

Treatment of the Non-motor Neuropsychiatric Aspects of Parkinson's Disease

Iracema Leroi, MD FRCPC MRCPsych
Lancashire Care Trust/University of
Manchester

Non-motor PD Features

- Pain
- Parathesias
- RLS
- Fatigue
- Skin symptoms
 - seborrhoea, facial oiliness
- Dysautonomia
 - bladder instability, altered thermal regulation, O. H.

Other non-motor PD Features

- **Psychiatric Symptoms**
 - depression
 - anxiety
 - sleep disturbance
 - psychosis
- **Cognitive Symptoms**
 - executive dysfunction
 - subcortical dementia
 - cortical dementia

Consequences of untreated mental disturbances?

- ↓ motor function
- ↓ cognitive function
- ↑ disability
- ↓ quality of life
- ↑ caregiver burden

Psychiatric Evaluation in PD

PD related factors

- Progressive disease
- Cognitive decline
- Disease-related psychopathology
- Medication effects

Non-PD related factors

- Past psych history
- Family history psych
- Temperament
- Coping styles
- Social resources
- Live events

Dementia in Parkinson's Disease

Cognitive impairment in PD

- Majority of PD sufferers will experience cognitive impairment, even in the early stages of PD
- Continuum:
 - Discrete cognitive deficits → MCI-PD → dementia in PD (PDD)
- OR
- Subtypes of PD:
 - “dementia prone” vs “non-dementia prone”

Treatment of MCI-PD

- No full scale trials yet
- Cholinesterase inhibitors vs placebo in MCI without PD have not favoured active drugs
- But, consider cholinesterase inhibitors if psychosis or fluctuating cognition is present

Why is PDD important?

- ↓ response to DRT (Hietanan 1988)
- ↑ psychosis & medication-induced delirium (Sudarsky 1989)
- ↑ disease progression (Starkstein 1990)
- ↑ mortality rate (Hughes, 1999)
- ↑ caregiver burden

How common is dementia in PD?

- Point prevalence:
 - 29% of all PD patients in area of Finland¹
- Meta-analysis of 12 studies: 25–30%²
- **3%** of all dementias
- **0.2–0.5%** of >65 year olds

¹ Marttila 1976; ² Aarsland 2005

Longitudinal Studies of PDD

“The Sydney Multicentre Study”

(Hely 2008)

- 20 yr f/up of n=136
- 100 died; most had dyskinesia and non-levodopa responsive complications
- ***PDD in 83% of 20-year survivors**
- other features in >70%:
 - EDS
 - falls
 - freezing
 - hallucinations

“The Sydney Multicentre Study”

(Hely 2008)

- Mean age at PDD diagnosis **71.6** years
- Mean time to onset after dx **10.9** years
- After PDD diagnosis, mean survival 54 months

Risk Factors for Conversion to PDD

- Demographic
- Cognitive
- Psychiatric
- PD-motor
- Other physical: autonomic
- Biomarkers, neuroimaging

Who converts to PDD?

Demographic Factors

- **Older age** *most important risk factor
 - 41% of people with PD from a population of 180,000 in New York
 - Age <50 years: 0% dementia
 - Age >80 years: 69% dementia
- Male gender
- Low education (Cohen 2007)

Who converts to PDD?

Cognitive Factors

- Visuospatial impairment (Mayeux 1998)
- **Impaired verbal fluency and intersecting pentagons at 3-5 yrs**
(Williams-Gray 2007)
- Impaired auditory verbal learning and nonverbal reasoning (Janvin 2005)
- BUT
- frontostriatal executive tasks are NOT predictive of PDD (more dopaminergic in etiology) (Williams-Gray 2007)

Who converts to PDD?

Psychiatric Factors

- Depression ?unclear
- ?Apathy (Pluck and Brown, 2002)
- **Visual hallucinations** (Hobson & Meara, 2004; Burn 2006; Ramirez-Ruiz 2007)
- Psychosis needed treatment with antipsychotics (Ballard 2005)

Who converts to PDD?

PD-motor Factors

- **Akinetic-rigid type of PD** (Aarsland 2003)
- **If present at onset, 4x ↑ risk of PDD** (Williams-Gray 2007)
- **Axial impairment** (Levy 2000)

Who converts to PDD?

