

The clinical diagnosis and management of Parkinson's disease

Alison Charleston

September 6th 2018

Introduction

- Clinical features of Parkinson's disease
- Differential diagnosis
- Management of the motor features
- Non-motor and neuropsychiatric aspects

Epidemiology

- 100-200 per 100,000 prevalence over 40 years
- Lifetime risk at 40 years 1:15 for men
- Mean age at diagnosis 70

Diagnosis - history

- Tremor
- Reduced mobility and dexterity
- Change in swallowing/speech
- Anosmia
- Constipation
- REM Sleep Behaviour Disorder (RSBD)

Diagnosis - examination

- Tremor
- Bradykinesia
- Rigidity
- Impaired postural reflexes

Other features

- Hypomimia, dysarthria, hypophonia, dysphagia, sialorrhea
- Blepharospasm, reduced contrast sensitivity
- Micrographia, dystonia, camptocormia
- 'Freezing of gait', festination
- Seborrheic dermatitis

Diagnosis

- Rate of 'expert' misdiagnosis is quite high:
(sensitivity = true positives 88% and specificity = true negatives 68%)
- Response to levodopa is not diagnostic

'Red flags'

- Symmetry
- Absence of tremor
- Early falls/ loss of independent mobility
- Early cognitive decline
- Poor response to levodopa
- Early bulbar dysfunction
- Breathing problems (stridor)
- Early autonomic failure

Differential diagnosis

- Lewy body disease
- Progressive supranuclear palsy
- Multiple system atrophy
- Cortico-basal degeneration
- Vascular parkinsonism
- Drug-induced parkinsonism

