

NEUROPSYCHIATRY OF PARKINSON'S DISEASE: PRACTICAL CONSIDERATIONS

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DISCLOSURES



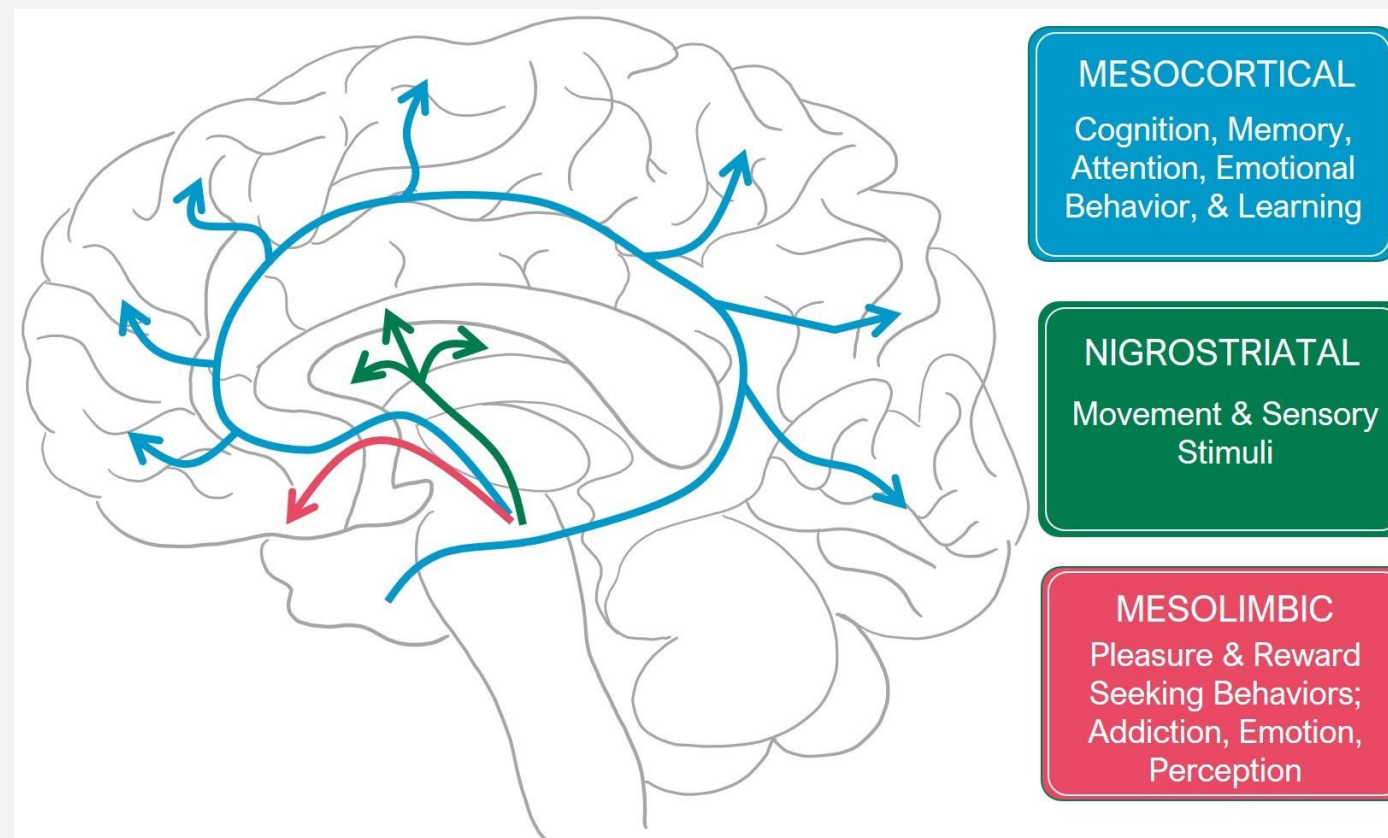
I have no actual or potential financial conflicts of interest related to the content of this talk.



This talk includes information regarding off-label use of medications.