Other Physical Factors & Biomarkers

- ? orthostatic hypotension
- ? weight loss (Uc 2006)
- Prolonged anticholinergic drug use
 - may ↑ plaques and tangles (Perry 2003)
- ? ↑ homocysteine levels
 - associated with CVD
 - l-dopa affects ↑ Hcy
- ? CSF beta-amyloid (Aarsland 2008)

Post-mortem PDD: heterogeneous pathology

| | Hughes 1993 (n=31) | Hely 2008 (n=17) |
|-------------------------|-----------------------|---------------------------|
| AD-changes | 9 (29%) | 3 (17%) |
| Vascular | 2 (6%) | 2 (12%) |
| Cortical Lewy bodies | 3 (10%) | 8 (47%) |
| Other | 17 (55%) | Pick bodies, FTD 1(6%) |

Cholinergic deficits in PDD

- ↓ choline-acetyl transferase (ChAT) activity in neocortex in PDD >> AD¹
- **PET**: cholinergic ↓ in both PD and PDD with +++ deficits in PDD²
- **SPECT**: cholinergic ↓:
 - anterior cingulate gyrus (ACG) & parahippocampus & STM³
- **Cholinergic ↓ á cognitive ↓**⁴

1Perry 1993; Tiraboschi 2000; Braak 1990

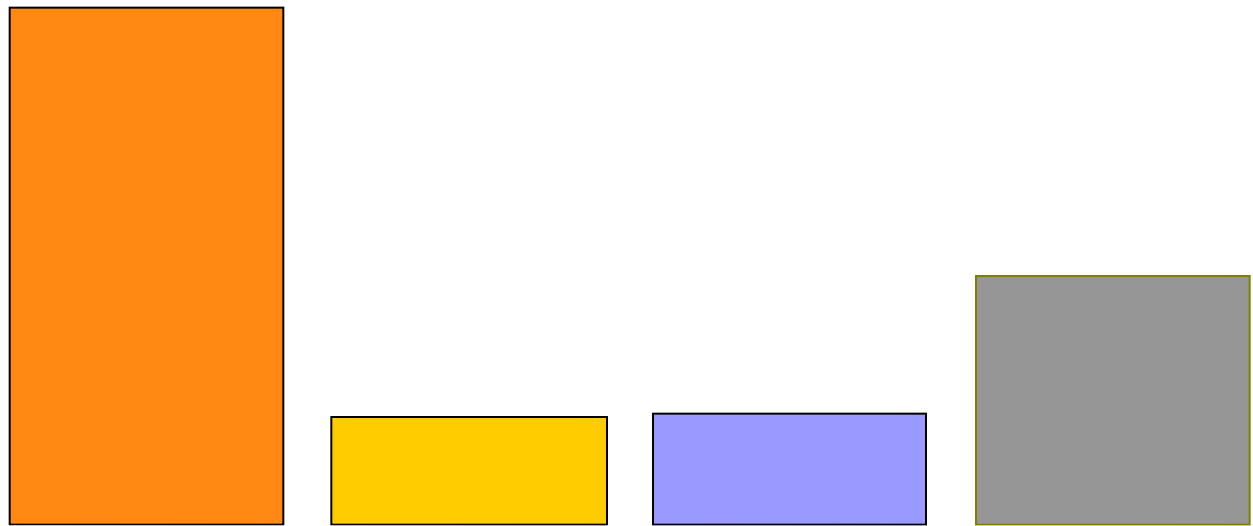
2Bohnen, 2003

3Lee 2004

4Nakano 1984; Bohnen 2006

Severe Cholinergic Deficiency in PDD

ACh loss in DLB, PDD and AD



Lewy bodies outside the striatum

- **Neocortex:** Does not always correlate with dementia in PD (Colosimo 2003)
- **Temporal:** correlates with psychosis and dementia (Harding 2002)
- **Parahippocampal:** correlates with dementia (Harding 2002)

Vascular pathology in PDD

- role of white matter lesions in PDD is unclear
- vascular mixed pathology in dementia without PD is more common than pure VaD
- vascular lesions may add to brain burden in PD causing PDD

“The 10-year rule”

(Aarsland et al, 2006; Mov Dis; 21:96)

- If dementia < 10 years of onset of motor symptoms, pathology is more likely to be **DLB** like
- If onset >10 years after onset of motor symptoms, more likely to be **AD pathology** (cholinergic deficiency)

