Neuropsychiatry of Movement Disorders: Practical Considerations

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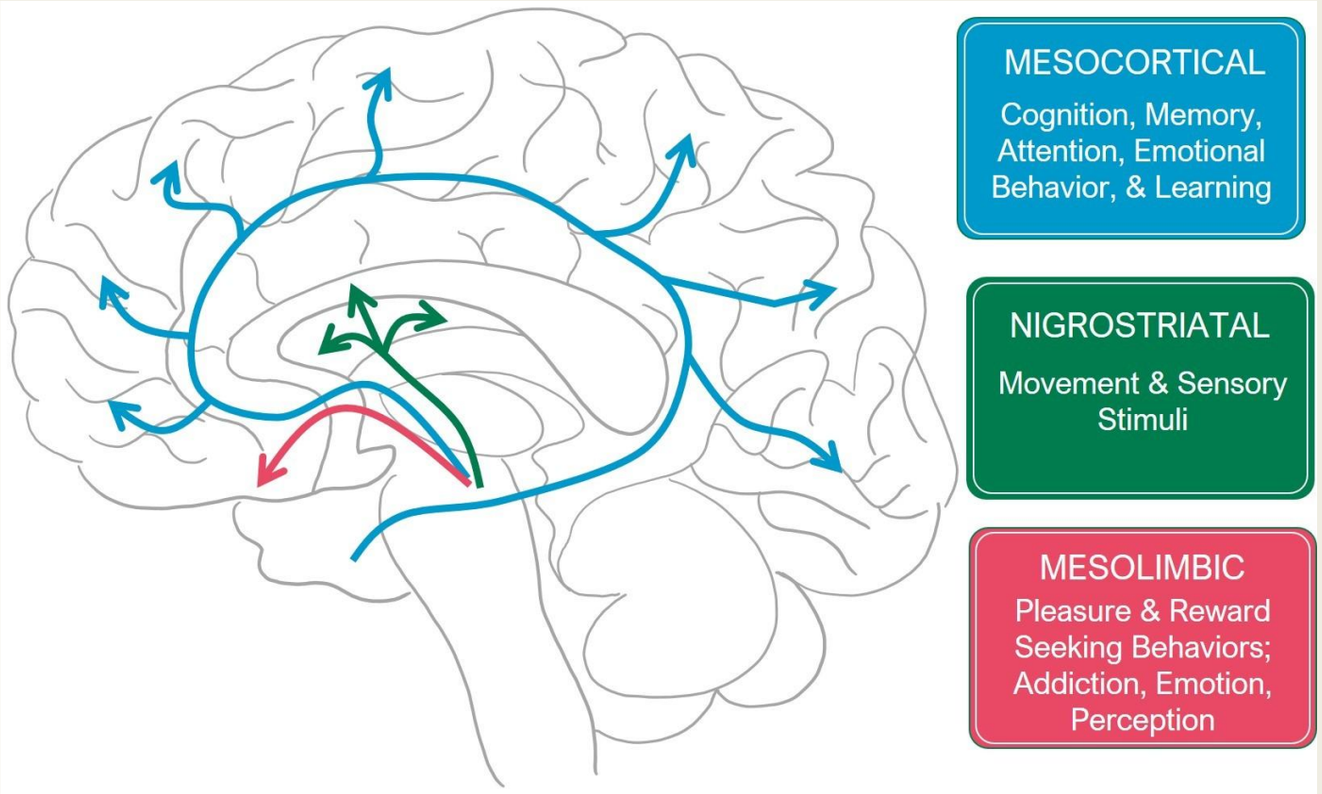
Disclosures

- 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, amyg, 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 <u>not</u> increase specificity of diagnostic criteria for depression
- DSM criteria for depression <u>are</u> 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 in 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

