Late Onset Depression
Working Group

Chairs: Peter De Boer, PhD
Patricia Capaccione, RPh
February 20, 2018
Objectives

To explore the “State of the Science” in Late Onset Depression*** (LOD)

1. Identify the challenges and opportunities to develop pharmaceutical interventions for a psychiatric disorder based on pathology rather than symptoms
2. Use late-life, late onset (LLLO) depression as an example to explore:
   - Its pathological basis
   - Boundaries and overlap with other conditions
   - Challenges and opportunities for pharmaceutical development
3. Capture observations and recommendations in position paper.

Questions to Explore

- How can this population be defined and distinguished?
- What are the differences between LOD and Major Depressive Disorder?
- How is LOD currently treated?
- Is LOD a valid target for regulatory approval?

***Note: Throughout this presentation and discussion, late onset depression, late life depression (LLD) and geriatric depression are used interchangeably. Moving forward, this working group may decide which is the most appropriate term and if these terms are indeed interchangeable.
Work Plan

- Today- introduction of the topic, presentation of ideas with time for discussion and questions
  - Collect names of individuals who would like to continue throughout the year

- Throughout the year- quarterly teleconferences to develop the concept and refine the proposed Whitepaper

- Next year’s ISCTM meeting- finalize the Whitepaper
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<td>Overview of Late-onset Depression (LOD)</td>
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Late life, late-onset Depression
A separate diagnostic entity?

Peter de Boer, PhD
Senior Director Experimental Medicine
Janssen Research and Development
Why LLLO depression?

1. Aging of the population is anticipated to increase the burden of age-related neurodegenerative / psychiatric disorders
2. Depression has a major health and societal impact and the prevalence in elderly subjects is high (9 - 18 percent)
3. LLLO is associated with relative treatment refractoriness
Psychiatric diagnoses

Behaviors, Thoughts, Physiological Symptoms

Psychiatric Syndrome

Diagnostic

Causal

Pathophysiology
Psychiatric drug development - serendipity

Chemical Entity

Chance clinical observations

Promising behavioral effect in animals

Benefit in psychiatric patients

New Drug

Studies into MoA

Test models

Compound optimization
Late-onset depression

- Depressed mood
- Bodily changes
- Cognitive symptoms
- Treatment refractory

Non-specific
- Onset > 50/65 years
- Vascular pathology
- AD-like pathology

Specific
Psychiatric drug development - pathology based

Pathophysiological model → Test systems → Compound selection → Clinical observations

- Compound optimization
- New drugs
A pathological model
(adapted from nature vascular depression hypothesis)

- Somatic disease burden
  - Systemic inflammation
- Vascular risk factors / disease
- Hemodynamic changes
  - Altered brain function
  - Disconnection
- Local (brain) inflammation
- Myelin damage

Sadness Cognitive impairment
Overlap with vascular cognitive disorders (Lancet)
Developmental hypothesis

MDD episodes

vascular disease burden

depression threshold

time

Adult - 50/65 yrs

> 50/65 years

“Early Onset MDD”

“LLLO”
Implications

1. Is LLLO depression a special case of cerebrovascular disease or may it be considered a specific indication?

   *Consider that depression is treated by specialists separate from CV disease*

2. If considered depression with specific pathophysiological features, what are the possibilities for diagnosis?

   *Consider MRI (white matter hyperintensities), cognitive endpoints*

3. Given that the pathology is emergent, early disease-modifying rather than symptomatic interventions may be indicated

   *Is there prodromal LLLO depression? How to study the effect of interventions? What endpoints.*
Phenotypic Differences in the Elderly with Late- vs. Early-Onset Depression

Arun Singh, DO
Project Physician
Neuroscience
Janssen Research and Development
Phenotypic Differentiation: Introduction

- **Neuropathophysiology & depression:**
  - Complex interaction of genetics, epigenetics, environment
    - Yet to be fully elucidated
  - Likely numerous, distinct depressive illnesses
    - Optimal prevention & treatment expected to differ, depending on degree of possible neuropathophysiological overlap
  - Late-onset depression (LOD) is a distinct class of depression, relative to early-onset depression (LOD)
    - Risk factors differ
    - Phenotypic differences
Neuroanatomical differences

- **White matter hyperintensities (WMHs)**
  - Odds of periventricular WMHs in LOD\(^1\):
    - 2.57 x greater than HCs (<0.001) and 4.51 x greater than EOD (p<0.001)
  - Odds of deep WMHs in LOD\(^1\):
    - 2.64 x > than HCs (p<0.05) and 4.33 x greater than EOD (p<0.001)
  - ↑lesions in deep brain structures associated with ↑ depressive symptoms, ↓ physical health\(^2,3,4\)

- **Gray matter changes**
  - Evidence suggests ↓ hippocampal volume in LOD vs EOD\(^5,6\)

- **Limited functional imaging data**\(^7,8,9\)
Cognitive Differences

- Greater burden of cognitive dysfunction in elderly with LOD vs EOD
  - ↑ Executive dysfunction\textsuperscript{10,11}
  - ↑ verbal learning and memory impairment, in older adults with depression and executive dysfunction\textsuperscript{12}
    - 171 older adults participating in psychotherapy study (72 LOD vs 99 EOD)
  - ↑ clock drawing test impairment\textsuperscript{13}
    - Comparison of 36 HC, 26 EOD, 27 LOD on Turbingen Clock Questionnaire
    - Consistent with semantic memory impairment
Differences in Non-Cognitive Symptoms

- Inconsistent evidence of non-cognitive differences in elderly with LOD vs EOD in a systematic review\textsuperscript{14}

- Among melancholic patients (n=284: 73% EOD vs 27% LOD)\textsuperscript{15}
  - ↑ vegetative symptoms at baseline for LOD vs EOD
  - ↑ age at onset possible risk factor for dementia

- Apathy (not depressed mood) suggested as consequence of lesions within cortical-subcortical pathways\textsuperscript{16}

- EOD associated with ↑ depressive symptom severity; LOD associated with ↑ cognitive impairment\textsuperscript{5}
  - N=135, 51.9% LOD
Future Directions?

