Working Group:
Behavioral and Psychiatric Symptoms in Dementia

Co-chairs
Larry Ereshefsky
David Miller (via TC)
Luca Pani
• Introductions
  BPSD Working Group Objectives (5 minutes)

• Identify a session secretary

• Abbreviated report from 2nd meeting in August 2015, Amsterdam; update on survey results from Summer 2015 (10 minutes)

• Update on NPS PIA activities and trials for behavioral syndromes (10 minutes) David

• Developing a program proposal
  • Identifying smaller working groups to move our process forward
  • Content experts (academic, industry, regulatory)
  • Topic focus
  • Lessons learned/challenges
From Amsterdam WG; Substantive Congruence with Washington DC

- Focus down on achievable scope – launch the planning process for a program on Treatment of BPSD: Methodological Challenges and Considerations
  - Lessons learned from current clinical trials (Agitation), but not necessarily make agitation the ‘focus’ of our program
  - Other lessons learned from Regulatory progress in other CNS indications, i.e., Negative symptoms, CIAS, Agitation, and ‘depression in dementia’
- Methodological Issues: Developing a framework to characterize symptoms
  - Describe symptom progression across severities of Dementia,
  - Prognostic value of behavioral symptoms early in disease to predict declines
  - Incorporate Neurocircuitry/biomarkers strategies, as applicable
  - Statistical considerations to support syndromal treatment targets
    - Validity considerations, Factor/Cluster analyses
- Look at existing assessment tools and assess/recommend approaches
  Identify 1 or 2 relevant syndromes to apply study principles i.e., Apathy, Sleep disorders in dementia
### BPSD Working Group Survey

<table>
<thead>
<tr>
<th>Details</th>
<th>Count</th>
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<tbody>
<tr>
<td>37 Recipients</td>
<td></td>
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<tr>
<td>19 Responses</td>
<td></td>
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<tr>
<td>1 bounceback</td>
<td></td>
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<td>51% response rate</td>
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</table>

Additionally 25 discussants at Amsterdam Working Group
Terminology to use: BPSD vs NPS

<table>
<thead>
<tr>
<th>Answer Options</th>
<th>Response Percent</th>
<th>Response Count</th>
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<tbody>
<tr>
<td>BPSD</td>
<td>67%</td>
<td>33</td>
</tr>
<tr>
<td>NPS</td>
<td>33%</td>
<td>16</td>
</tr>
</tbody>
</table>

answered question 49
skipped question 0
All dementia with neurodegenerative processes linked to clinically relevant behavioral and psychiatric symptoms, i.e., Lewy Body, FTLD, Parkinson’s Disease, and etc.

MCI-AD ‘spectrum’

Alzheimer’s Dementia

Rank order the patient populations with dementia we should initially focus upon in our Working Group: 1 being the best group through to 4, of lowest priority.
Which symptom/symptom cluster should be our focus: Combined highest priority 1+2 (DC + Amsterdam)

- Pain
- Psychosis
- Apathy/Motivation/Anhedonia
- Agitation/Aggression
- Anxiety disturbances
- Sleep disturbances
- Depression/Affective Disturbances

Bar chart showing

- Pain: 6
- Psychosis: 5
- Apathy/Motivation/Anhedonia: 13
- Agitation/Aggression: 13
- Anxiety disturbances: 1
- Sleep disturbances: 1
- Depression/Affective Disturbances: 11
The mechanism of action of the medicinal product would be relevant and specific for the treated neuropsychiatric symptoms.

An indication “requires reliable and valid measurement tools for the studied patient population”

Study design and methodologies; study design considerations for ‘stand-alone’ indications should be evaluated in separate dedicated trials.