Drugs that frequently cause parkinsonism

- **Typical antipsychotics:**

Chlorpromazine

Promethazine

Perphenazine

Fluphazine

Haloperidol

Pimozide

- **Atypical antipsychotics:**

Risperidone

Olanzapine

Ziprasidone

Aripiprazole

- **Dopamine depleters:**

Reserpine

Tetrabenazine

- **Antiemetics:**

Metoclopramide

Prochlorperazine

- **Calcium channel block**

Flunarizine

Cinnarizine

Verapamil

Drugs that infrequently cause parkinsonism

- **Atypical antipsychotics:**

Clozapine

Quetiapine

- **Mood stabilisers:**

Lithium

- **Antidepressants:**

SSRIs - citalopram, fluoxetine, paroxetine, sertraline

- **Antiepileptic drugs:**

Valproate

Phenytoin

- **Antiemetics:**

Domperidone

Risk factors for drug-induced parkinsonism

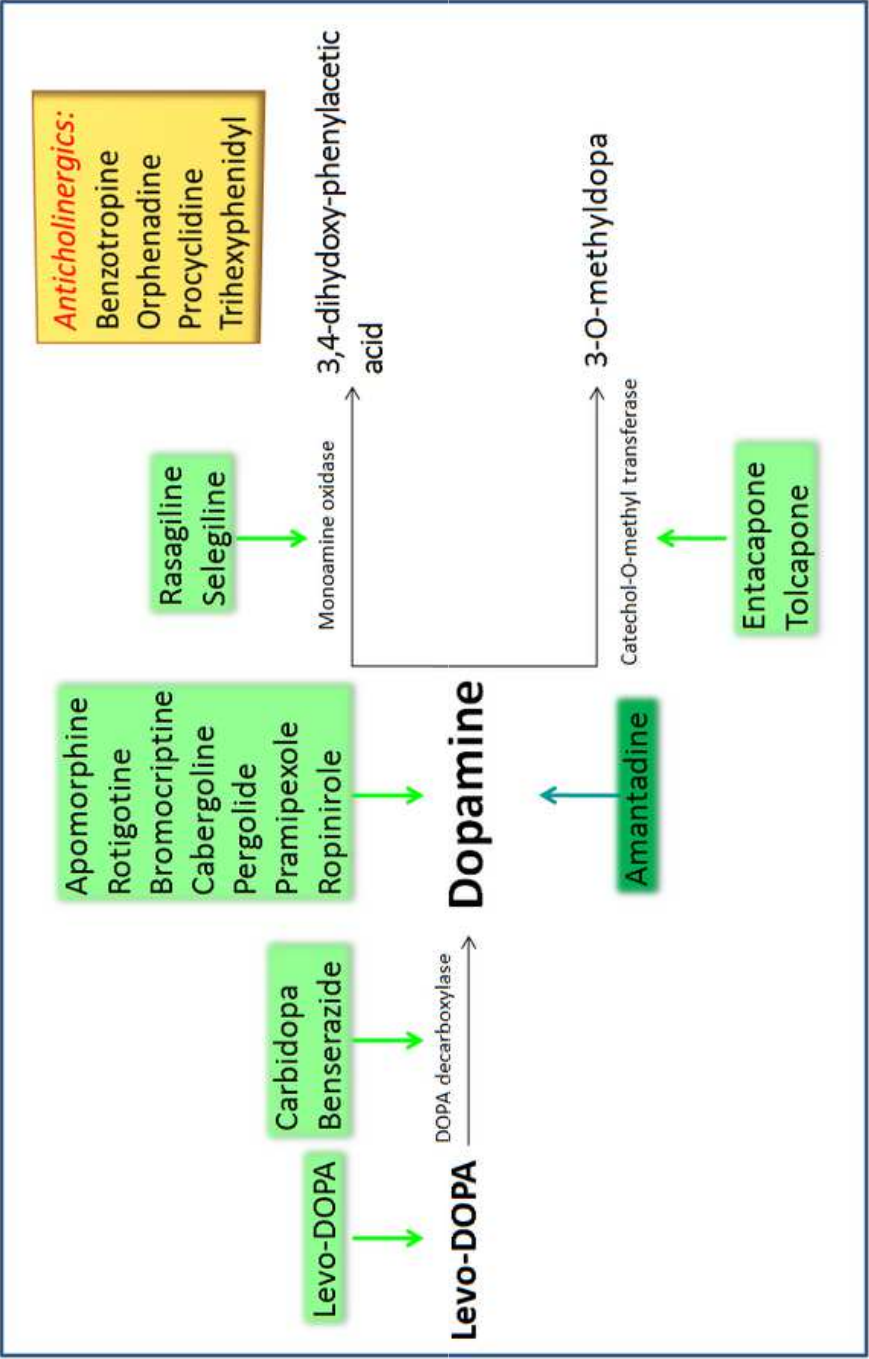
- Dementia
- Advanced age
- Female gender
- Family history PD
- High dose and rapid titration of agent
- Co-existent tardive dyskinesia

Features of drug-induced parkinsonism

- Symmetrical (mostly)
- Tremor not prominent
- Doesn't progress
- Can take up to 18 months to recover

Management of Parkinson's disease

- Differs for different ages/goals
- Changes as disease evolves
- Multidisciplinary approach



Medications

- Levodopa
- Dopamine agonists
- Monoamine oxidase B inhibitors
- Anticholinergics
- Amantadine
- COMT inhibitors
- Apomorphine

All medications can induce or worsen

- Confusion
- Hallucinations
- Postural hypotension
- Nausea

When to begin therapy

- Diagnostic role
- Timing of symptomatic therapy is individual
 - Degree of functional impairment
 - Handedness
 - Lifestyle of patient
 - BUT - no reason to delay initiation of treatment and harder to regain lost function

Case 1

- February 2010
- 72 year-old woman
- 6 months tremor
- Positive family history for ET and PD
- On prochlorperazine
- Action and postural tremor both hands
- Rest tremor left hand, minimal bradykinesia, mildly impaired postural reflexes

