Teaching Course 14

Neuropsychiatric and behavioural symptoms in neurodegenerative diseases - Level 1

Management of neuropsychiatric symptoms in Parkinson’s disease and movement disorders

Dag Årsland
London, United Kingdom

Email: dag.aarsland@kcl.ac.uk
Background

This presentation will focus on Parkinson’s disease (PD) and dementia with Lewy bodies (DLB), which are the two most common movement disorders. In addition to the typical movement symptoms, i.e. tremor, rigidity, bradykinesia, postural and gait disorders, PD and DLB are both characterized by cognitive, sleep, and psychiatric disorders, as well as autonomous dysfunction. The majority of PD patients will develop dementia, and mild cognitive impairment (MCI) is common already at time of diagnosis. Of note, until recently, people who develop dementia before, simultaneously with or within one year after the diagnosis of PD have been classified as DLB, but recently proposed PD criteria suggest that these patients are diagnosed as PDD-DLB type. The neuropsychiatric symptoms have a major clinical impact on patients, carers, and health care system, and there are a range of treatment strategies available. To provide optimal care for these patients, clinicians need to be able to diagnose the neuropsychiatric symptoms and adequately implement the available management strategies.

• Syndromes

Cognitive impairment and Dementia. The profile is usually with a less dominant memory impairment and a relatively more severe executive and visuospatial impairments compared to Alzheimer’s disease. However, the profile varies among patients and memory impairment is very common also in PD and DLB. The rate of cognitive decline is at least as rapid as in Alzheimer’s disease, but there are wide variations. Of note, the time from onset of motor symptoms to dementia in PD also varies considerably, with some having an early onset dementia within the first years after diagnosis whereas others remain dementia-free for more than 20 years, with a mean
duration of 10 years. Identifying patients with a higher risk for early dementia is important in order to plan adequate monitoring and management. Established risk factors include old age, more severe motor symptoms, in particular non-tremor dominant motor symptoms, visual hallucinations, and evidence on MRI of cortical atrophy or reduced concentrations of abeta42 in cerebrospinal fluid.

*Psychosis in PD and DLB*, in particular visual hallucinations, typically consist of formed images, often of people or animals. They tend to be stereotype and repetitive, often not very disturbing but can sometimes be distracting, and even threatening and scary. Frequently occurring “minor” symptoms in PD include passage, presence, and illusions, which often progress towards well formed hallucinations. With normal cognition the patients usually have insight in the pathological nature of the vision, but with worsening cognition insight is often lost. Misidentification syndromes are common and characteristic, including the Capgras syndrome, where a familiar person is thought to be replaced by an imposter. In PD, these symptoms are often, but not always, linked to changes in drug treatment, in particular initiation or dose-increase of dopamine agonists.

*Depression*, typically with low mood and reduced interest, is usually of mild severity and often related to functional impairment. However, symptoms are sometimes more severe and unrelated to other symptoms and impairments.

*Apathy*, defined as reduced motivation and initiative, is among the most common neuropsychiatric symptoms both in PD and in DLB. Apathy is often combined with depressive symptoms, but can also occur with normal mood.
Sleep disorders, including REM sleep behavioural disorders (RBD) and Excessive daytime sleepiness. RBD is typically verbal and/or physical output during REM sleep.

- Assessment

  Cognition.
  
  Cognitive functioning can be assessed using MMSE, but better alternatives are Montreal Cognitive Assessment (MoCA), which is a short screening instrument but addresses executive and visuoconstructive domains better than MMSE. However, both are similarly sensitive to cognitive decline in PD and DLB. More specific and comprehensive neuropsychological testing is useful in people with MCI. In order to diagnose “dementia” the clinician needs to ascertain that the cognitive impairment is sufficiently severe by itself in order to have an impact on the daily functioning of the patient. If not, in PD, the diagnosis will be PD-MCI. Tests such as the Trail making B and Stroop test are often sensitive to even very mild impairment.

Neuropsychiatric symptoms

The Neuropsychiatric Inventory (NPI) is a highly structured carer-based questionnaire of that measures intensity and frequency of 12 neuropsychiatric symptoms. It can be used by different health-professionals after training, and also exists as a nursing home version and also a questionnaire. The Non-motor Symptom Scale (NSMM) exists as an interview and a questionnaire and covers a range of common non-motor symptoms in PD, including neuropsychiatric symptoms.
Psychosis
The NPI includes two items, the Hallucinations and Delusions items. The NPI can be administered as a highly structured carer-based clinical interview, including a Nursing home version, or as a questionnaire (NPI-Q). More in-depth scales are the North-East Visual Hallucinations Inventory (NEVHI) and the Scale for Assessment of Positive Symptoms adapted for PD (SAPS-PD).