What is the specificity of endpoints now available and in development (as reflected in drug mechanism, pathophysiology, and inter-relationship with other symptoms);

Utility of specified cut-offs at entry to select and enrich the population
Do any attendees have an update or info on current trials as well as those that have recently completed, i.e., failed or succeeded?
Results from « recent » RCTs

- 2008-2014: **14 completed RCTs** of drugs for A/A in AD
  - Lessons learned from large number of trials
    - Pharma, Regulatory, and Academic perspectives

- 1 RCT with no reported results
- 10 RCTs did not report greater benefit from drug than placebo
- 3 RCTs reported greater benefit from drug than placebo:
  - PRAZOSIN: pilot study with 22 participants
    - Porsteinsson et al., JAMA, 2014
  - CITALORAM
    - Cummings et al., 2014 American Neurological Association, 2014
  - DEXTROMETHORPHAN/quinidine (AVP-923)
    - Soto et al., Int Psychogeriatrics, 2014
40% of citalopram participants had moderate or marked improvement from baseline severity vs 26% of placebo participants (OR 2.13, 1.23-3.69; \( P = .007 \))

**Limits:** further study is needed regarding optimal dose
« Historical » Randomized Clinical Trials: Antipsychotics

• Benefits: based upon RCT data and meta-analyses, these are modestly effective

AHRQ Comparative Effectiveness Review 2011

......with severe adverse events
## 6 ongoing RCTs of drugs for Agitation in AD

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Sponsor</th>
<th>Primary Aim Definition</th>
<th>Inclusion Criteria</th>
<th>Primary Outcomes</th>
<th>Study locations</th>
<th>N</th>
<th>Dates Start/ End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>NY State Psychiatric Institute NIA Ph 2</td>
<td>Agitation with or without Psychosis NPI A/A≥ 4</td>
<td>CD 55-95 y NIA criteria MMSE 5-26</td>
<td>NPI-A/A</td>
<td>USA</td>
<td>80</td>
<td>June 2014/ April 2019</td>
</tr>
</tbody>
</table>
| Nabilone  
TEVA (delta-9-tetrahydrocannabinol) CB-1 & CB-2 receptor agonist | Sunnybrook Health Sciences Centre Ph 2/3 | Agitation NPI-A/A ≥ 3                                                                  | CD & NH ≥ 55 y DSM-5 MMSE ≤ 20 Mixed dementia                                      | CMAI             | Canada           | 40 | Jan. 2015/ Dec 2017    |
| Prazosin  
α1-adrenoreceptor antagonist | NIA Seattle Institute Ph 2             | Disrupted agitated behavior at least twice/wk                                           | CD No age limit                                                                   | ADCS-CGIC        | USA             | 120| March 2010/ July 2015  |
| OPC-34712 (Brexpiprazole)        | Otsuka Lundbeck Ph 3                   | Agitation NPI A/A≥ 4                                                                  | NH & CD 55-89 y MMSE 5-22                                                         | CMAI total score | USA Europe Canada| 560| July 2013/ June 2017   |
| Aripiprazole                     | Otsuka Ph 3                            | Agitation NPI A/A≥ 4                                                                  | NH & hospitalized 55-89 y DSM-5 MMSE 5-22                                          | CMAI total score | USA Europe Canada| 230| Sept. 2013/ May/2017   |
## Recent and Ongoing Clinical Trials Evaluating Pharmacologic Treatment Options for NPS in AD

