PSYCHIATRIC SYMPTOMS AND SYNDROMES IN PD

Ramit Ravona-Springer
Spectrum of psychiatric symptoms and syndromes in PD

- Anxiety
- Depression
- Apathy
- Psychosis
- Impulse control disorders
Spectrum of psychiatric symptoms and syndromes in PD

• Depression
• Apathy
Apathy
Apathy definition

- State of decreased motivation
- Manifests as a decrease in goal-directed behaviors
- Can be variably characterized by reduced interests or emotions
- Cannot be attributed to diminished level of consciousness, cognitive impairment, or emotional distress (Pagonabarraga, Lancet Neurology 2015)

Epidemiology of apathy in PD

- Can precede motor symptoms
- Prevalence decreases after introduction of dopaminergic drugs, but then increases
- May appear as an isolated behavioral syndrome in PD
  - Range 7-70%
  - Newly diagnosed, untreated patients: 20-36%
  - In non-demented PD: 40%
  - In demented PD patients: 60%
PD with predominant apathy- patient profile

- Males
- Older
- More severe motor impairment
- Worse executive dysfunction
- Worse temporal lobe dependent tasks (e.g. memory)
- At higher risk for dementia
- Faster functional decline
- Decreased response to treatment
Is apathy a uniform disorder?

- Appears in many neuropsychiatric disorders, each with a different mechanisms
- Several brain regions are involved
- Several neurotransmitters are involved
- Phenomenology differs between patients
- Individualized approach?
Components of Apathy

• Absence of spontaneous activation of mental processes reduced goal-directed behavior (auto-activation deficit),
  - Lack of effort, initiative and productivity
  - Inability to activate oneself

• Decrease in cognitive interests (executive dysfunction)
  - Difficulty in redirecting attention to novel stimuli
  - Decreased interests
  - Lack of plans and goals
  - Lack of concern about one’s own health or functional status

• Decrease in emotional resonance (reward deficiency syndrome)
  - Flattened affect
  - Emotional indifference
  - Restricted responses to important life events
Components of Apathy

- **Autoactivation mechanism**
  - Lesions to the basal ganglia and dorsal-medial aspect of prefrontal cortex
    - Inability to initiate actions or thoughts, while response to external drive is relatively spared

- **Cognitive mechanism**
  - Lateral prefrontal cortex
    - Impaired cognitive functions needed to elaborate a plan of actions required to achieve goal directed action

- **Emotional-affective mechanism**
  - Orbital-medial prefrontal cortex, connections in the striatum
    - Disconnection between emotional signals and motivational values of ongoing and forthcoming behaviors

*Levy & Dubois 2006*
Parkinson’s Disease is a model of the neural substrate of apathy

Dopamine
- Dopaminergic denervation is inherent to PD
- Dopaminergic system involved in motivation
- Dopaminergic disruption of the mesolimbic and mesostriatal pathways is involved in non-motor manifestations: apathy, depression, anxiety, fatigue, impulse control
Neurotransmitters

Serotonin (Maillet et al, Brain, 2016)

• Newly diagnosed untreated PD patients
  - Apathetic (n=15), non apathetic (n=15)
• Healthy age matched controls (n=15)
• PET imaging with presynaptic radioligands
  - Dopaminergic & serotonergic
• Overlap depression, anxiety and apathy
  - Associated with dysfunction of the limbic cortico-basal ganglia circuit
  - Role of dopaminergic alteration was not observed
Neurotransmitters

Serotonin (Maillet et al, Brain, 2016)

- Severity of apathy was associated with serotonergic denervation in the limbic cortical and subcortical circuits
  - Right-sided OFC and the anterior part of caudate nucleus
- Severity of depression and anxiety was associated with serotonergic lesions in the cortical limbic areas
  - The subgenual ACC
Neurotransmitters

Other neurotransmitters associated with motivation:

• **Acetylcholine**: cholinergic neurons responsive to novel and motivationally related sensory events.