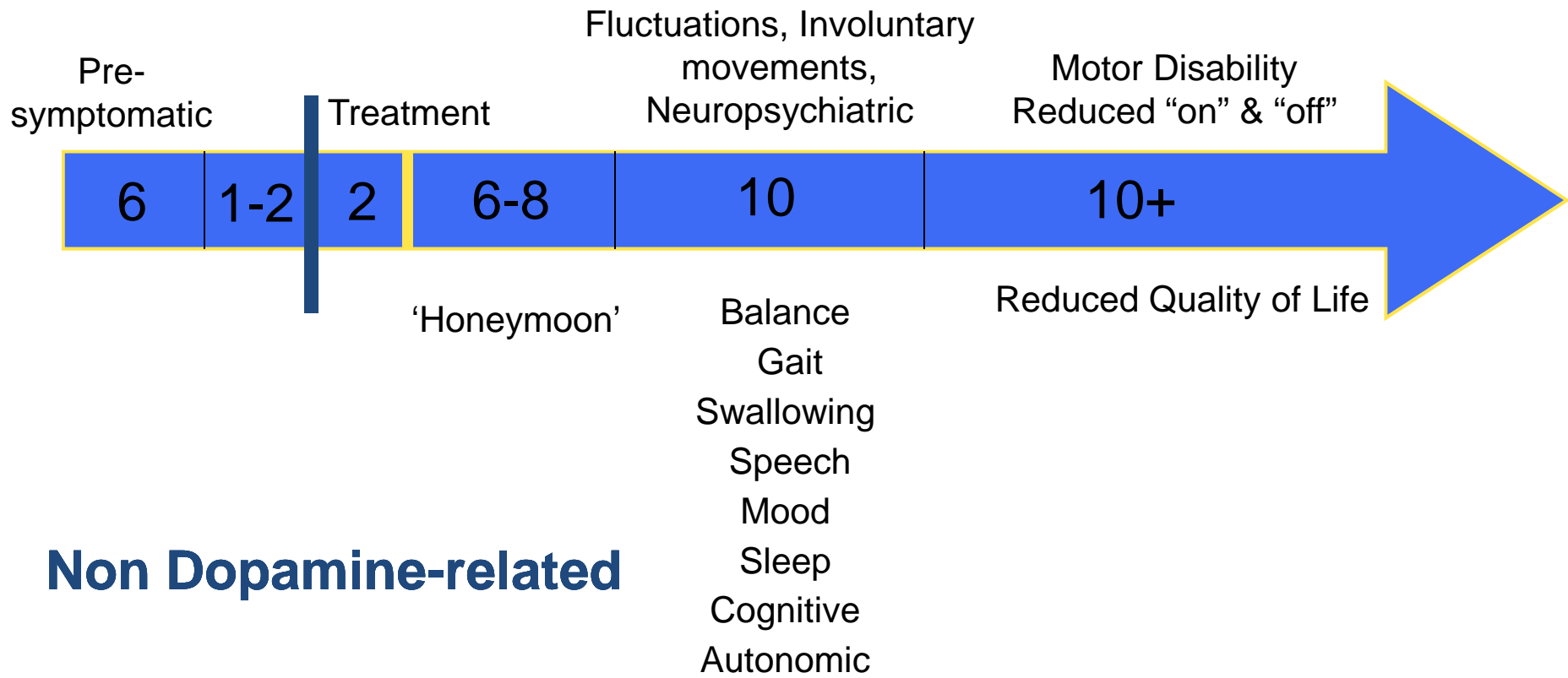
Case 1

- Did nothing for a year (turned out to be 2 ½)
- Mid 2012 had worsening rest tremor, problems with balance, bradykinetic and very anxious
- Decided not to be treated

Case 1

- Mid 2013 returned with worsening tremor and bradykinesia
- Started Sinemet (levodopa and carbidopa) to good effect (one 25/100 tds)

Dopamine-related



Non Dopamine-related

Non-motor features

- Cognitive decline
- Psychosis and hallucinations
- Mood disorders – depression, anxiety and apathy
- Sleep problems, fatigue, sleepiness
- Autonomic dysfunction (postural hypotension, bladder dysfunction)
- Gastrointestinal dysfunction – constipation
- Pain and sensory disturbances
- Seborrhoeic dermatitis
- Olfactory disturbance

Case 2

- 69 year-old retired businessman PD for 11 years
- Followed from 2009
- Fluctuating mobility with poor balance and falls
- Severe dyskinesia
- Behavioural changes – impulsivity, hypersexuality, gambling, punding, ACE-R 95/100
- Bladder dysynergia with incontinence – SPC put in 2011
- Anxiety and depression
- Residential care 2011
- Died 2016