Neuropsychology of AD vs PDD

| | AD | PDD |
|---------------------------------|-------------|-------------|
| Memory | encoding | recall |
| Orientation | <i>poor</i> | fair |
| Language | <i>poor</i> | fair |
| Attention | fair | <i>poor</i> |
| ECF | fair | <i>poor</i> |
| Visuoperceptual function | fair | <i>poor</i> |

Neuropsychiatric Features of PDD: “BPSD-PD”

(Leroi & Burns, JNNP, 2007)

- delusions (especially Othello syndrome)
- apathy
- depression
- excessive daytime sleepiness (EDS)
- REM sleep behaviour disorder (RBD)
- repetitive behaviour (punding)

Neuropsychiatric Features of PDD: “BPSD-PD”

(Leroi & Burns, JNNP, 2007)

- visual hallucinations
 - Associated with:
 - increased mortality
 - ↑ carer strain.
 - Most important predictor of nursing home placement

Detecting PDD

- Have a high index of suspicion
- Risk factors: age, early psychosis, poor verbal fluency
- Concomitant clinical presentation:
 - EDS, apathy, falls, levo-dopa non-responsiveness, lack of tremor

How do we detect PDD?

Get collateral from carers

- Don't trust "sharp as a tack"
- Ask if they'd leave their loved one alone overnight and WHY they wouldn't
- WHY have they taken over the finances etc...

Pill Questionnaire

(Dubois, oral communication, Chicago 2008)

- Ability of a patient to verbally describe his/her anti-parkinsonian treatment with the time schedule, the nature and dose
- Correlates with impaired ADL

How do we detect PDD?

Apply Diagnostic Criteria for PDD

- DSM-IV criteria for dementia
- RCT criteria: Cognitive impairment appears 1(2)-year after onset of motor symptoms (in contrast to DLB)
- MDS diagnostic criteria

Clinical Diagnostic Criteria for PD-D

(Emre 2007)

Features of PDD:

- I. Core features
- II. Associated clinical features (cognitive & behavioural)
- III. Features which do not exclude PDD, but make the diagnosis uncertain
- IV. Features suggesting other conditions or diseases which make PDD diagnosis impossible

Criteria

Probable PD-D

Possible PD-D

Operationalized MDS Criteria for PDD: simple 5 step algorithm

(Dubois et al, 2007)

- 1. diagnosis of iPD
 - 2. PD prior to dementia
 - 3. PD with ↓ global cognitive efficiency
 - 4. Cognitive ↓ impairs ADL
 - 5. Impairment of >1 cognitive domain
- Queen's Square
 - History/records
 - MMSE < 26
 - Carer interview/pill questionnaire
 - Domains: attention, ECF, visuospatial, memory

“Possible PDD”

- If time interval between motor and cognitive symptoms is not known
- Comorbid pathology (eg CVD)
- Reversible factors (B12 deficiency, infection etc)
- Cognitive impairment due to anti-parkinsonian treatment

How do we detect PDD?

Screens of Global Cognition in PDD

| | | | |
|------------|---|--------|-----------------------|
| CAMCOG-R | Class I evidence in PD; >94% sensitive; 94% specific; *extract MMSE | 25 min | Recc'd by AAN 2006 |
| MMSE | >94% sensitive; 77% specific; better for "cortical" total score not helpful | 7 min | AAN (Level B) |
| ACE-R | no evidence in PD; good frontostriatal testing | 30 min | *extract MMSE |
| Mattis DRS | Used in RCT of PDD (Leroi et al, 2004)*MMSE | 40 min | Cut-off <123/144 |
| Clock | Good screen but low specificity; | 5 min | DLB can't copy! |

SCOPA-Cog:

Scales for Outcome of PD-cognition

(Marinus et al, 2003)

- Short, practical validated instrument
- Sensitive to specific cognitive deficits in PD
- 10 items; max score of 43 (higher is better)
- Test-re-test reliability .78
- Correlates well with CAMCOG and MMSE

PD-Cognitive Rating Scale (PD-CRS)

(Pagonabarraga 2008)

- Can distinguish PD, MCI-PD and PDD
- newly validated
- Global cognition & sub-domains of cognition
- 94% sensitivity to detect PDD
- Can differentiate MCI-PD from cognitively intact PD with verbal fluency & delayed verbal memory test
- 10 sub-cortical-type assessments (including attention, working memory, Stroop test, verbal fluency, memory etc)
- 2 cortical-type (clock drawing, naming).