• **Noradrenaline**: noradrenergic neurons more responsive to the motivational relevance (or meaning) of a stimulus than to its sensorial properties
  - Noradrenaline mediates novelty seeking behavior, the focusing of attention and resistance to distraction
Mechanisms

My differ by disease stage & apathy type

- Controversies regarding neurotransmitters involved at different disease stages

- Structural abnormalities (Levy et al, J Neurol 2006)
  - 60 PD patients with neither dementia nor depression
    - Premotor dysfunction → less motivation to initiate movements
    - Insular atrophy → loss of emotional responsiveness
    - Cingulate atrophy → deficits in autoactivation
Apathy after DBS in PD

• Early transient (1st postoperative year):
• Associated with complete withdrawal of dopamine agonists and ↓ of levodopa
• Dopamine dependent
  - Predominant degeneration of midbrain dopaminergic neurons in the substantia nigra and ventral tegmental area (but without much cortical synucleinopathy)
Apathy after DBS in PD

• Long-term, treatment resistant:
  - In association with levodopa-resistant frontal dysexecutive syndrome and dementia
    • Diffuse cortical synucleinopathy
Multidimentional nature of apathy in PD

• PD
  - Denervation in multiple neurotransmitters
  - Heterogeneous pathologies in different brain regions at different disease stages

• Apathy in PD is a heterogeneous disorder
Treatment

• Why treat apathy?
  - Patient does not suffer
  - No direct danger to self or others
  - Caregiving burden
  - Decreased hedonia (?)
Obstacles Towards Treatment Development

• Lack of consensus on diagnostic criteria
  - Several diagnostic criteria have been suggested
• Differential diagnosis from motor and non-motor symptoms of PD
Apathy
Differentiation from motor and non motor symptoms (PD)

- Reduced energy
- Reduced activities
- Psychomotor retardation
- Mental slowing and concentration difficulties
- Flattening of effect vs hypomimia
Apathy

Differentiation from depression

- **Controversies regarding phenomenology of depression in PD**
  - Depression in PD differs from the primary affective disorder
    - More motivational symptoms, fatigue, apathy, psychomotor slowing, delusions
    - Less mood related symptoms (depressed mood, anxiety), guilt, fewer suicidal thoughts, less prominent vegetative symptoms
    - Severity milder
  - Depression in PD does not differ from the primary affective disorder
# Differentiation between apathy and depression

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</table>
Overlap: apathy/depression/dementia

Disagreements:

- Most apathy cases in PD occur in the absence of depression (Kirsch-Darrow et al, Neurology 2006)
  - 80 PD patients
    » 29% of the sample had apathy but no depression

- High overlap with depression and dementia (Starkstein et al. Mov Disord 2009)
  - 164 PD patients, 52 diagnosed with apathy
    » 35% concomitant depression, 8% concomitant dementia, 48% both dementia and depression
    » 3% had apathy only

• Results differ by methods used for diagnosis, patient population
Overlap of apathy with fatigue

• Two highly common non-motor symptoms in PD
  - Study aimed to assess the coincidence of apathy with different fatigue domains in the presence or absence of depression (Skovranek et al., Acta Neurologica Scandanavica, 2015)
    - N=151
      » Prevalence & severity of fatigue and apathy higher in depressed PD patients
      » Apathy was associated with reduced motivation in depressed and non-depressed patients
      » Apathy was associated with mental fatigue aspects only in non-depressed patients
      » Apathy was not related to the physical aspects of fatigue in any of the studied groups
Overlap of apathy with fatigue

- In a proportion of PD patients, apathy & fatigue are associated with depression
  - In some PD patients, improvement in apathy
    - Adequate management of depression
    - Optimal dopaminergic medication
Apathy and novelty processing

- Efficient processing of novelty is critical to goal-directed behavior
  - Drives flexible allocation of attention to changing environmental demands/events
    - Potential sources of engagement or
    - Irrelevant distracters

- Event-related potential (ERP) methods used for tracking attentional orienting process toward deviant events
  - Distracter-related P3 potentials
Apathy and novelty processing

- Non demented PD patients (n=14), age matched controls (n=12) (Kaufman et al, Frontiers in Neurology, 2016)

- ERP reflections of distractor visual novelty
  - PD patients: ↓ distractor-related ERPs
    - ↓ Attentional orientation toward novelty
  - Apathy corresponded with reduced P3 amplitude in all PD patients
    - Depression and anxiety correlated with P3 amplitude
      - Relationships disappeared controlling for apathy
    - Executive functioning in PD correlated with P3 amplitude
      - Apathy remained a significant predictor even when accounting for executive functions
Obstacles Towards Treatment Development

• Rating scales are available— which should be used?
  - Self report?
  - Caregiver interview?
  - Clinician’s impression?