Depression
Depressive symptoms can sometimes be difficult to differentiate from cognitive impairment and the parkinsonian motor syndrome. The NPI also includes depression. Severity of depressive symptoms can be assessed by clinical rating scales, including Montgomery and Åsberg Depression Rating Scale (MADRS) and Hamilton Depression scale (HAMD), or by self-report questionnaires such as Beck Depression Inventory, Geriatric Depression Scale or Hospital Anxiety and Depression Scale. For people with dementia the Cornell scale for depression in dementia is the best validated depression scale. This scale is more time-consuming and includes a clinical interview of the patients and the carer, separately.

REM-sleep Behavioral Disorder
A definite diagnosis requires Polysomnography (PSG), but clinical instruments such as the Mayo sleep scale includes screening questions which can identify RBD quite accurately.

Apathy
In addition to the NPI apathy item, specific apathy scales exist such as the Apathy Evaluation Scale.
• Non-pharmacological management

Education, information and support are always important and will reduce anxiety for patient and carers, and improve their ability to cope. Cognitive Behavioral Therapy (CBT) has been shown to be effective against depression in PD patients without dementia and should be tried in milder cases. In addition to improving light, coping strategies for visual hallucinations include visual strategies such as focusing on other objects, or paradoxically focusing on the vision. Arguing rarely works, but a calm discussion questioning the reality of the vision, and trying to re-direct attention towards other topics may be helpful. There is emerging evidence that cognitive training may have a beneficial effect on cognition.

• Pharmacological treatment

These are summarised in the tables. In general there is little systematic evidence in DLB and PDD beyond the cholinesterase inhibitors for dementia. In practice, evidence from PD or AD is used to guide treatment of patients with DLB and PDD.

Cholinesterase inhibitors

The cholinesterase inhibitors donepezil and rivastigmine have good evidence of moderate cognitive effects in PDD and DLB, including meta-analysis evidence. Side-effects can occur but usually one of the drugs is tolerated. They generally do not worsen parkinsonism. The evidence for memantine is more mixed, with one study reporting positive effect on a global outcome measure in a combined group of DLB and PDD.

There are also anecdotal reports suggesting that cholinesterase inhibitors may reduce visual hallucinations in PD and DLB. However, there is no
convincing evidence supporting this, although rivastigmine seems to be particularly effective for cognition in PDD with hallucinations. In DLB, donepezil was shown in one study to improve a combination of neuropsychiatric symptoms including hallucinations, although specific antipsychotic effect does not exist.

**Antidepressants**

There is relatively good evidence for paroxetine, venlafaxine and nortriptyline in PD. Dopamine is also involved in mood and reward and thus dopaminergic drugs may improve mood, with evidence for example for pramipexole to have a positive effect on mild depressive symptoms, in addition to the positive effect on motor symptoms. ECT should be considered for severe and treatment refractory cases and cases with mood-congruent delusions. There is no evidence for treatment of depression in DLB, thus strategies employed in PD are often tried.

**Treatment of psychotic symptoms**

The clinician should always consider changes in drug regime, in particular for patients taking antiparkinson drugs, which may reduce psychotic symptoms. Lowering dosage or withdrawing dopamine agonist is often helpful. However, this may lead to worsening of parkinsonism, and in that case symptomatic treatment should be considered, but only if the symptoms are troublesome, which is not always the case.

In PD, there is good evidence from two RCTs with clozapine (low doses, 12.5 - 50 mg/d) in mixed PD/PDD cohorts, showing good effect size. The challenge is that due to the low risk for agranulocytosis, a challenging regime with weekly blood testing is mandatory. Parkinonism does not seem to worsen. There is no systematic evidence supporting the use of
other atypical antipsychotics, many with poor tolerability in this group, with an increased risk for severe hypersensitivity reactions to antipsychotics.

A recent study with pimavanserin, a 5HT2 antagonist, showed good antipsychotic effect in PD, and particularly good response in PDD. The drug is approved by the FDA but not yet by EMEA.

There are some trial evidence that cholinesterase inhibitors may have a beneficial effect on neuropsychiatric symptoms, but no specific effect on psychotic symptoms have been shown.

There is no systematic evidence for how to treat psychotic symptoms in DLB, thus again, treatment should be guided based on the evidence in PD.

**Table:** Treatment of psychotic symptoms in PD and DLB:

1. Identify and treat possible consider secondary factors
2. Consider changing PD-drug treatment
3. Information, coping strategies (distract, better light, focus)
4. Pimavanserin, if available
5. Consider ChEI (if cognitively impaired)
6. Consider clozapine if needed (low doses, short duration)
7. Consider quetiapine
   i. Monitor AE, incl cQT, BMI, cholesterol, glucose, BP
8. Lewy body dementias.
Suggested reading.


Disclosures
Dr Aarsland has received research support and/or honoraria from AstraZeneca, Heptares, Abbvie, H. Lundbeck, Novartis Pharmaceuticals, Eisai, and GE Health, and serves as paid consultant for H. Lundbeck, Heptares, and Axovant.