NEUROPSYCHIATRY OF PD

- Dopamine Pathways:
 - Nigrostriatal (motor symptoms): SN to BG (striatum)
 - Mesocortical (cognitive symptoms): ventral tegmental area to frontal cortex
 - Mesolimbic (emotional symptoms): ventral tegmental area to nucleus accumbens, limbic system



DEPRESSION IN PD

- Prevalence estimates vary: 10-80%
- Likely underreported, underdiagnosed; reduced QOL
- Correlates with severity of motor symptoms, cognitive and functional decline, and hospitalisations
- Reactive vs Inherent:
 - More prevalent than in other chronic illnesses
 - Twice as common as in conditions with equal disability
 - Reduced catecholaminergic innervation in depressed PD patients (ACC, LC, thal., amygdala, vent. striatum)
 - Reduced 5-HT tone in depressed PD patients

DIAGNOSIS OF DEPRESSION IN PD

- Overlap between symptoms of depression and PD
 - Psychomotor slowing/bradykinesia
 - Cognitive slowing/bradyphrenia
 - Loss of energy, motivation
- Distinguishing etiology of symptoms does not increase specificity of diagnostic criteria for depression
- DSM criteria for depression are useful in PD
- Depression rating scales also valid (HAM-D, MADRS, BDI) but timing of assessment to on/off motor symptoms may affect scores

TREATMENT OF PD DEPRESSION

- Optimize dopamine agonists if tolerated
 - Best evidence for pramipexole and ropinirole
 - Newer evidence (also strong) for rotigotine
 - Few trials with levodopa, but should work
- Bupropion – moderate evidence, but good rationale exists
 - Dopaminergic
 - Improves motivation
 - Helps depression as well as apathy
- SSRIs, SNRIs and TCAs - moderate evidence
 - Venlafaxine (SNRI) and Paroxetine (SSRI)
 - TCA superiority (nortriptyline>paroxetine) is likely artefactual (2009 study), but noradrenergic, anticholinergic effects of TCAs may be beneficial for tremors in early PD
 - SSRIs can worsen apathy

TREATMENT OF PD DEPRESSION

- Few trials with MAOIs, but like with bupropion, good rationale and several case reports exist (selegiline and rasagiline)
 - Drug-drug interactions and dietary restrictions
- Mirtazapine is safe in PD and help improve sleep and appetite, with moderate-good effect on depression
- CBT modified for PD showed benefit in open trial
- TMS is an excellent option for PD depression treatment
- ECT is also effective, and may transiently help parkinsonism

TREATMENT OF PD DEPRESSION

- If there is some response, increase the dose slowly up to to the maximum recommended dose
 - Easiest titration: escitalopram 5 mg daily, increased by 5 mg daily weekly, up to 20 mg daily
- If some response at the highest dose and more benefit is desired:
 - Augment with T3 (liothyronine; 25-50 µg/d)
 - Augment with mirtazapine (7.5-45 mg/d)
 - Augment with low-dose lithium (100-300 mg/d)
 - Switch to a different antidepressant
- If no response, switch to a different antidepressant in the same class first, and if still no response, to an antidepressant in a different class

DEPRESSION VS APATHY

- Is it depression or apathy?
 - Apathy is a deficit in goal-directed behavior (DA) and associated cognitive and emotional processes
 - Can be (and often is) comorbid with depression
 - Prevalence 17-70%; apathy without depression ~28%

Apathy	Depression
• Reduced initiative	• Sadness
• Diminished interest in environment	• Guilt
• Blunted emotional response	• Hopelessness
• Decreased concern for others' feelings	• Pessimism
Overlapping symptoms	
• Dysphoria	
• Low social engagement	
• Decreased enthusiasm for previously enjoyable activities	

TREATMENT OF APATHY IN PD

- Increased doses of dopamine agonists, if tolerated
 - Pramipexole and rotigotine have the best evidence
- Amantadine has modest benefit, is well-tolerated
- Antidepressants: esp. SNRIs and bupropion have benefit (SSRIs may cause or exacerbate apathy)
- Cholinesterase inhibitors show some benefit in open trials (but not memantine)
 - Galantamine has the best evidence
- Stimulants (amphetamine, methylphenidate) are generally poorly tolerated. Atomoxetine is *not* effective
- Modafinil has limited evidence but is better tolerated

ANHEDONIA AND FATIGUE IN PD

- Anhedonia
 - DA: Pramipexole and rotigotine
- Fatigue
 - Levodopa
 - DA: pergolide
 - Also, rotigotine, but the improvement may be related to improvement in depression
 - Stimulant: Methylphenidate 10 mg TID