• There are probably several types of apathy
Previous Clinical Trials

- Possible therapeutic agents, proved some efficacy:
  - Cholinesterase inhibitors
  - Antidepressants
  - Dopaminergic agents
    - Dopamine agonists, methylphenidate

- Limitations of previous clinical trials
  - Number of subjects
  - Apathy rarely defined as target symptom
Are non-pharmacological treatment of apathy feasible?
Efficacy of music therapy treatment based on cycles of sessions: A randomised controlled trial

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(Received 6 August 2009; final version received 21 December 2009)

We undertook a randomised controlled trial to assess whether a music therapy (MT) scheme of administration, including three working cycles of one month spaced out by one month of no treatment, is effective to reduce behavioural disturbances in severely demented patients. Sixty persons with severe dementia (30 in the experimental and 30 in the control group) were enrolled. Baseline multidimensional assessment included demographics, Mini Mental State Examination (MMSE), Barthel Index and Neuropsychiatry Inventory (NPI) for all patients. All the patients of the experimental and control groups received standard care (educational and entertainment activities). In addition, the experimental group received three cycles of 12 active MT sessions each, three times a week. Each 30-min session included a group of three patients. Every cycle of treatment was followed by one month of wash-out. At the end of this study, MT treatment resulted to be more effective than standard care to reduce behavioural disorders. We observed a significant reduction over time in the NPI global scores in both groups ($F_{7,357} = 9.06, p < 0.001$) and a significant difference between groups ($F_{1,51} = 4.84, p < 0.05$) due to a higher reduction of behavioural disturbances in the experimental group at the end of the treatment (Cohen’s $d = 0.63$). The analysis of single NPI items shows that delusions, agitation and apathy significantly improved in the experimental, but not in the control group. This study suggests the effectiveness of MT approach with working cycles in reducing neurological disorders of severely demented patients.
Non-pharmacological interventions for apathy in dementia

- Literature review (Brodaty et al, American Journal of Geriatric Psychiatry, 2012)
  - Assessment of efficacy of 56 nonpharmacological studies:
    - Interventions: exercise, music, multisensory, animals, special care programming, therapeutic activities and miscellaneous
  - Therapeutic activities, particularly those provided individually, have the best available evidence for effectiveness in dementia
The Impact of Physical Activity on Non-Motor Symptoms in Parkinson’s Disease: A Systematic Review

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Parkinson’s disease (PD) is a neurological disorder that is associated with both motor and non-motor symptoms (NMS). The management of PD is primarily via pharmaceutical treatment; however, non-pharmaceutical interventions have become increasingly recognized in the management of motor and NMS. In this review, the efficacy of physical activity, including physiotherapy and occupational therapy, as an intervention in NMS will be assessed. The papers were extracted between the 20th and 22nd of June 2016 from PubMed, Web of Science, Medline, Ovid, SportsDiscuss, and Scopus using the MeSH search terms “Parkinson’s,” “Parkinson,” and “Parkinsonism” in conjunction with “exercise,” “physical activity,” “physiotherapy,” “occupational therapy,” “physical therapy,” “rehabilitation,” “dance,” and “martial arts.” Twenty studies matched inclusion criteria of having 10 or more participants with diagnosed idiopathic PD participating in the intervention as well as having to evaluate the effects of physical activity on NMS in PD as controlled, randomized intervention studies. The outcomes of interest were NMS, including depression, cognition, fatigue, apathy, anxiety, and sleep. Risk of bias in the studies was evaluated using the Cochrane Collaboration’s tool for assessing risk of bias. Comparability of the various intervention methods, however, was challenging due to demographic variability and methodological differences. Nevertheless, physical activity can positively impact the global NMS burden including depression, apathy, fatigue, day time sleepiness, sleep, and cognition, thus supporting its therapeutic potential in neurodegenerative conditions such as PD. It is recommended that further adequately powered studies are conducted to assess the therapeutic role of physical activity on both motor and non-motor aspects of PD. These studies should be optimally designed to assess non-motor elements of disease using instruments validated in PD.
What is the Drive? Motivating Factor?

Basic needs?

Reward?