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Studied in AD for</th>
<th>Study Design</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Antidepressant</td>
<td>Citalopram</td>
<td>Agitation</td>
<td>N=186, double-blind w/placebo, CitAD¹</td>
<td>Signif. improvement in NBRs agitation subscale, CMAI, total NPI. No sig difference on NPI agitation subscale. Worsening of cognition and cardiac AEs.</td>
</tr>
<tr>
<td>NMDA receptor + antiarhythm</td>
<td>AVP-923</td>
<td>Agitation</td>
<td>N=220, double-blind w/placebo²</td>
<td>Signif. improvement in NPI agitation subscale and NPI total. No evidence of cognitive decline on MMSE or ADAS-cog.</td>
</tr>
<tr>
<td>Antihypertension</td>
<td>Prazosin</td>
<td>Agitation</td>
<td>N=22, double-blind w/placebo³</td>
<td>Signif. improvement in NPI and BPRS.</td>
</tr>
<tr>
<td>Inositol stereoisomer</td>
<td>Scyfloinositol (ELND005)</td>
<td>Agitation</td>
<td>N=400 (estimated)⁴</td>
<td>Currently recruiting. Primary endpoints: NPI and ADCS-CGIC. Secondary endpoint: BPRS.</td>
</tr>
<tr>
<td>Nicotinic receptor agonist</td>
<td>Encenicline</td>
<td>Cognition NPS Function</td>
<td>N=790 (estimated)⁵</td>
<td>Currently recruiting. Primary endpoint: NPI-C agitation/aggression subscale. Secondary endpoints: mADCS-CGIC, NPI total, MMSE, ADCS-ADL.</td>
</tr>
<tr>
<td>5-HT2A receptor inverse agonist</td>
<td>Primavanserin</td>
<td>Psychosis</td>
<td>N=212 (estimated)⁶</td>
<td>Currently recruiting. Primary endpoint: NPI Nursing Home version (NPI-NH).</td>
</tr>
<tr>
<td>5-HT6 receptor antagonist</td>
<td>Idalopirdine</td>
<td>Cognition NPS Function</td>
<td>N=4260 (estimated)¹¹⁻¹⁴</td>
<td>4 studies currently recruiting. Primary endpoint: ADAS-cog. Secondary endpoints: NPI total, single NPI items, NPI anxiety, CGIC, ADL-23, EuroQOL 5D 3L, C-SSRS.</td>
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- Improve the conceptual framework, definition, and criteria for “agitation” in AD
- Identify specific behavioral syndromes of agitation and aggression
  - Characterize the course of agitated behaviors in AD, relationships with other NPS, and differences across dementia diagnoses
- Develop instruments to better measure agitation and aggression in cognitive disorders
- Define the neurobiological underpinnings of distinct agitated behaviors
  - Develop biomarkers
  - Study biological risks for developing agitated behaviors
- Develop practical and efficient treatments, both behavioral and pharmacological
  - Identify specific agitated behaviors that respond best to treatment
  - Use more refined definitions of agitated behaviors in targeted clinical trials
  - Evaluate combined behavioral/pharmacological approaches to treatment
  - Identify predictors of adverse treatment effects
  - Characterize the optimal duration of treatment and predictors for relapse
**Table 1. Diagnostic criteria for apathy in neurodegenerative disease**

Diagnosis requires fulfillment of criteria A, B, C and D

A. **Loss of or diminished motivation in comparison to the patient’s previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others**

A. **Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time**

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<tr>
<td>Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:</td>
<td>Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:</td>
<td>Loss of, or diminished, emotion as evidenced by at least one of the following:</td>
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<tr>
<td>Loss of self-initiated behavior (e.g., in starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)</td>
<td>Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs).</td>
<td>Loss of spontaneous emotion, observed or self-reported (e.g., subjective feeling of weak or absent emotions, or observation by others of a blunted affect)</td>
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</table>
### Table 1. Diagnostic criteria for apathy in neurodegenerative disease

<table>
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<tr>
<th>Loss of environment-stimulated behavior (e.g., in responding to conversation, participating in social activities)</th>
<th>Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person’s residence, neighborhood or community).</th>
<th>Loss of emotional responsiveness to positive or negative stimuli or events (e.g., observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)</th>
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</table>

A. These symptoms (A & B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning

A. The symptoms (A & B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication)
Neurocircuitry based strategies suggested as part of strategy to develop Rxs (drug and nondrug for apathy)

Neuroimaging studies collectively suggest that apathy in AD is associated with regions that mediate behavioral initiation, motivation, and reward mechanisms.

Do the distinct components of the apathy syndrome (cognitive, emotional, and behavioral) differ in this regard? Can they be used to predict treatment response?

There is a need for both pharmacologic and nonpharmacologic trials with apathy as a primary outcome measure. For nonpharmacologic studies, interventions may have to be individualized. Collectively, these studies should use current diagnostic criteria and take advantage of advances in neuroimaging and biomarkers, combined with pharmacologic challenge to better understand the relationship between apathy and treatment response.