SLEEP DISTURBANCE IN PD

- Daytime fatigue is a common symptom of PD, due to or exacerbated by fragmented sleep.
- REM sleep behavior disorder (RBD) is a common sleep disorder in PD, often precedes observable parkinsonism
- Patients with idiopathic RBD have increased risk of PD or DLB (up to 65% at 10 years)
- RBD is loss of normal REM atonia, allowing movement or speech during dreams, often “acting out” in violent or aggressive ways
- **Rx:** Melatonin up to 50 mg has been studied and is effective. Clonazepam, if tolerated, is also effective. For fragmented sleep without RBD, melatonin and trazodone

ANXIETY IN PD

- Prevalence up to 50%
- “Wearing-off” anxiety is particularly troublesome
- Anxiety in “off state” may resolve entirely in “on”
- Unlike with depression, DSM criteria are inadequate
- Rating scales also tend to be confounded by motor symptoms

TREATMENT OF ANXIETY IN PD

- Few treatment trials overall
- Treatment to reduce "on/off" fluctuations may reduce “wearing-off” anxiety
- Open trial of citalopram showed benefit. Escitalopram is safer, easier to titrate, and should have equal efficacy
- Mirtazapine is effective
- Buspirone – few trials, but works well in PD with minimal adverse effects, especially at high doses
- Gabapentin is effective at high doses (if tolerated)
- Use of benzodiazepines limited by cognitive symptoms
- CBT for anxiety in PD effective in one trial

PSYCHOSIS IN PD

- Prevalence up to 60%
- Primarily associated with dopaminergic medications
 - Rarely pre-existing psychosis
- Hallucinations typically predate delusions
- Hallucinations > delusions
- Visual > auditory hallucinations
- Arises later in disease course, ~10y after dx
 - Medication sensitivity increases progressively
 - Dopamine agonists > levodopa

TREATMENT OF PSYCHOSIS IN PD

- Simplifying PD and other drug regimen is most helpful
- Eliminate: benzos, opioids, anticholinergics (including TCAs)
- Keep: rivastigmine
 - Improves behavior and cognition in those with VH
- Reduce dopaminergic meds as tolerated:
 - MAOIs, amantadine, COMT inhibitors
 - Dopamine agonists: ropinirole, pramipexole
 - Levodopa
- Worsened motor symptoms are often acceptable if psychosis is reduced

TREATMENT OF PSYCHOSIS IN PD

- NO typical antipsychotics
- Atypical antipsychotics have more 5-HT_{2A} antagonism than D₂ antagonism
- Quetiapine is most used, clozapine is most effective
 - Low-dose clozapine is sufficient (6.25-50)
 - Exception: Pre-existing psychosis (higher dose = more anticholinergic activity)
 - Agranulocytosis risk reduces exponentially with time
- Pimavanserin is a 5-HT_{2A} inverse agonist
 - Only FDA approved agent for PD psychosis
 - More effective for hallucinations than psychosis
 - Cardiovascular risk higher or same as atypicals

Table 1 Dissociation constants for antipsychotic drugs at the human cloned dopamine D2, D3, D4 and serotonin-2A receptors. The binding of three different radioligands was inhibited by each antipsychotic drug. These three inhibition constants were then related to the membrane/buffer partition coefficients of the radioligands. By extrapolating to ‘zero’ partition coefficient, one obtained the true dissociation constant which was independent of the radioligands.^{21–26} This dissociation constant agreed with that determined directly using the radioactive form of the same antipsychotic drug. Abbreviations: @ YM-09151-2; # SM 9018; * rat cortex tissue