Intensive emotions-family

Game? Sport?
Conclusions

- Apathy is highly prevalent in PD and other neuropsychiatric disorders
- Associated with decreased cognitive and functional abilities and increased caregiver burden
- No consensus
  - Definition
  - Subtypes
  - Pathophysiology
  - Tools for assessment
- Difficult to differentiate from other PD symptoms
- Requires an individualized approach
Depression
Epidemiology depression PD

- Prevalence varies: 3-80%
- Different diagnostic criteria and assessment tools
Implications

• Patient
  - Increased cognitive/functional/motor disabilities
  - Poor quality of life
  - More rapid progression of motor impairment
  - ↑ Mortality

• Caregiver burden
  - Physical, emotional, financial

• Cost of health care
Depression in PD clinical context

- Progressive neurological disorder associated with increasing disability
- Overlap with other PD symptoms:
  - Social withdrawal, disability, loss of energy, sleep disturbances
- Symptoms change over time
- Ascertainment of depressive symptoms and signs to a single factor is difficult
  - Loss of pleasure may be a symptom of depression at early stages and a symptom of apathy at later stages
Clinical characteristics of depression in PD

Controversies:

- Depression in PD differs from the primary affective disorder
  - More motivational symptoms, apathy
  - Less mood related symptoms (depressed mood, anxiety), guilt, fewer suicidal thoughts, less prominent vegetative symptoms
  - Severity milder

- Depression in PD does not differ from the primary affective disorder
Diagnostic Challenges

• Differentiating depression from:
  - Apathy
  - Motor, cognitive and fatigue symptoms in PD
Differentiation between apathy and depression

**Depression**
- Negative affect (sadness/ anxiety)
- Negative thoughts about oneself
- Worthlessness
- Past failure perception

**Apathy**
- No affective evaluation self or event
- No affective response to negative or positive events
- Lack of initiation
- Lack of effort
Depression and PD—bidirectional relationship

- Depression is a risk factor for PD
  - In a 6.8y f.u study 140,000 individuals with depression vs 420,000 controls
    - OR for PD was 6.4 (95% CI 4.4–9.3) in those with depression within 1st 3 months
    - Risk decreased subsequently but remained 1.5 (95% CI 1.1–2.0) 15–25 years after diagnosis of depression
    - Severity and recurrence of depression were associated with increased risk for PD

Gustafsson, et al., Neurology 2015
Depression and PD - bidirectional relationship

- Depression is a risk factor for several disorders
  - Dementia
  - Stroke, vascular disease
- Other psychological symptoms are risk factor for PD
  - Anxiety
- Depressive symptoms do not precede PD in all patients
  - The majority of depressed cases are diagnosed after being diagnosed with PD

Leentjens, Nature Reviews/Neurology 2015
Contributors to depression in PD

• Biological: genetic, pathophysiology of PD, medication use
• Psychological: Coping mechanisms, personality
• Social
• PD-related (↑ disease duration, ↑ severe motor symptoms, use of levodopa) & non-specific factors (♀, history of anxiety and/or depression, family history of depression, ↓ ADL functioning, and ↓ cognitive status) (Leentjens et al, neurology 2013)
Efficacy of treatments

- **Movement Disorder Society Evidence-Based Medicine Review Update (2011)**
  - **Likely efficacious**
    - Pramipexole
    - Nortriptyline
    - Desipramine
  - **Insufficient evidence**
    - Other TCA’s
    - SSRI’s
    - MAO inhibitors
    - ECT
    - rTMS
Factors Affecting Results

- **N**
- Varying inclusion criteria (MDD/ minor depression/ dysthymia/ clinically significant depressive symptoms)
- Population
  - Cognitive function
  - Depression severity
- Scales
  - Not necessarily validated for population
- Existence of several depression types in PD?
Conclusions

• Apathy and depression are prevalent in PD
• Significant implications
• Different subtypes may exist
• Future goals
  - Consensus
    • Diagnostic criteria
    • Assessment tools
  - Understand underlying mechanisms
Spectrum of psychiatric symptoms and syndromes in PD

• Psychosis
Definition of psychosis

- Delusions and hallucinations
- Highly co-occur
  - Hallucinations seldom occur in the absence of delusions
Psychotic symptoms differ in dementia vs schizophrenia

- **Common delusion in dementia**
  - Persecution (theft)
  - Abandonment
  - Infidelity
  - Diseased individuals are still alive
  - Misidentification
    - Usually not bizarre, not complex

- **Hallucinations**
  - Can occur in any sensory modality
    - Visual
Psychotic symptoms in Alzheimer’s disease (AD)

• Prevalence 25-40%
  - Prevalence increases with increasing severity up to a certain stage, after which, prevalence decreases