Sydney Multicenter Study of Parkinson's Disease: Non-L-Dopa-Responsive Problems Dominate at 15 Years

Mariese A. Hely, MBBS,^{1*} John G.L. Morris, MD,¹ Wayne G.J. Reid, PhD,¹ and
Robert Trafficante, BAppScMaths²

¹*Department of Neurology, Westmead Hospital, Westmead New South Wales, Australia*

²*Covance Pty Ltd, Ainslie, Australian Capital Territory, Australia*

Sydney study

At 15 years of follow up:

1/3 of the original cohort of 136 still alive

Major disability:

Dementia 48% (cognitive decline in 84%)

Loss of balance and falls (81%; #23%)

Autonomic failure (postural hypotension 35%;
urinary incontinence 41%)

Dysphagia 50%

Hallucinations 50%

Depression 50%

40% in residential care

The Sydney Multicenter Study of Parkinson's Disease: The Inevitability of Dementia at 20 years

Mariëse A. Hely, MBBS,^{1*} Wayne G.J. Reid, PhD,¹ Michael A. Adena, PhD, ASTAT,²
Glenda M. Halliday, PhD,³ and John G.L. Morris, MD¹

¹*Department of Neurology, Westmead Hospital, Westmead, New South Wales, Australia*

²*Covance Pty Ltd, Braddon, Australian Capital Territory, Australia*

³*Prince of Wales Medical Research Institute, Randwick, New South Wales, Australia*

Sydney study

At 20 years of follow up:

26% of the original cohort of 136 still alive

Major disability:

Dementia 83% (mean duration at onset 10.9 years)

Falls (87%; #35%)

Autonomic failure (postural hypotension 48%;
urinary incontinence 71%)

Dysarthria 81%

Dysphagia 50%

Hallucinations 74%

Depression 50% (at least)

48% in residential care

Neuropsychiatric disorders in Parkinson's disease

- Depression
- Anxiety
- Apathy
- Cognitive impairment / dementia
- Psychosis
- Impulse control disorders (ICDs)
- Disorders of sleep and wakefulness

Depression

- Common - 40-50%
- Makes everything worse (UPDRS motor)
- Symptoms overlap those of the disease
- Dopamine agonists can make depression better
- Watch for cyclical mood variation
- GDS best screen

Depression

- Younger patients more at risk
- Patients dislike drugs
- CBT shown to help
- Psycho-geriatric opinion invaluable

Anxiety

- Common - 20-50%
- Often with depression
- Can be an 'off' period symptom
- Generalised anxiety disorder, panic disorder, social phobia, situational anxiety all described
- Treatment similar to the general population

Apathy

- Commonly associated with depression and/or cognitive decline
- Mood is blunted rather than sad
- Distressing for caregivers

Cognitive impairment and dementia

- Mild cognitive impairment in 20% of newly diagnosed PD
- Dementia related to disease duration – 83% by 10.9 years – risk increases with age
- Deficits in attention, working memory, executive function, memory and visuo-spatial skills

Approach to cognitive impairment

- Rule out delirium due to intercurrent illness and/or medication
- Review medications
- Consider cholinesterase inhibitors (some evidence for rivastigmine and donepezil)
- Think ahead – social/legal implications, ACP, driving

Rivastigmine for Dementia Associated with Parkinson's Disease

Murat Emre, M.D., Dag Aarsland, M.D., Ph.D., Alberto Albanese, M.D.,

E. Jane Byrne, F.R.C.Psych., M.B., Ch.B., Günther Deuschl, M.D.,

Peter P. De Deyn, M.D., Ph.D., Franck Durif, M.D., Ph.D., Jaime Kulisevsky, M.D.,

Ph.D., Teus van Laar, M.D., Ph.D., Andrew Lees, M.D., Werner Poewe, M.D.,

Alain Robillard, M.D., F.R.C.P.C., Mario M. Rosa, M.D., Erik Wolters, M.D., Ph.D.,

Peter Quarg, M.Sc., Sibel Tekin, M.D., and Roger Lane, M.D.

N Engl J Med 2004;351:2509-18.

Copyright © 2004 Massachusetts Medical Society.