Human clone:	D2	D3	D4	K values (radioligand-independent)		D2	D3	D4	5-HT2A
	nM	nM	nM	5-HT2A	Human clone:	nM	nM	nM	nM
				nM					
1. Amoxapine	16		2	0.5	23. Moperone	1.8		2	
2. Benperidol	0.027		0.066		24. [³ H]Nemonapride @	0.068	0.097	0.165	
3. Bromocriptine	2				25. Norclozapine	100		20	
4. Butaclamol–(+)	0.05		4.5		26. Olanzapine	3	7.8	1.6	3
5. Chlorpromazine	0.66	0.84	1.2	1.8	[³ H]Olanzapine	2.7		1.6	1.6
([³ H]Chlorpromazine	0.72		1.15		27. Perlapine	60	100	30	13
6. Chlorprothixene	3.3		0.64		28. Perospirone #	0.6		0.09	~1.3*
7. Clozapine	44	150	1.6	3.5	29. Perphenazine	0.16	0.13	17	
[³ H]Clozapine			1.6	3.5	30. Pimozide	0.6			
8. Droperidol	0.25		0.84		31. Prochlorperazine	1.2		5.4	
9. Epidepride	~0.01				32. Raclopride	0.64	2	620	4000
10. Flupentixol-cis	0.14	0.3	1.6		[³ H]Raclopride	1.6	1.6		
11. Fluperlapine			21		33. Remoxipride	30	640	2800	5200
12. Fluphenazine	0.32	0.11	50	3.2	34. Risperidone	0.3	2.5	0.25	0.21
13. Glaxo 1192U90	4		0.8		35. Ritanserin	10		30	0.54
14. Haloperidol	0.35	6.2	0.84	46	36. Seroquel	78	160	3000	110
[³ H]Haloperidol	0.4		0.84		37. Sertindole	2.6	2.5	~1	0.3
15. Iloperidone (HP873)	3.5	14	2.5	0.12	[³ H]Sertindole	1.9		0.84	0.28
16. Isoclozapine	6	11.5	5.8	1.8	38. SM 13496	1.2		0.3	8.2
17. Isoloxapine	6		4.5	3.7	39. [³ H]Spiperone	0.065	0.32	0.089	0.57
18. Loxapine	5.2	18	7.8	2	40. Sulpiride-S	5	6.4	200	
19. MDL 100, 907	9000			0.14	41. Thioridazine	0.4	1.5	1.5	1.1
20. Melperone	~50	160	410	150	42. Thiothixene-cis	0.12		6.4	
21. [³ H]Methylspiperone	0.094				43. Trifluoperazine	0.96	0.45	44	7.4
22. Molindone	6	20	2400	5800	44. Trifluoperidol			0.35	
					45. Ziprasidone	1.2	1.1	0.8	3.3

MANIA AND HYPOMANIA IN PD

- Often medication-induced: Dopamine agonists most common, levodopa less common; hypomania ~11% & mania ~6%
- Can occur without prior bipolar history
- Higher doses of DRT, DDS, and younger age more likely
- Euphoria, grandiosity, insomnia, increased motor activity
- May include hallucinations and delusions/psychosis
- Rx:
 - Reduce or stop the offending agent
 - Consider atypical antipsychotics (quetiapine, clozapine)
 - Mood stabilisers if persistent (e.g. valproate)
 - Avoid lithium (motor side effects, toxicity risk)
 - Monitor closely for recurrence, esp. w/ dose adjustments

PD DEMENTIA

- Prevalence up to 80%, often late into the illness
- Bradyphrenia and executive dysfunction are characteristic
- Memory deficit characterized by poor recall (vs. poor storage in AD)
- **Rx:** Cognitive symptoms respond to dopaminergic Rx, also to pro-cholinergic Rx (cholinesterase inhibitors like rivastigmine, donepezil, etc.)
 - In DLB, dopaminergic rx are not as effective, but cholinergic rx are even more effective
- Anti-cholinergic treatment (e.g. trihexylphenidyl, benztropine) for motor sx of PD may worsen dementia

IMPULSE CONTROL DISORDERS

- Seen with treatment, particularly dopamine agonists
- Generally, a sudden dramatic change in personality
- Compulsive gambling, spending, sexual promiscuity
 - No other symptoms of mania
- Pramipexole is most often implicated
 - Most D3 affinity
- **Rx:** Removal of the offending medication
 - Also: CBT
 - Prelim. evidence: naltrexone, valproate, clozapine

DOPAMINE DYSREGULATION SYNDROME

- Addiction-like dependence on l-dopa or dopamine agonists
- Drug-seeking, prescription abuse, etc.
- Anticipatory anxiety towards “off” state
- Overuse of medication with disregard of side effects (dyskinesias)
- **Rx:** Use of carbidopa/levodopa CR, COMT or MAO inhibitor to minimize on/off fluctuations; family monitoring use
 - Prelim. evidence: aripiprazole, valproate

PSYCHIATRIC EFFECTS OF DBS

- Incidence of depression and new onset suicidal ideation may increase after DBS: 1.9% vs 0.9% for BMT [$p=0.61$]
- SI: STN vs GPi: 1.5% vs 0.7% [$p=0.61$]
- STN implant may also slightly worsen cognitive sx (verbal fluency, working memory) and apathy
- DBS at STN may allow reduction of dopaminergic medications
 - Reducing meds may help with impulse control or psychosis
 - Continued or worsened apathy, cognition, and depression with reduced levodopa
- Patients receiving DBS should be screened for suicidality, depression, mania, psychosis, and followed psychiatrically