• With increasing prevalence of AD, by 2050, psychosis in AD is expected to be the 2\textsuperscript{nd} most prevalent psychotic disorder (after schizophrenia)
Psychotic symptoms in FTD

- Neuropsychiatric symptoms are common in FTD
  - Alterations in interpersonal conduct and personal regulation
  - Disinhibition
  - Socially inappropriate behavior
  - Emotional disengagement
  - Repetitive compulsive-like acts
  - Poor insight

- Psychotic symptoms are rare
Psychotic symptoms in patients with synucleopathies

- Delusions and hallucinations in 60-80% of patients
- More common at night
- Role of visual impairment/processing
Visual misperceptions in patients with synucleopathies

- **Visual hallucinations**
  - DLB: 80%
  - PDD: > 50%
  - PD no dementia: 10%

- **Visual illusions**
  - DLB: 30-50% of patients with DLB
  - PDD: 58%
  - PD no dementia: 6-19%

*Uchiyama et al, Parkinsonism and Related disorders, 2015*
Implications of psychosis in dementia

- Patient suffering
- Co-occurrence of other behavioral manifestations
  - Aggression
  - Agitation
  - Depression
- Associated with increased
  - Risk to patient and caregivers
  - Caregiver distress
  - Functional impairment
  - Rates of institutionalization
  - Morbidity and mortality
Implications of psychotic symptoms compared to those of other BPSD

Study on the impact of behavioral symptoms on wellbeing of patients and caregivers

- **Memory** was frequent but least distressing
- **Most prevalent:**
  - Apathy
  - Depression
  - Agitation
- **Most intense (severity X frequency):**
  - Appetite
  - Motor behaviors
  - Apathy
- **Most distressing:**
  - Delusions
  - Agitation
  - Irritability
  - Disruptive behavior
- The most frequent are not necessarily the most distressing

*Fauth et al. Int J Geriatr Psych 2013 Jul*
Treatment with antipsychotics

• Limited efficacy
• High toxicity
  - EPS
  - Cerebrovascular events
  - Metabolic
  - Worse cognition
  - Mortality

• Possible reasons for low efficacy:
  - Mechanisms underlying psychosis differ from those underlying psychosis in schizophrenia
  - Heterogenic entity
Characteristics of AD patients with psychosis
Characteristics of psychosis in AD - cognition

• Significantly associated with degree of cognitive impairment
  - Global cognition
  - Frontal lobe functions

• Not attributed to
  - Demographic factors
  - AD-duration
  - Family history of psychiatric illness

• Associated with higher rate of cognitive decline prior to psychosis onset
Characteristics of psychosis in AD- genetics

• The risk for psychosis in AD is transmitted in families
• Linkage to loci on chromosomes 2, 7, 8, 15
• Mixed results regarding association with:
  - Apo E4
  - Candidate genes- monoamines
<table>
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<tr>
<th>Imaging method</th>
<th>Finding</th>
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<tr>
<td><strong>CT</strong></td>
<td>Right frontal lobe atrophy</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Decreased gray matter volume (Frontal lobe)</td>
</tr>
<tr>
<td></td>
<td>White matter hyper intensities: inconsistent results</td>
</tr>
<tr>
<td><strong>SPECT</strong></td>
<td>Reduced perfusion across cortical regions (more pronounced frontal lobe)</td>
</tr>
<tr>
<td><strong>FDG-PET</strong></td>
<td>Hypo metabolism in neo cortex, mainly bilateral frontal and prefrontal</td>
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<tr>
<td></td>
<td>Hyper metabolism in sensory association areas (sensory disinhibition?)</td>
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<td></td>
<td>Higher striatal D2/3 availability</td>
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### Characteristics of psychosis in AD-neuropathology

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<tr>
<td>Amyloid</td>
<td>No association with load of neuritic plaques</td>
</tr>
<tr>
<td></td>
<td>Increase in Aβ1-42:Aβ1-40 ratio in dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>TAU</td>
<td>Increased aggregation in dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>Synapses</td>
<td>Increased synaptic disruption in superior temporal gyrus, dorsolateral prefrontal cortex, and inferior parietal cortex</td>
</tr>
<tr>
<td></td>
<td>No differences in medial temporal lobe (amygdala) and cerebellum</td>
</tr>
<tr>
<td>Neocortical Lewy bodies</td>
<td>Associated with visual hallucinations, not other psychotic symptoms</td>
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Characteristics of psychosis in AD-neurotransmitters

- Higher dopamine D3 receptor density in nucleus accumbens
- Reduced serotonin (5-HT) in the ventral temporal cortex
Psychosis in AD

- **More severe form of disease:**
  - Psychosis is preceded by increased rate of cognitive decline
  - More synapse loss
  - Lower gray matter volume
  - Lower regional metabolism and blood flow

- **Greater impairment across neocortical regions**
  - **Heteromodal association regions** predominate
    - Frontal cortical regions

- Increased accumulation of TAU, fibrillar forms of Aβ (?)