Work Product of our Working group

Focusing on a program at ISCTM - 2017

Potentially after an ISCTM program, evolve to co-Host a Consensus Conference to meaningfully move drug development in this field further along

1. Statement on unmet need
2. Understand underlying neurobiology to identify drug targets ??
3. Understanding how evolving AD diagnostic and biomarker approaches affect development of Rx for BPSD (pre dementia, early, late categorizations with various diagnosis and staging structures (DSM V, NIA-AA, IWG))
4. Proposing innovative trials designs, statistical approaches, and identify paths for regulatory agency consideration
5. Managing intrinsic variability of symptoms
6. Rx of existing symptoms or delays/prevention of likely to occur symptoms
7. Methodologies to address ‘pseudospecificity’ concerns
8. Rating and evaluations assessment tools limitations
Discuss the need to better characterize and understand neurobiology...many believe we should champion use of neurocircuitry (1/2 of survey support) and targeted neurobehavioral paradigms to inform (1/2 not):

1. Drug development and translational neuroscience strategies
2. To enrich populations for trials
3. Consideration of companion ‘diagnostics’
4. Illustrative domain anhedonia/reward/apathy
For Discussion – volunteers to assist with program Development and need recommendations for speakers?

- Survey of current field
- Lessons learned from current/completed trials for BPSD, especially agitation
- Gap analysis
- Use the approach taken by CIAS and MATRICS toward consensus
  - Statistical methods to determine clusters and independent domains
  - Current thinking might be reflected by growing acceptance of depression in dementia
- Select the BPSD ‘target’ indication for our program, justify?
- Stage of illness and assessment tools
- Study design considerations
- Is a known mechanism of action necessary?
- Review of lessons learned from ongoing and prior clinical trials for NPS
- For agitation, agreed to focus on non atypical antipsychotics drugs
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?
Current objectives

We will primarily focus on the development of a program proposal for a future ISCTM meeting.

• Communicate with other organizations,
  • ISTAART PIA coordinate with Joanne Bell new co-Chair, request 5-10 minutes on the PIA day agenda to brief AAIC meeting attendees about ISCTM, encourage joint efforts
  • Consider reaching out to IPA (International Psychogeriatric Association) per Jill Rasmussen’s suggestion
• Agree on the 1 or 2 relevant symptoms/syndromes to focus upon, which demonstrate relevant therapeutic targets for drug development
• Apply the learnings from current clinical trials and to the extent available, regulatory responses, for treatments managing Agitation or Depression in Dementia
• Begin to perform a gap analysis evaluating the current clinical trials methodologies employed and the state of the field
Current objectives

- Status of the scientific/clinical neurosciences characterization of the target symptoms
- Potential application of biomarker, neurocircuitry, and translational strategies (development or application)
- Assessment tools (characterize construct validity, sensitivity to change, threats to validity and reproducibility, etc)
- Patient selection (i.e., stage of AD, complexity of symptom presentation, enrichment strategies if applicable)
- Describe symptom progression across severities of Dementia, focus on symptom presentations early v later stages of illness
  - Would Rx of symptoms lead to a delay in time to disability?
- Study designs such as placebo/active control, various treatment administration strategies (staggered start/stop/start and placebo substitution/discontinuation of active drug), pseudospecificity, effects on cognition, functional correlates, key safety measures, health outcome metrics
  - Potentially suggest a framework to characterize relevant symptoms ‘value’ in the health care market
Please volunteer for one of these ‘buckets’ to assist in program development

- Survey of current field/Background
  - Choose focus for symptoms to evaluate (agitation or apathy)
  - Lessons from agitation trials, other relevant AD/MCI trials, and from CIAS and Negative Symptoms experience

- Defining symptoms, staging of illness, pseudospecificity,
- Considerations in trials design, study population, enrichment strategies

- RDOC neurophysiology/circuitry biomarkers

- Rating Scales and assessment challenges, outcome measures

- Statistics, meta analyses, public data bases available from ACDS, requires time and $
  - Funding support

- Regulatory challenges, engagement of FDA