- Characterize and subtype depressions secondary to vascular brain injury
  - Defined by pathophysiology, not age
    - However, at this stage, age of onset may be useful for feasibility and interpretability
- Challenges: Limited existing data, nomenclature, taxonomy
  - Division between early and late?
  - How many depressions are there?
    - Even EOD is extremely genetically diverse
  - When is age of onset distinction too limiting?
  - EOD may be at higher risk of vascular depression later in life\(^\text{17}\)
    - How to differentiate LOD from EOD patients with LLD?
  - Does DSM-5 identify depression with early and late onset equally well?
  - Age of onset not always described in the literature
    - “geriatric depression”, late-life depression (LLD)…
References


References


Current Treatment of LLD

Adam Savitz, MD, PhD
Overview

- Overall, treatment of LLD is similar to that of non-elderly depression.

- Vast majority of studies do not distinguish between late and early onset depression.

- LLD tends to be more chronic and more relapsing so may need chronic treatment earlier (definitely after 3 episodes).

- Need to individualize care with available evidence based psychological, medication, and somatic (ECT) treatments.
Psychological Treatment

- Psychological treatments work (results are similar to younger adults)
- Tend to be not as available as desired (many elderly want therapy over meds given a choice)
- A good option for mild to moderate or where there are concerns about drug-drug interactions
  - Problem solving
  - CBT
  - IPT (weaker evidence)
  - Brief psychodynamic psychotherapy
  - Cognitive remediation
  - Collaborative care (focus on improved treatment in primary care with case managers)
  - Specific interventions for medical comorbidity including COPD (PID-C)
Medication Treatments

- SSRI/SNRIs work but risk of relapse
  - 40% respond and only 1/3 remit similar to younger adults
  - More side effects though no increase in falls
  - Risk of DDIs and poor adherence
- TCAs are effective with smaller NNT but this may be age or design of trials. More adverse events
- Stimulants-one positive trial, potentially safer in the medically ill (than TCAs at least) and work faster
- Augmentation options: quetiapine, aripiprazole, lithium, and stimulants (at least one study or meta-analysis (lithium)) but risk of significant side effects
- Predictions of poor outcome include: cognitive impairment (particularly executive dysfunction), higher medical illness, and anxiety.
- Insufficient dose often used with recommendations of using 1/3 to 1/2 of the adult dose but often this results in doses that are too low
- Treat for at least one year
  - Longer for multiple episodes. After 3 episodes, very high risk for relapse and at least 3 years of treatment - 28% reduction in risk for relapse with antidepressants.
ECT Treatment

- Effective and safe in the elderly though need to monitor for delirium due to anesthesia and cognitive dysfunction
- Higher remission in elderly than non-elderly adults; treatment of choice for refractory depression and suicidality
- Move toward Right unilateral compared to bilateral though evidence base is not strong
- Underutilized
- Maintenance ECT should be considered
- Other somatic treatments: rTMS has not shown positive results in the elderly (small trials) and not enough evidence for other neuromodulatory treatment.
Is LOD a Valid Target for Regulatory Approval?

Patricia Capaccione, RPh
What Does Current Guidance Say About Depression in Elderly Subjects?

- Guideline On Clinical Investigation Of Medicinal Products In The Treatment Of Depression

  (30 May 2013 EMA/CHMP/185423/2010 Rev. 2)

  - Depression in older people is not uncommon
  - Recently studies have been conducted in older people, that could not distinguish between test product and placebo, even though the design of the studies and the dose of the test product were as expected and efficacy of the product had already been shown in adults.
  - Extrapolation of the adult dose may be difficult due to pharmacokinetic properties of the product and/or to a different sensitivity in the older people for the pharmacodynamics of the product.
  - Not only efficacy, but defining a safe dose (range) in these patients is a main concern.
  - Usually this should be addressed before licensing. Either by analysis of the whole database, or to conduct specific trials in a specified patient population. The optimal design would be a placebo-controlled dose response study

- CHMP Guidance expected revision 4 Q 2018
- FDA Guidance under preparation
- No mention of any distinction between late onset and early onset depression
Regulatory Considerations

- Current guidance does not recognize LOD
- In targeting a narrow subpopulation such as Elderly for an indication several factors need to be taken into account
  - Provide evidence that the indication you wish to seek is separable from a more “global” indication and that treatment for each could be expected to be different
  - Demonstrate that improvement in the targeted symptoms is clinically meaningful
  - Show that your study drug has a statistically significantly difference in efficacy in LOD compared to the greater population of patients with MDD* or
  - Show that your drug demonstrates superiority over other drugs in the same class when tested in this specific subgroup of patients with LOD*

*(i.e., show your drug works better in LOD than it does in MDD or show it works better in the LOD population than other drugs in the MDD class)*
Questions and Discussion