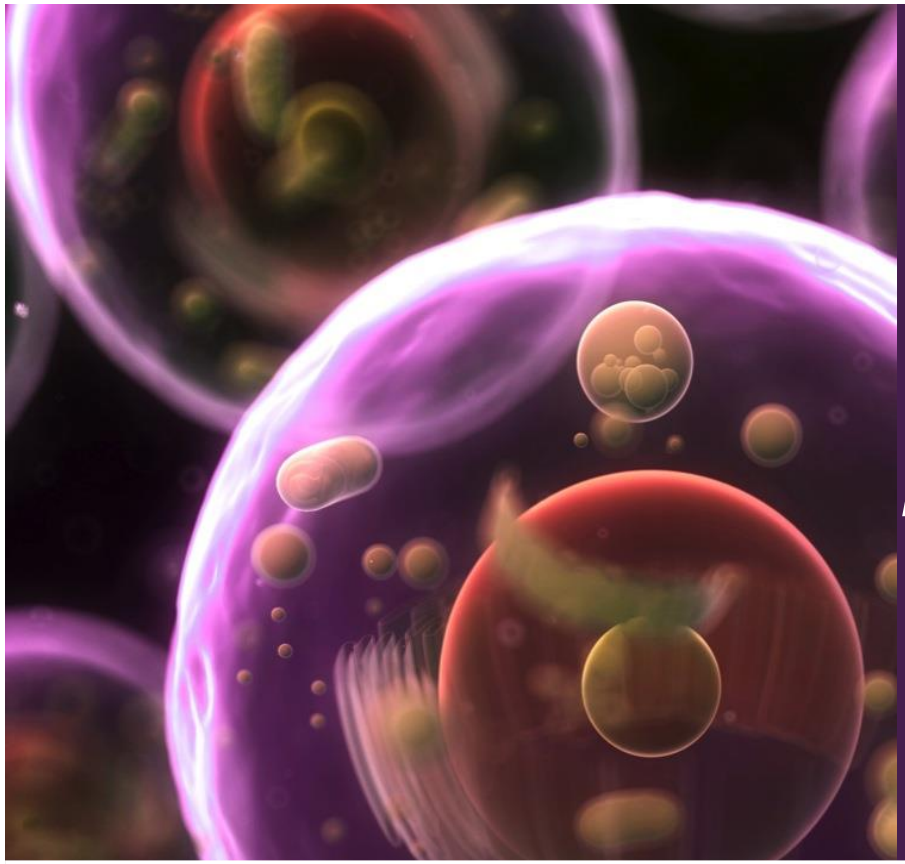
ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

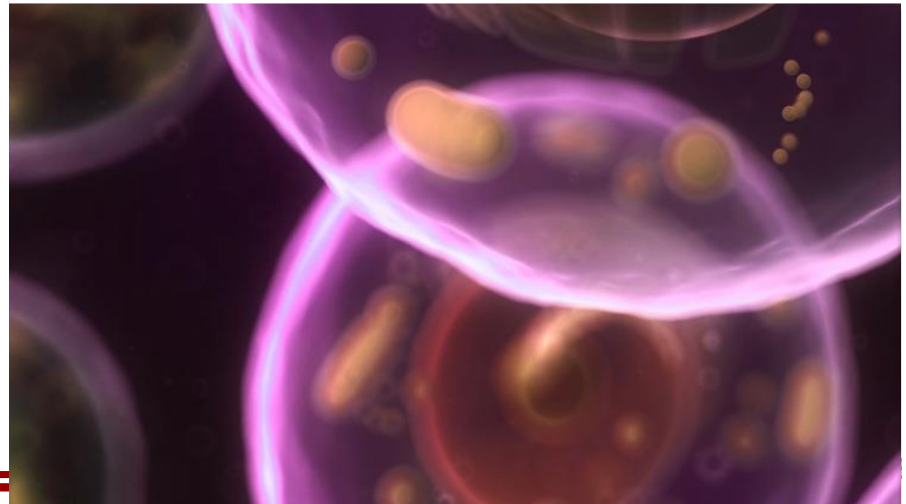
BPSD Working Group Report

- **Introductions**
- **Background** (Larry Ereshefsky, co-chair)
- **Briefing on EMA Alzheimer's Disease Workshop session on BPSD**
  - Luca Pani, co-chair (IMA/EMA)
  - Rachel Schindler (Pfizer Inc)
- **Update on activities of AAIC PIA and opportunities to collaborate**
  - David Miller, co-Chair (PIA, AAIC)
- **Objectives of the Working Group**
- **Focus on Alzheimer's Disease or broader topic of Dementia?** Jill Rasmussen (ASENT)
- **Discuss topic prioritization and focus of WG**
- **Next steps**
  - ISCTM meeting in Europe

Briefing information provided to participants used to ‘jump-start’ discussions (double click to open)



WORKING GROUP: BEHAVIORAL AND PSYCHIATRIC SYMPTOMS IN DEMENTIA



Co-chairs

Larry Ereshefsky

David Miller

Luca Pani **(not attending)**

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Discussion PIA (ISTAART)-ISCTM