ATYPICAL PD

- DLB

- Shared α -synuclein pathophysiology with PD: Lewy bodies start in cortex in DLB vs. midbrain in PD
- Same cognitive-motor spectrum as PD: Cognitive symptoms before motor (resembles PD in late stages)
- Core sx: Fluctuating alertness, vivid visual hallucinations (poor insight), mild motor Parkinsonism, RBD
- Cholinesterase inhibitors are more efficacious than in AD
- Rivastigmine has the best evidence: Improves cognition + hallucinations; Memantine can worsen hallucinations
- Motor symptoms in DLB are less responsive to Sinemet
- Avoid typical antipsychotics; Use quetiapine, aripiprazole, clozapine, pimavanserin
- SSRIs/SNRIs much preferred over TCAs for depression
- ECT and TMS are safe and effective
- Melatonin and clonazepam for RBD

ATYPICAL PD

- MSA
 - Prominent autonomic sx; Few trials for depression
 - RBD treatment is the same, but r/o stridor and OSA before using clonazepam. Melatonin may be preferable to those prone to upper airway obstruction.
- PSP
 - Donepezil does not improve cognition and can worsen motor symptoms
 - Coenzyme Q10 may be neuroprotective (FAB scores)
 - Zolpidem effective for agitation and aggression
- CBS
 - Apathy and depression are burdensome
 - Little evidence overall, to suggest specific treatments here

REFERENCES

- Armstrong MJ, Okun MS. Time for a New Image of Parkinson Disease. *JAMA Neurol*. Published online July 27, 2020.
- Ballard C et al. Impact of Current Antipsychotic Medications on Comparative Mortality and Adverse Events in People With Parkinson Disease Psychosis. *Journal of the American Medical Directors Association* 2015; 16(10): 898.e1 - 898.e7
- Burn DJ. The treatment of cognitive impairment associated with Parkinson's disease. *Brain Pathol* 2010;20:672-678
- Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet* 2013; 383:533-540
- Dobkin, R., Menza, M., Allen, L., Friedman, J., Gara, M., Mark, M. et al. (2011) Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. *Am J Psychiatry* 2011 168: 1066–1074.
- Eng ML, Welty TE. Management of hallucinations and psychosis in Parkinson's Disease. *Am J Geriatr Pharmacother* 2010;8:316-330
- Forsaa EB et al. A 12-year population-based study of psychosis in Parkinson disease. *Arch Neurol* 2010;66:996-1001
- Giannini G et al. Suicide and suicide attempts after subthalamic nucleus stimulation in Parkinson disease. *Neurology* 2019 Jul 2;93(1):e97-e105.
- Ishihara L, Brayne C. What is the evidence for a premorbid parkinsonian personality: A systematic review. *Mov. Disord* 2006;21:1066–1072
- Kirsch-Darrow L, Fernandez HF, Marsike M, Okun MS, Bowers D. Dissociating apathy and depression in Parkinson disease. *Neurology* 2006;67:33-38
- Leentjens AFG, Verhey FRJ, Lousberg R, Spitsbergen H, Wilmink FW. The validity of the Hamilton and Montgomery-Asberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease. *Int J Geriatr Psychiatry*. 2000;15(7):644–649.

REFERENCES

Levy R, Czernecki V. Apathy and the basal ganglia. J Neurol 2006;253:54-61

Merims D et al. Dopamine dysregulation syndrome, addiction and behavioral changes in Parkinson's disease. Park Rel Dis 2007;14:273-280

McGrane I, et al. Melatonin therapy for REM sleep behavior disorder: a critical review of evidence. Sleep Medicine 2015;16:19-26

McKeith I, Dickson D, Lowe J, et al. Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB Consortium. Neurology 2005;65:1863–1872

Pontone GM et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. Movement Disorders 2009;24:1333-1338

Reijnders JSAM, Ehrt U, Weber WEJ, Aarsland D, Leentjens AFG. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008;23(2):183–189.

Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 2005;128:1314-1322

Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology. April 2012; 78(16):1229-36.

Smeding HM, Speelman JD, Koning-Haanstra M, Schuurman PR, Nijssen P, van Laar T, et al. Neuropsychological effects of bilateral STN stimulation in Parkinson disease: a controlled study. Neurology 2006;66:1830-6.

Weintraub D et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 2010;67:589-595

Weintraub D, Duda JE, Carlson K, Luo P, Sagher O, Stern M, Follett KA, Reda D, Weaver FM; CSP 468 Study Group. Suicide ideation and behaviours after STN and GPi DBS surgery for Parkinson's disease: results from a randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2013 Oct;84(10):1113-8