Specific Cognitive Function Assessments

Executive dysfunction

Clock drawing; verbal fluency (animals; animals in zoo)

Visuospatial dysfunction

Bisecting a line;
Intercalating fingers/butterfly hands;
3-D cube; intersecting pentagons

Attention

Verbal trails (A-1; B-2...);
Serial 7s; months backwards

Memory

3 word-recall but use cueing;
3 shapes; 3-line address;
Hide keys at beginning of interview

Cut-offs for clinical cognitive screens

(Dubois et al, 2007)

- Serial 7's: ≥ 2 incorrect responses
- Months backwards: omitting ≥ 2 months
- MMSE pentagons: inability to draw or copy
- 5 min recall of 3 words: missing at least one word

Clock Drawing Task

- Ask to place hands at 10 past 11
- Score 0-4
- Closed circle: 1 point
- All 12 numbers correct: 1 point
- Long hand correctly placed: 1 point
- Short hand correctly placed: 1 point

Verbal Fluency

- Letter fluency:
- All the words in 1 min beginning with “F”, “A” and “S”
 - Normal is >9 per min for each (Dubois 2000)
- Category fluency:
- All the animals in 1 min
 - Normal is >17 per min

cholinesterase inhibitor therapy?

- Rule out reversible causes of dementia (TSH, B12, Folate etc)
- Aim for levodopa monotherapy
- Stepwise removal of “deliriogenic”, hallucinogenic medications
 - Graded, gradual withdrawal
 - Anticholinergics > selegiline > amantadine > dopamine agonists > COMT inhibitors

What to do before starting cholinesterase inhibitor therapy?

Medical Work-up: Relative contraindications

Cardiac:

- LBBB
- RBBB + L ant or post fascicular block
- QTC >420ms
- Unexplained blackouts
- bradycardia

GI:

- History of severe peptic ulcer disease
- s/p gastroplasty
- Weight loss/anorexia

What to do before starting cholinesterase inhibitor therapy?

Baseline Measures

- No consensus protocol: must be easy to administer, demonstrate meaningful change
- Cognition: same as screen or modified screen
- Behavioural: Neuropsychiatric Inventory (NPI)
- Motor: UPDRS motor
- Quality of Life: PDQ39

Are there any diagnostic tests for PDD?

- 123 I-FT-CIT SPECT (“DaTSCAN”) is now licensed for diagnosing DLB vs AD
 - See “full stop” vs “comma”
- Based on detecting loss of functional dopaminergic neuron terminal in the striatum
- BUT, cannot differentiate DLB from PDD

When Do We Start Drug Therapy?

- No guidance is available
- New NICE guidance for AD suggests “moderate stage” (MMSE 10-22)
 - This does not apply for PD
 - Licensed for “*the symptomatic treatment of mild to moderately severe dementia associated with idiopathic Parkinson’s disease (PD)*”
- Start once diagnosis of dementia is made
- Caution with “MCI”
 - No data for “MCI-PD”
 - Data in AD suggest lack of efficacy/? increased mortality

What Drugs Do We Use?

| | | |
|-----------------------------------|---|--|
| Donepezil (Aricept) | 5mg daily → 10mg daily | Leroi et al, 2004 (RCT); Ravina et al 2005 (RCT) |
| *Rivastigmine (Exelon) | 1.5 mg daily/BD → 6mg BD; Patch once daily | Emre et al, 2004 (RCT)* |
| Galantamine XL (Reminyl) | 8mg daily → 24 mg daily | Aarsland et al, 2004 |
| Memantine (Ebixa) | 5mg daily → 10mg BD | Leroi et al, 2008 |

Side Effects of All Cholinesterase Inhibitors in PDD

Concern in PDD

*GI
(nausea, vomiting, diarrhea)

Anti-PD drug side effects

Anorexia

Weight loss; mechanical difficulties eating

Insomnia

Sleep fragmentation; insomnia; nocturia; EDS

Nightmares

Prodrome to hallucinations; REM problems

Hypersalivation

Common in PD

Side Effects of Cholinesterase Inhibitors in PDD

| | Concern in PDD |
|-------------------------------|---|
| ↓ motor function/tremor* | ? Ach ↑ DA↓ |
| Leg cramps | wearing off; dystonia |
| Orthostatic hypotension/falls | gait ↓; ANS failure; impaired righting reflex |
| Agitation | YES |
| Paradoxial psychosis | PD-related psychosis |