- Differentiation from PIA NPS (Neuropsychiatric Symptoms)
  - 500 members, established 2010
  - Academia/Pharma
  - Focused on review/analysis of state of the art, publications on various domains
  - Supporting innovation in treatment of NPS
- ISCTM is complementary, i.e., focus on methodology/study designs/endpoints/statistical; well integrated regulatory involvement; application of biomarkers/cutting edge technologies; and action oriented approaches to 'problem solving' (consensus conferences, white papers, public-academic-private symposia)
- Activities might include joint planning sessions, future symposia supported by both groups at AAIC, ISCTM, and related Alzheimer's Meetings

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Objectives

- Focus down on achievable scope
- Low hanging 'fruit'
  - Identify 1 or 2 relevant syndromes to focus upon, i.e., Sleep disorders in dementia
  - Learning from current clinical trials (Agitation)
  - Applying lessons learned from Regulatory progress in Negative symptoms, CIAS, Agitation, and recent FDA discussions identifying 'depression in dementia'
- Developing a framework to characterize relevant symptoms (data sharing from pharma, i.e., pooled data from 'older' acetylcholinesterase inhibitors)
  - Factor and Cluster analyses – requires statistician involvement (offers from Pfizer and JnJ to assist)
  - Describe symptom progression across severities of Dementia, including pre-dementia Alzheimer's; prognostic value of behavioral symptoms early in disease to predict declines
- Look at existing assessment tools
  including recently developed approaches

Written Statement for FDA Advisory Committee Meeting on Drug Development for Treating Psychiatric Disturbances Associated with Dementias

Submitted by Jeffrey L. Cummings, M.D., Director, Alzheimer's Disease Center; UCLA School of Medicine

I. Introduction

The Food and Drug Administration (FDA) Division of Neuropharmacological Drug Products (DNDP) provided an issues paper (March 9, 2000) framing the discussion for the meeting of the Psychopharmalogic Drugs Advisory Committee on the Various Psychiatric and Behavioral Disturbances Associated with Dementia. The issues paper focuses on the information necessary for drug approval; specifically that: 1) the condition be identified and defined unambiguously; 2) appropriate instruments be used for assessment and measurement of the condition; and 3) appropriately designed clinical trials demonstrate efficacy and effectiveness. The current meeting of the Advisory Committee will emphasize the first of these --- to promote clear and unambiguous definitions of psychiatric and behavioral disturbances associated with dementia that may be appropriate targets for drug therapy.

In this response, a series of related points are made that lead to recommendations regarding the definitions of major neuropsychiatric symptoms of dementia. Responses to the concept of Behavioral and Psychological Symptoms of Dementia (BPSD) and to the recent editorial by Dr. Jeste and Finkel (Am J of Geriatric Psychiatry 2000; 8:29-34) suggesting diagnostic criteria for psychosis of Alzheimer's disease are offered.

- (double click doc to read, arrow keys to scroll)

Areas of focus, to be further discussed, decided

Focus on Alzheimer's Dementia or the broader Dementia category? No clear consensus reached at WG meeting, to be followed up in first WG TC.

Focus on Symptomatic dementia , or also on pre-dementia diagnostic groups? To be followed up in first WG TC

Several suggested steps (Terry Fullerton/others):

1. Rank order 'need'
2. Focus on dementia first
3. Define populations for Regulatory Process
4. Apply advances in brain science, Neurocircuitry/RDoC, and 'Neurofunctional domain strategies'; Imaging technologies (PET: Tau, Amyloid, Inflammatory; MRI: fMRI, ASL, sMRI

Debate about the need to better characterize and understand neurobiology…many believe we should champion use of neurocircuitry (LE, Terry), and targeted neurobehavioral paradigms to inform:

1. Drug development and translational neuroscience strategies
2. To enrich populations for trials
3. Consideration of companion 'diagnostics'
4. Illustrative domain anhedonia/reward/apathy

Study design considerations to be discussed

Stage of illness

Assessment tools and endpoints

Sensitivity and specificity of assessments (ratings scale, neurocircuitry)
Ceiling or floor effects depending on stage of illness
Address pseudospecificity, measuring memory, function, and BPSD; Inter-relationships and Regulatory implications

Realistic inclusion/exclusion criteria

Enriched population selected by observed behaviors/scales or by biomarker/neurocircuitry?

Non-pharmacological interventions, how to include this important area, yet not dilute drug development focus?

- Given reports of efficacy for many symptoms how might this affect 'drug readouts' from trials?

Study design considerations to be discussed

NEXT steps:

Disseminate these slides to WG; seek email comments from the WG

Schedule first of a series of recurring calls

Decide on focus based on discussions held at WG in DC

Establish smaller subgroups to develop recommendations addressing the identified items

Identify 2 statisticians to join the WG (pending)

Explore feasibility of pooled data from prior dementia trials from pharma (non-competitive)

Plan for a WG meeting in Amsterdam