- Risk of psychosis, at least in part, is genetically mediated
Why are psychotic symptoms rare in FTD?

• In AD, delusions are associated with cognitive performance and with frontal hypofunction
  - Facilitation of psychotic symptoms through
    • Poor mapping of internal feelings on observed reality
    • Inappropriate correction of subsequent inaccurate conclusions

• So, why are psychotic symptoms rare in FTD?
  - Unlike FTD, in AD- involvement of mid-temporal lobe which links perception to emotional states
    • Fear
    • Disturbed sense of threat or familiarity

• Temporal-limbic system is necessary to develop false beliefs
What can we learn from synucleopathies?

• **Cholinergic mechanisms**
  - More extensive and earlier cholinergic loss compared to AD
  - Hallucinations are associated with loss of cholinergic activity in the temporal cortex, particularly in regions associated with visual recognition
  - Receptor targets are preserved
  - Greater response to cholinesterase inhibitors compared to AD
What can we learn from synucleopathies?

• Serotonergic system:
  - Polymorphism in the 5HTTLPR, a serotonin transporter gene, is associated with persistent delusions but no hallucinations in DLB/PDD

Creese et al 2013
Loss of Dopamine Transporter Binding and Clinical Symptoms in Dementia With Lewy Bodies

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ABSTRACT:
Background: Little is known about the underlying mechanisms of clinical symptoms in dementia with Lewy bodies. The aim of this study was to explore the association between loss of striatal dopamine transporter binding and symptoms in dementia with Lewy bodies.

Methods: Thirty-five patients with dementia with Lewy bodies underwent single-photon emission computerized tomography brain imaging with N-0-fluoro-propyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (123I]FP-CIT). Associations between striatal binding ratios and motor (UPDRS), psychiatric (Neuropsychiatric Inventory; NPI), and cognitive (Mini–Mental State Examination [MMSE] and neuropsychological tests) symptoms were assessed by linear regression analysis.

Results: The explorative analysis showed that the motor UPDRS was negatively associated with putamen dopamine transporter binding, whereas no association with striatal dopamine transporter binding was found for total NPI, hallucinations, apathy, depression, anxiety, and MMSE scores. However, in post-hoc analysis, executive impairment was positively associated with dopamine transporter loss after adjustment of age and gender.

Conclusions: Dopamine deficiency in patients with dementia with Lewy bodies was associated with severity of motor symptoms, but did not correlate significantly with ratings of neurobehavioral disturbances or overall cognition. © 2015 International Parkinson and Movement Disorder Society

Key Words: Lewy body; dementia; SPECT; dopamine transporter; 123I]FP-CIT

Siepel et al, Movement disorders, 2016
Delusion and hallucination subtypes?

- Study on the relationship of psychotic symptoms and cognitive/behavioral performance in AD (n=108) (Quaranta et al 2015)
  - No delusions
  - Paranoid delusions
  - Misidentification delusions
  - Paranoid + misidentification delusions
  - Visual hallucinations
  - No visual hallucinations
Delusion and hallucination subtypes?

• Cognitive performance
  • Paranoid delusions = no delusions
  • Misidentification delusions << Paranoid delusions , no delusions
  • Visual hallucinations << no hallucinations

• Abnormal motor behavior (NPI)
  • ↑↑ Misidentification delusions, visual hallucinations

• Disinhibition (NPI)
  • ↑↑ Paranoid delusions
Psychotic symptoms in dementia

- Mechanisms differ between dementia types
- Heterogenic entity, even within the same disease
  - In AD, psychosis may represent a disease subtype
What about treatments for psychosis in dementia?