Pilot RCT of Memantine vs PLC in PDD

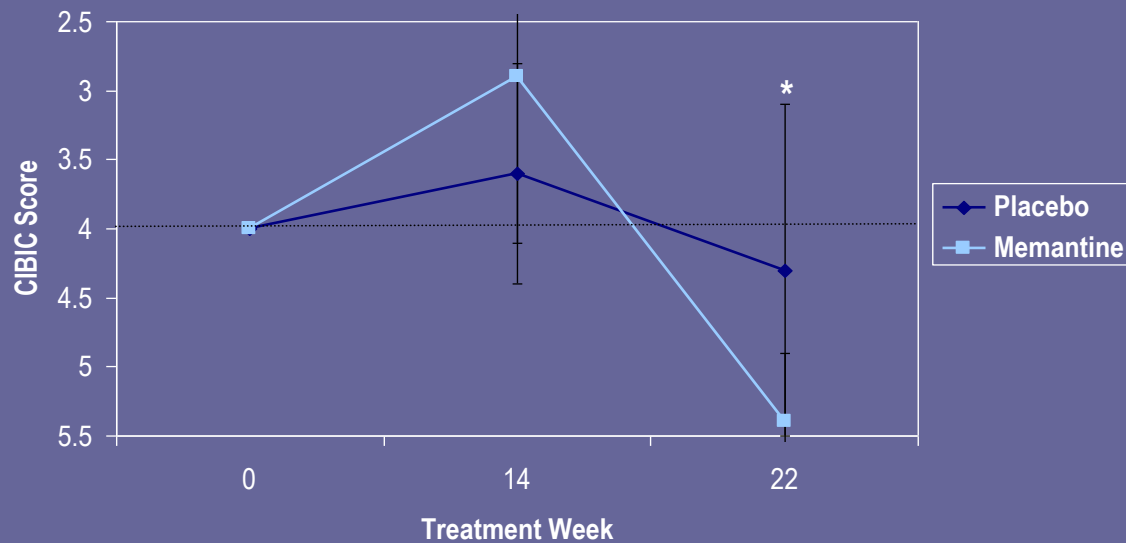
(Leroi et al, Mov Dis 2009)

- Memantine: an uncompetitive NMDA-antagonist **Methods:**
- 22-week RCT in PDD (DSM-IV criteria)
- Primary outcome: Mattis DRS
- Secondary: NPI, Burden Scale, QOL, CIBIC+, MMSE
- **Results:**
- Memantine was well tolerated at 20mg/day
- Improvement on CIBIC at end of treatment phase
- 95% completed the trial

RCT of Memantine in PDD

(Leroi et al, 2008)

Figure 2: CIBIC-Plus Mean Score by Visit



Treatment of PDD:

Non Pharmacological interventions

- Principles of basic dementia care
 - Education and financial planning (wills, POA)
 - Driving
 - Caregiver support, support groups, respite
 - Memory cueing techniques (OT)
 - Safety and ease in the home setting (OT)
 - Monitoring medical condition
 - Improving sensory deprivation

Depression in PD

Epidemiology and co-occurrence of depression in PD

Epidemiology of Depression in Parkinson's Disease

- Global PD Survey (2002):
 - >1000 PD patients in 6 nations
 - >50% depressed on Beck DI
 - only 1% had told clinician
- Prevalence:
 - Community: 3-8% (2-3x non-PD elderly, 1.8%)
 - Outpatient: 25-40%

?problems with diagnosis and cut-off scores for depression

Depression in PD

- Independent risk factor for impaired quality of life (40% of variance in QOL)
- If untreated, can worsen motor functioning
- May be a precursor to onset of motor impairment

Lack of Recognition & Treatment of Depression in PD

- Only 35% of depressed PD get antidepressant
(Weintraub, 2003)
- Carson et al (2003)
 - n=226 with PD
 - 40% untreated depression (major & minor)
 - 78% still depressed at 8 months follow-up
 - most had MDD

PRODEST Study

- Profile of Depression Symptoms in PD patients
- Prospective, observational study
- To date: n=1023
- 27% of PD pts had symptoms of depression
- **>33% continued to suffer depression despite antidepressant therapy**

Bidirectional Relationship of Depression & PD: intrinsic to disease process

- **Depression precedes motor symptoms** (Mayeux et al, 1981; Fukunishi et al, 1991)
- **Depression overlaps with dementia** (Brown & Wilson, 1971; Starkstein et al, 1989)
- **Motor improvement is not associated with improved mood** (Robins, 1974; Marsh & Markham, 1973)
- **Depression severity is not correlated with motor impairment**

Is Depressive Syndrome Specific to PD?