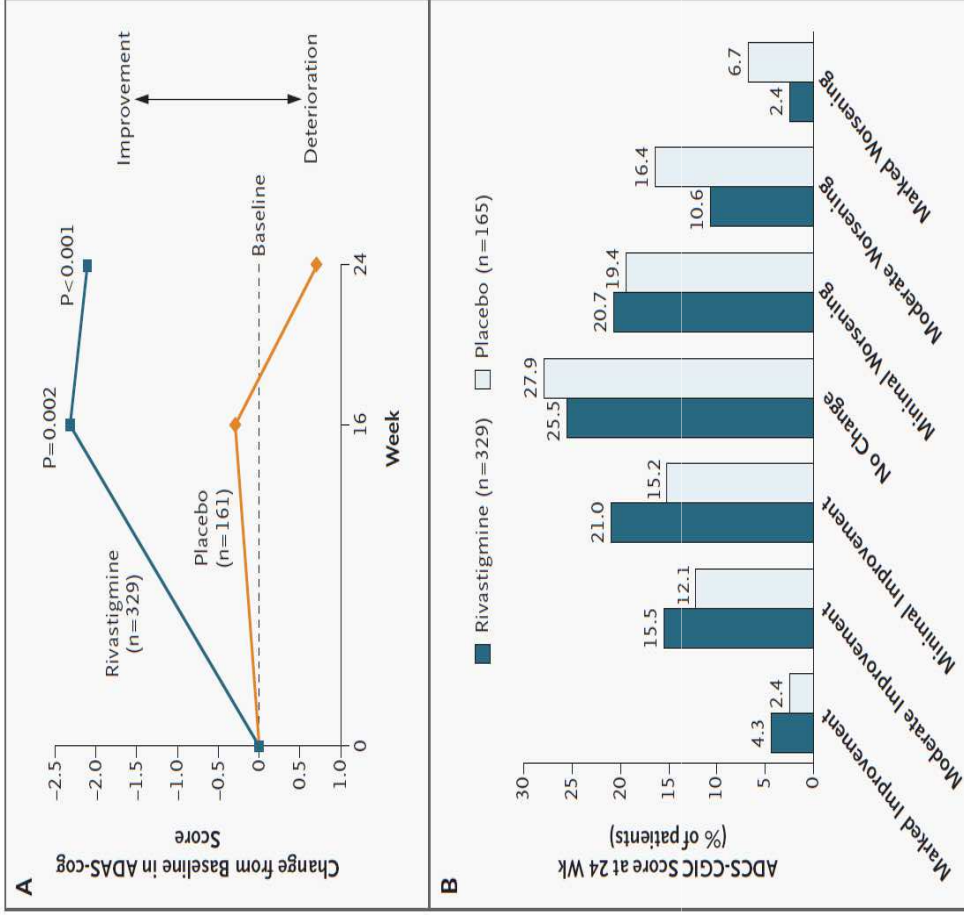


Figure 2. Results of the Primary Efficacy Analysis in the Efficacy Population. Panel A shows the changes from baseline in the score for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). Scores can range from 0 to 70, with higher scores indicating more severe impairment and decreases in scores indicating improvement. Panel B shows the scores for the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC) at 24 weeks. Minimal changes were predefined as those that were clinically detectable but that did not affect a patient's clinical status; moderate changes were defined as definite, detectable changes that had a corresponding effect on clinical status; and marked changes were defined as those that had a dramatic effect on clinical status. P=0.007 for the overall difference between groups at 24 weeks. A few patients in the efficacy analysis had missing data on either of the two primary end points at week 24.

Psychosis

- Experienced by 60% of patients by 12 years
- More likely if older, on more levodopa, history of RBD
- Predicts carer stress, mortality and residential care

A 12-Year Population-Based Study of Psychosis in Parkinson Disease

Elin B. Forsaa, MD; Jan Petter Larsen, MD, PhD; Tore Wentzel-Larsen, MSc; Christopher G. Goetz, MD;
Glenn T. Stebbins, PhD; Dag Aarsland, MD, PhD; Guido Alves, MD, PhD

Arch Neurol. 2010;67(8):996-1001

- 230 PD patients followed up for 12 years
- 137 of 230 patients (59.5%) developed psychosis
- Onset on average 13.0 years after motor onset, (2.2-25.1 years)