• Paucity of reports on efficacy of treatments for psychosis per se
Antipsychotics for aggression and psychosis

- **Atypical antipsychotics** *(Ballard et al, Cochrane review, 2006)*
  - 16 trials
  - Risperidone and olanzapine ↓ aggression and risperidone ↓ psychosis
    - Both are associated with serious adverse cerebrovascular events and extrapyramidal symptoms
    - Significant increase in mortality (OR 1.7)

- **Clozapine**: the only antipsychotic with proven efficacy in Parkinson’s disease psychosis

- **Typical antipsychotics** *(peer-reviewed meta-analysis (Schneider 2005))*
  - Similarly increased risk in mortality (OR=1.54, 95% CI 0.004 to 0.02, p=0.01)
Cholinesterase inhibitors

• Apparently do not improve behavioral symptoms in AD
  - Benefits observed in a meta-analysis of RCT in demented subjects with mild neuropsychiatric symptoms (Sink et al JAMA 2005) – small and significant, but of questionable clinical significance
  - Not applicable in severe agitation

• DLB- cholinergic deficit more prominent → RCT with Rivastigmine showed ↓ in hallucinations
Medical Cannabis oil

• Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study (Shelef et al, 2016)
  - N=10
    • Significant decrease NPI:
      - Delusions
      - Agitation/aggression
      - Irritability
      - Apathy
      - Sleep
      - Caregiver distress
Rationale for currently prescribed treatments

• Based on similarity to psychiatric symptoms/ syndromes

• The need for tranquilization in disruptive behaviors
  - Risk for patient and caregivers
  - Coping abilities of support system

• Patient suffering

• Is there rationale for using currently available (but unapproved) medications?
Pros and cons for applying currently available treatments

• **Pros:**
  - The symptoms are very disturbing
    • Patient distress
    • Increased dangerous activities
    • Caregiver burden
    • Stress imposed on physicians

• **Cons:**
  - Very limited efficacy
  - Increased risk for side effect
  - Increased risk for polypharmacy
  - Polypharmacy itself—↑risk for dementia
Despite limited efficacy and increased risk

- CNS active drugs - the most commonly used in elderly, prevalently in combination with other medications
  - Psychotropics + opioid analgetics
    - 20% in community dwelling aged 75-59, 40% > 85.
  - Above the age 75 (Rikala et al, 2011):
    - ≥ 1 psychotropic drug 38% (31% BDZ, 12% antidepressants, 6% antipsychotics)
    - ≥ 2 psychotropic drugs 28%
    - Continuous use: 60% (at 3 years follow up)

- In dementia
  - Some decrease after black box warning 2005, but still 10% of demented elderly are prescribed atypical antipsychotics (Dorsey et al 2010)
So, what can we do?
Course of behavioral symptoms

- In nursing home patients:
  - Prospective study (4.5 y) in 931 NH patients with dementia (Selbæk, Int Psychogeriatr. 2013)
  - Results:
    - Mild dementia: increased severity of psychosis at fu
    - Moderate or severe dementia: decrease severity of psychosis at fu

- Withdrawal versus continuation of chronic antipsychotic drugs (Cochrane 2013)
  - 9 trials (n=606)
  - Both abrupt and gradual withdrawal schedules were used
  - Conclusions:
    - Withdrawal with no detrimental effects on behavior is possible
    - Continuation may be beneficial in subjects with more severe symptoms at baseline and those who responded well to treatment
Non-pharmacological approaches to the treatment of behavioral disturbances in dementia

Underlying assumptions regarding behavioral symptoms:

- Expression of unmet needs
- Reinforced in response to environmental triggers (screaming attracts increased attention)

Gitlin et al, JAMA 2012
Non-pharmacological approaches to the treatment of behavioral disturbances in dementia

Treatment goals - general:
- Prevention, management, reduction or elimination of behavioral manifestations
- Reduction of caregiver distress
- Prevention of adverse consequences (harm to patient or caregiver)

Gitlin et al, JAMA 2012
Non-pharmacological approaches to the treatment of behavioral disturbances in dementia

• Screen for behavioral symptoms
• Characterize behavioral symptoms
  - Type of behavior
  - Onset?
    • Sudden: patient related factors: medical illness, pain, medications, constipation
    • Caregiver behaviors- negative communication
  - Safety concern?
  - Caregiver distress?
• Identify potential modifiable triggers
• Treatment plan
  - Identify and eliminate modifiable triggers
  - Exercise, pleasant events, purposeful activities (sense of significance), environmental simplifications, caregiver education- efficacious in clinical trials
  - Day center