No consistent Profile of Depressive Symptoms in PD

More common:

Anxiety
Irritability
Dysphoria
Cognitive impairment
Apathy

Less common:

Suicidality
Self-blame
Guilty ruminations

Depression and motor symptoms in PD

- Motor-related dysphoria:
 - Off-period depression and anxiety
 - Associated with pattern of on/off syndrome
 - Other non-motor symptoms present (urinary problems, confusion, pain, panic)
 - Improves with better motor control
- Non-motor related depression:
 - Sustained
 - Not related to motor or medication state
 - May be unrelated to disease severity or stage

Differential Diagnosis of Depressive symptoms in PD

Non-depression:

- Drug-induced mood changes
 - Drug withdrawal
- Pathological tearfulness
- Dementia
- Apathy/anhedonia
- Delirium
- “Pseudoanhedonia” (lack of emotional expression)

Subtypes of Depression in PD

- **Psychological Reaction**
 - Grief/demoralisation, Adjustment Disorder
- **Major Mood Disorder**
 - Major depression, Bipolar Disorder
- **Minor Depression**
- **Dysthymia**
- **Brief, recurrent depressive episodes**

Etiology of Depression in PD

Demographic Risk Factors
Premorbid Depression
Pathophysiology
Psychological Risk Factors

Etiology:

Demographic Risk Factors

- Same as general population
 - Female sex
 - Older age
 - Family/personal history of depression
 - Co-morbid somatic disease
 - Psychosis or dementia

Etiology:

Premorbid Depression is Risk for PD Population-based Studies

(review: Ishihara & Brayne, 2006)

- **n=164,385; 3 cohorts** (Nilsson et al, 2001)
 - Patients with depression were significantly more likely to develop PD than patients with osteoarthritis or diabetes (OR 2.2 95% CI=1.7-2.9)
- **n=105,416** (Leentjens, 2003)
 - at time of PD diagnosis, 9.2% had lifetime history of depression vs 4% in controls

- Hence, depression may be a function of the progression of degenerative stages of PD (Braak & Braak), which affect brainstem nuclei early

Etiology: Pathophysiology

- Neurotransmitters – DA, NA, 5HT
- ↓ CSF 5HT_{1A} levels
- ↓ 5HT_{1A} receptor binding
- ↓ DA & NA transporter binding in locus coeruleus & limbic system in depressed PD (PET; Remy et al, 2005)

Etiology:

Psychological Factors

- **Metacognitive Style** (Allott et al, 2005)
- **PD patients with a specific style** (negative beliefs, worries) **had ↑ vulnerability to distress over and above other disease factors** (hallucinations, cognitive impairment, stage of illness, functional disability)

Diagnosis and criteria for depression in PD

Tips to diagnosis of depression in PD

- **1. Consider collateral sources**
- **2. Work-up for reversible causes**
 - FBC, TSH, testosterone levels, B12, folate
 - Dementia, delirium, medical illness
- **3. Screening Tools**

Depression Rating Scales in PD: MDS Task Force Recommendations

(Schrag et al, 2007)

- Literature review of depression scales
- Expert consensus
- **Screening:**
 - HAM-D, Beck, HADS, MADRS, GDS are valid in dPD
- **Severity:**
 - HAM-D, Beck, Zung
 - Cornell scale (CSDD) needs validating in PD

Cut-off scores for key depression rating scales in PD

- HAM-D
 - MADRS
 - BDI
 - GDS 30
 - GDS 15
- 9/10
 - 14/15
 - 13/14
 - 9/10
 - 4/5

Diagnostic Criteria for MDD: DSM-IV

- Depressed mood or anhedonia \geq 2 weeks
- 5/9 symptoms:
- Depressed mood/loss of pleasure or interest
- Insomnia/hypersomnia
- Psychomotor retardation or agitation
- Fatigue or loss of energy
- Worthlessness or guilt, poor concentration
- \downarrow or \uparrow appetite
- Suicidal ideation