The Changing Face of Parkinson's Disease-Associated Psychosis: A Cross-Sectional Study Based on the New NINDS-NIMH Criteria

Gilles Fénelon, MD, PhD,^{1,2*} Thierry Soulas, MA,³

Franck Zenasni, PhD,⁴

and Laurent Cleret de Langavant, MD^{1,2}

Movement Disorders, Vol. 25, No. 6, 2010

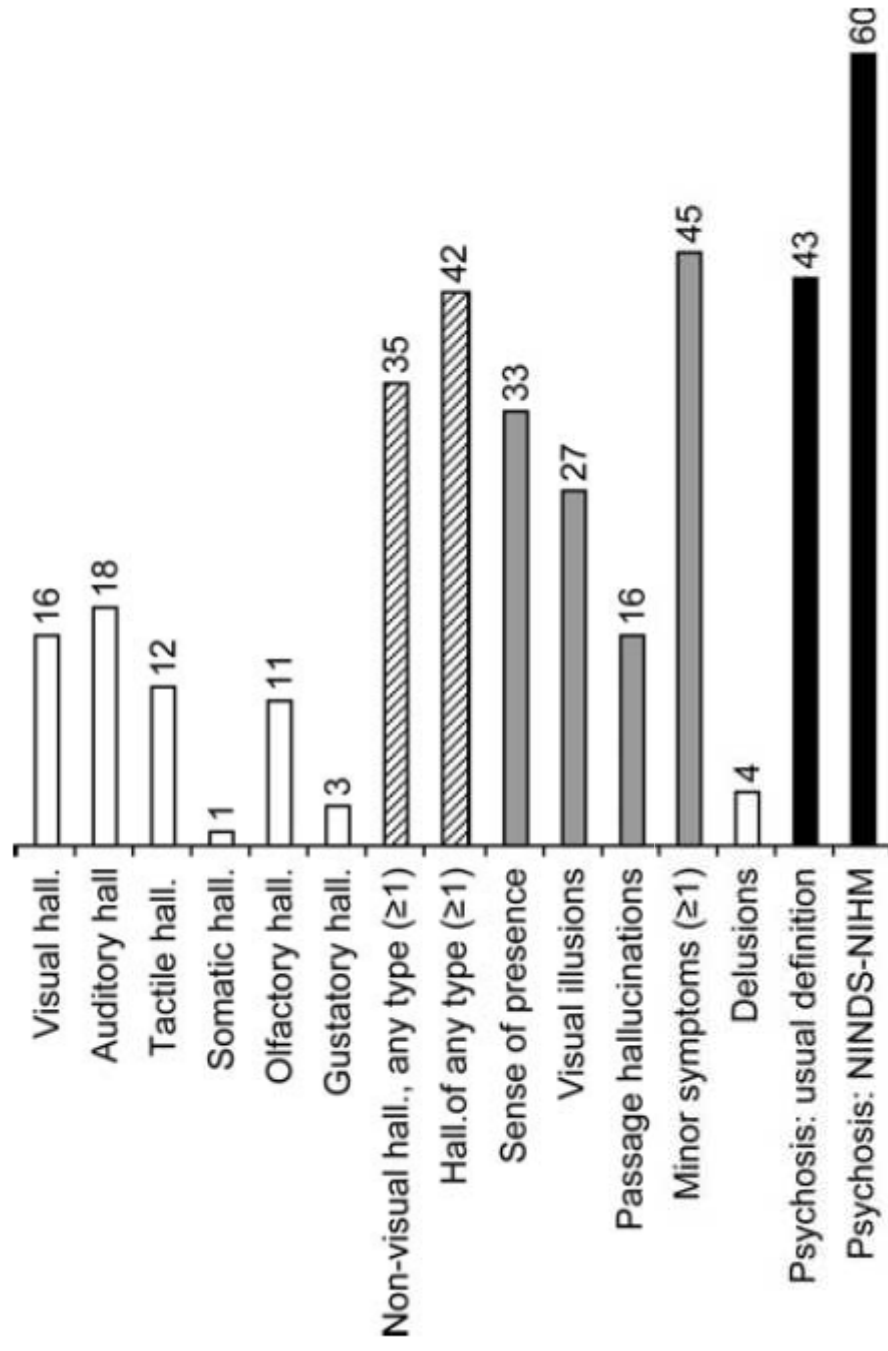


FIG. 1. Distribution of psychotic symptoms in 116 consecutive PD outpatients. Psychotic symptoms include hallucinations and delusions (white bars) and minor phenomena (gray bars). The proportion of patients with psychosis (black bars) is shown, based on the usual definitions (hallucinations or delusions) and the new NINDS-NIMH criteria (hallucinations, delusions, sense of presence, or visual illusions). Values are given in percentages.

Hallucinations

- Unformed visual hallucinations common
- Auditory and tactile can occur
- Older patients with sensory deficits and cognitive impairment more vulnerable
- Associated with depression and daytime sleepiness

Delusions

- Relatively uncommon 4-10%
- Common themes – infidelity, abandonment

Case 3

- 71 year-old woman PD since 2004
- Admitted with falls, hallucinations, collapses
- Hallucinating, dyskinetic, hypotensive
- Levodopa changed from CR to straight and dose reduced; rehydrated and given fludrocortisone; amantadine stopped
- Quetiapine sedated, donepezil caused diarrhoea, rivastigmine patch resulted in resolution of hallucinations

Management of psychosis

- Exclude/treat intercurrent illness
- Review medications

Management of psychosis

- Stop drugs in the following order:
 - Anticholinergics
 - MAO-B inhibitors
 - Amantadine
 - Dopamine agonists
 - Levodopa – reduce to the minimum needed
- } all gradually

Management

- Benzodiazepines (short term)
- Atypical antipsychotics
- Best evidence for clozapine
- Quetiapine sedates and causes postural hypotension
- Clozapine causes agranulocytosis (0.7%), severe constipation, myocarditis
