Agitation in Alzheimer's Disease: Challenges in Drug Development: An Industry Perspective

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Background:

- Agitation is one of several BPSD that co-occur: depression, psychosis, apathy, agitation/anger/irritability, motor aberrations
  - Secondary to delirium, pain, UTI, environmental triggers
  - Intermittently chronic presentation
  - NO single Rx likely to be of benefit all BPSD
- Role of non-pharmacological interventions
  - Benefits in less severely agitated patients
  - Helpful in excluding secondary causes of Agitation
  - Limitations: qualified personnel, standardized therapies, sustained benefit
- Majority pf patients on many medications
  - SOC Pharmacological treatments + Agitation medication
    - Anti-dementia, Antidepressants, antipsychotics, benzodiazepines etc

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Considerations for Clinical Development and Trial Design

Key Challenges/Issues in Designing Clinical Trials of Agitation

- 1. Heterogeneity in target population (variability)
- 2. Assessment and Endpoint Analyses
- 3. General design considerations
- Meaningfulness of change

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High Disease Variability & Treatments

- Reducing variability of target population is an important design consideration
- IPA consensus definition provides a standard guidance for identifying patients with agitation.
  - Phenotypic variability: physically or non physically aggressive, or verbally agitated (or combination)
  - Presentation may vary by setting (community dwelling/ inpatient) and cognitive status
  - Benefits to be demonstrated in a backdrop of worsening dementia (and worsening agitation)
  - Inclusion criteria for baseline severity vary: Agitation(mod-sev); cognition (Mild to mod)
- Most trials are “add on” to anti-dementia / SOC drugs (antipsychotics, SSRIs): potential for DDIs/ AEs/Pharmacokinetic interactions and negative safety profile eg. falls, cognitive impairment
  - Efficacy of a broad spectrum agent eg NMDA antagonist have not been impressive
  - Is it feasible to stop all “concurrent” treatments for agitation eg antipsychotics?

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Unique Challenges for Selection of Endpoints and Analysis

- Commonly used outcome measures include:
  - Uni or Multidimensional scales: CMAI, NPI, NPIC, NBRS (frequency scores; severity of scores)
  - Caregiver vs patient report vs clinician assessment eg NPIC
  - Patient/ caregiver burden and distress scores
  - Role for Cumulative outcomes: eg NPI-4: Agitation/Aggression, Anxiety, Aberrant Motor and Disinhibition (Trzepacz et al. 2012)
- Endpoint Analyses:
  - Total score vs domain scores
    - Statistical issues: multiplicity corrections etc(Hendrix et al., 2017 AAIC)
    - Patients not enriched for any domain and do not present in silos defined by any domain
  - No worsening in cognition
- Role for subgroup for endpoint analysis : eg. severity; aggressive subtype

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Consideration for Trials Design

- General issues: duration of treatment, patient/caregiver burden (# of scales, frequency, cognitive status of caregiver etc)
- New Trial Designs
  - High Placebo response in recent Agitation trials (Rosenberg et al., 2015, Abushakra et al.,, 2012)
  - Utility of innovative designs eg; Sequential Parallel Comparison Design (SPCD)
  - Relapse Prevention Designs (Devanand et al, 2012)
    - Clear definitions of response/relapse;
    - Time to relapse vs rate of relapse
      - » Duration of study: Does antidepressant model work?

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What is a Clinically Meaningful Improvement?

- Are components of a composite endpoint important to the patient and reflect how does the patient feel, function or survive?
- Relationship between globally relevant endpoints eg CGI/ PGI “very much or marked improvement” and primary outcome measure measuring agitation eg CMAI, NPIC
  - ROC analysis eg: Sensitivity/ Specificity of change that is clinically meaningful
  - Responder analysis: proportion of responders assessed by clinician or patient interviews
- Could improvement in caregiver distress a measure of meaningful improvement?
- What do caregivers consider a meaningful change in an outcome measure?
- Could reduction in caregiver burden, caregiver time be used as measures of meaningful change?

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Conclusions

- Successful development of new treatments for Agitation in AD remains challenging
- Issues that will define success include an appropriate definition of agitation, defining the appropriate target population (severity, cognitive status, trials design and duration, allowed con-meds and use of valid and reliable outcome measures that are sensitive to change)
- Placebo response that plagues trials in neuropsychiatric conditions is a concern and hence an agreement on the utility of innovative designs is important
- Are there subgroups of patients appropriate for inclusion in label
- Acceptance and interpretation of total/composite scores for vs domain/factor scores and interpretation of meaningful change

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Thank **you!**

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