NINDS/NIMH recommendations for dx of dPD

- **Use inclusive diagnostic criteria**
 - suggest modified DSM-IV criteria
 - More sensitive than
“etiologic/exclusive/substitutional” approach

Challenges to Diagnosis

- Motor symptoms mask depressive phenomena
- “explain away” depressive symptoms as understandable reaction to PD, aging, dementia
- Effects of medication
- Normal adjustment or sadness as psychological reaction to chronic illness
- Symptoms may co-occur/overlap

Pharmacologic Treatment of Depression in PD

- No clear guidelines
- Inadequate evidence: inadequately controlled & under-powered trials
- Elderly population
- Dosing as per “start low, go slow” rule
- Risks with selegiline
- Pramipexole (D2,D3) may have promise

Pharmacological Treatment of Depression in PD: Reviews

| Author | # Studies | Years | Type | Conclusion |
|-----------------------------|---|------------|-----------------------------|--|
| Klaassen et al, 1995 | 4/12 | 1966-1993 | Meta-analysis | Insufficient evidence |
| Movement D/O (supp 4), 2002 | 5/19 | ? | Review | Insufficient evidence |
| Cochrance 2003 | 3 RCT (SSRI) | 1800s-2001 | Review | Insufficient evidence |
| Weintraub et al, 2005 | 27 N=772(668 completers) >80% on SSRI | 1965-2003 | Meta-analysis & effect size | Large effect size in active & plc groups; larger in non-PD depressed |

PD NICE 2006: Depression

- Have a low threshold for detecting depression
- Caution with overlap of symptoms in mild depression
- Tailor the treatment to the individual
- More research needed!

Pharmacological Management of Depression in PD: Classes of Antidepressants

SNRI – Venlafaxine, Duloxetine

NDRI – Bupropion

SSRI – fluoxetine, paroxetine, fluvoxamine,
citalopram, escitalopram

(*caution with rasagiline)

SARI – trazodone, nefazodone

NASA - mirtazepine

Dopamine agonists and depression in PD

- Antidepressant in MDD (Corrigan, 2000) & bipolar (Zarate 2004)
- Pramipexole: high specificity for D3
- PD trials showed an antidepressant effect with pramipexole (Lemke et al, 2005) & pergolide (Rektorova et al, 2003)
 - But, hard to control for improvement in motor complications

Pramipexole & depression in PD

- Barone et al, 2006:
 - 14-week RCT *open-label* pramipexole vs sertraline in PD with no motor complications
 - N=67
 - DSM-IV MDD & HamD ≥ 16
 - Primary outcome: Δ HamD total

Pramipexole & depression in PD

- Levodopa only
- Early withdrawal n=8 (1 ppx vs 7 sert)
- Both groups improved on HamD from baseline (about 10 points)
- ↓ 50% in HamD: 70% ppx vs 49% sert (NS)
- No sign difference in total Δ HamD
- ppx improved UPDRS motor subscore

RCT of Pramipexole in dPD

Barone P *et al.* A Abstract AAN 61st Annual Meeting, Seattle, 2009

- 6 centres in 13 countries in Europe and Africa
- n= 296 patients
- primary efficacy endpoint: change in BDI
- • BDI scores improved -5.9 (adjusted mean) in PPX vs. -4.0 in plc ($p=.01$)
- • GDS had improved by 2.5 in PPX vs 1.7 in the placebo group ($P=0.03$)
- • UPDRS motor improved by -4.4 in PPX vs. -2.2 in plc ($P=0.003$)
- • UPDRS-ADL improved by -2.4 in PPX vs. -1.2 in plc ($P=0.003$)

Non-pharmacological Therapy of PD Depression

– ECT:

- few formal studies
- Safe, effective, rapid treatment of depression
- Improves PD motor symptoms
- Short-lived effects
- Caution: post-ECT confusion

– rTMS:

- n=42; RCT vs fluoxetine; same effect (Fregni et al, 2005)

Non-pharmacological Therapy: Psychotherapy

- No controlled studies
- 2 open trials of CBT
- effect size in drug trials may be due to non-medication effects
- at least as effective as drug treatment in minor depression in late-life (Lyness et al, 2004)

Refer to a Psychiatrist If:

- Suicidal
- Patient/family request it
- Partial remission/chronic
- Major depression with psychosis
- If psychosis without insight
- If MMSE < 27

Thank you