- Pimavanserin FDA approved 2016; safety concerns

Original Investigation

Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease

Daniel Weintraub, MD; Claire Chiang, PhD; Hyungjin Myra Kim, ScD; Jayne Wilkinson, MD, MSCE;
Connie Marras, MD, PhD; Barbara Stanislawski, MPH, MSW; Eugenia Mamikonyan, MS; Helen C. Kales, MD

JAMA Neurol. doi:10.1001/jamaneurol.2016.0031

Published online March 21, 2016.

Impulse control disorders

- Gambling, shopping, hypersexuality, eating
- Punding, hobbyism, hoarding, pacing
- Dopamine dysregulation syndrome

Impulse Control Disorders in Parkinson Disease

A Cross-Sectional Study of 3090 Patients

Daniel Weintraub, MD; Juergen Koester, PhD; Marc N. Potenza, MD, PhD;
Andrew D. Siderowf, MD, MSCE; Mark Stacy, MD; Valerie Voon, MD;
Jacqueline Whetteckey, MD; Glen R. Wunderlich, PhD; Anthony E. Lang, MD, FRCPC

Arch Neurol. 2010;67(5):589-595

DOMINION study

- 3090 patients with PD screened for ICD
- 66% on dopamine agonists and 87% on levodopa
- 14% had an ICD, and 29% of these had ≥ 2 :
 - Gambling 5%
 - Hypersexuality 3.5%
 - Compulsive buying 5.7%
 - Binge-eating 4.3%

Impulse control disorders

- Patients rarely reveal spontaneously.
- More likely with DA than levodopa
- Premorbid personality traits increase risk
- Young males, single, smokers
- Executive dysfunction

Case 4

- 73 year-old businessman
- 8 year history of gambling and hypersexuality
- On ropinirole
- Charged with indecent assault

Management

- Warn patients and partners
- Identify the problem
- Stop, reduce or change dopamine agonists
- Antidepressants, antipsychotics etc

Conclusions:

- Motor deficit responds best to levodopa
- PD is much more than dopamine deficiency
- Non-dopa responsive symptoms cause most of the long term disability in PD
- Non-dopa responsive symptoms can be treated
- PD is a multi-system disease that requires multi-disciplinary management