Gitlin et al, JAMA 2012
<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>n</th>
<th>Place</th>
<th>Symptoms treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woods and Dimond (2002)</td>
<td>Touch therapy</td>
<td>57</td>
<td>Long term care facilities</td>
<td>Manual manipulation (restlessness) and vocalization</td>
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<tr>
<td>Holmes et al. (2006)</td>
<td>Music therapy</td>
<td>32</td>
<td>Home care or nursing home facility</td>
<td>Apathy</td>
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<tr>
<td>Svansdottir and Snaedal (2006)</td>
<td>Music therapy</td>
<td>38</td>
<td>Nursing homes and geriatric wards</td>
<td>Agitation, aggressiveness, and anxiety</td>
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<tr>
<td>Lin et al. (2007)</td>
<td>Aromatherapy</td>
<td>140</td>
<td>Care and attention homes</td>
<td>Physically agitated behaviors and verbally agitated behaviors</td>
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<tr>
<td>Gitlin et al. (2008)</td>
<td>Activities program</td>
<td>60</td>
<td>Community</td>
<td>Shadowing and repetitive questioning</td>
</tr>
<tr>
<td>Burns et al. (2009)</td>
<td>Light therapy</td>
<td>48</td>
<td>Nursing care setting</td>
<td>Agitation, argumentative behaviors</td>
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<tr>
<td>Cerga-Pashoja et al. (2010)</td>
<td>Physical exercises</td>
<td>146</td>
<td>Community-dwelling individuals</td>
<td>Physically agitated behaviors, Sleep disturbance</td>
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<tr>
<td>Burns et al. (2011)</td>
<td>Aromatherapy</td>
<td>81</td>
<td>Care homes</td>
<td>Agitation</td>
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</tbody>
</table>

*Adjusted from: de Oliveira AM, 2015*
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<tbody>
<tr>
<td>Kolanowski et al. (2011)</td>
<td>Activities program</td>
<td>128</td>
<td>Nursing homes</td>
<td>Agitation and anxiety</td>
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<td>Sung et al. (2012)</td>
<td>Music therapy</td>
<td>60</td>
<td>Home care facility</td>
<td>Anxiety and wellbeing</td>
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<tr>
<td>O’Connor et al. (2014)</td>
<td>Activities program</td>
<td>160</td>
<td>Community</td>
<td>—</td>
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<tr>
<td>Chen et al. (2014)</td>
<td>Combination of nonpharmacological interventions</td>
<td>92</td>
<td>Residential care facility</td>
<td>Hallucinations, delusion, and agitation</td>
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<tr>
<td>Lowery et al. (2014)</td>
<td>Physical exercises</td>
<td>131</td>
<td>Community mental health or primary clinical service</td>
<td>BPSD, except hallucinations and delusions</td>
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<td>O’Connor et al. (2014)</td>
<td>Activities</td>
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<td>Community</td>
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<td>Nursing homes</td>
<td>Agitation/aggression, depression/dysphoria, aberrant motor behavior, and appetite/eating disorders</td>
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<tr>
<td>Yang et al. (2015)</td>
<td>Aromatherapy</td>
<td>189</td>
<td>Retirement homes for veterans and long term care facilities</td>
<td>—</td>
</tr>
</tbody>
</table>

Adjusted from: de Oliveira AM, 2015
Implementation of non-pharmacological approaches

• Despite their beneficial effects, non-pharmacological interventions are often not implemented (van der Ploeg et al, Int Psychogeriatr 2012)
  - Lack of time
  - Lack of knowledge
  - Pressure imposed on physicians by caregivers
What should be the outcomes of clinical trials?

• Reduction of psychotic symptoms?
• Reduction of behavioral outcomes?
• Caregiver burden?
Conclusions

• Psychotic symptoms are common in dementia
• Associated with significant impact on patients, support system and on cost of treatment
• Currently available treatments
  - Marginal and varying efficacy
  - Side effect
• Underlying mechanisms probably differ by
  - Type of dementia
  - Disease stage
• Management should include
  - Assessment of:
    • Triggers
    • Severity
    • Impact
  - Non pharmacological interventions should be 1st line (exceptions)
    • Caregiver interventions e.g. medical education
  - Pharmacological treatment
    • When
    • What
    • Dose
    • Duration
    • Set treatment goal
  - Consider clozapine
Future directions

• Study underlying mechanisms
  - Not as part of “BPSD”
  - By disease
  - By disease stage

• Appropriate endpoint in clinical trials
  - Pharmacological
  - Non-pharmacological
Thank You