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-HT2A 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-HT2A 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 nM*	*D3 nM*	*D4 nM*	*K values (radioligand-independent)*		*D2 nM*	*D3 nM*	*D4 nM*	*5-HT2A nM*
				5-HT2A nM	*Human clone:*				
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. Trifluperazine	0.96	0.45	44	7.4
22. Molindone	6	20	2400	5800	44. Trifluperidol			0.35	
					45. Ziprasidone	1.2	1.1	0.8	3.3

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 more effective*
- Anti-cholinergic treatment (e.g. trihexylphenidyl, benztropine) for motor sx of PD may worsen dementia

Impulse Control Disorders in PD

- 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 for PD

- Incidence of depression and suicide increases after DBS at STN (smaller effect at GPi), up to 1%
- 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
  - *Cholinesterase inhibitors are more efficacious than in AD*
  - *Rivastigmine has the best evidence*
  - *Memantine can worsen hallucinations*
  - *SSRIs/SNRIs much preferred over TCAs for depression*
  - *ECT and TMS are safe and effective*
  - *Melatonin and clonazepam for RBD*
- MSA
  - *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.*

Atypical PD

- 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*

Dystonias

- Again, few RCTs to inform treatment
- If neuropsychiatric symptoms are reactive to motor impairment, the treatment of motor condition may result in improvement of psychiatric symptoms
  - *Botulinum toxin has shown the best improvement*
- Anti-dopaminergic drugs can worsen dystonia, and can cause tardive dyskinesia
- SSRIs can also worsen dystonia so will need to be used with caution
- CBT has some evidence (dystonia was once considered a psychogenic condition and was treated as such)

Huntington's Disease

- Depression is very common and disabling
- Depression here is treated like primary depression
  - *However, **slow titration** is essential as patients are more sensitive to CNS adverse effects*
  - *SSRIs, SNRIs, TCAs, MAOIs and atypical antipsychotics have all been shown to be effective in open trials*
    - Venlafaxine has the best evidence, followed by citalopram
    - MAOIs cannot be used with tetrabenazine
- ECT is also safe and effective
- Not enough data for TMS
- Many failed trials for cognition, but most inadequately powered
  - *Donepezil, atomoxetine, modafinil have all failed*
  - *Citalopram did not improve cognition, but improved depression*

Wilson's Disease

- Depression, suicide, mania and psychosis are common
- Mainstay of treatment is copper chelators (penicillamine and trientine) and copper-depleting agents (zinc and tetrathiomolybdate) as they improve psychiatric symptoms
- Quetiapine, olanzapine and clozapine are effective for mania/psychosis
  - *More EPS risk due to lenticular degeneration*
  - *More agranulocytosis risk with clozapine because of hypersplenism*
- Lithium is less effective, but useful
  - *Not metabolized by liver*
  - *But can cause tremor*
- Encouraging evidence for ECT

Ataxias

- Cerebellar Cognitive-Affective Syndrome (CCAS) with all types
  - *Executive function*
  - *Spatial cognition*
  - *Linguistic difficulties*
  - *Personality change including blunting of affect and disinhibited behavior*
- Depression is common with certain ataxias like Friedreich's Ataxia and SCAs
- Little evidence exists for treatment considerations
- CBT generally used for CCAS

Tics and Tourette Syndrome

- OCD and ADHD are highly comorbid; treat as usual
- Comprehensive Behavioral Intervention – Tics (CBIT)
  - *Habit Reversal Training (HRT) and Functional Analysis (FA)*
- Alpha-2 agonists (clonidine, guanfacine)
  - *Mild tics*
  - *Lowest side effects*
- Atypical neuroleptics w/ high D2 receptor potency
  - *Aripiprazole is FDA approved*
  - *Risperidone also effective*
  - *Clozapine can worsen tics*
  - *Medium side effects*

Tics and Tourette Syndrome

- Typical neuroleptics w/ high D2 receptor potency
  - *Haloperidol and pimozide are FDA approved*
  - *Fluphenazine has good evidence also*
  - *Highest side effects so reserved for severe tics*
- Tetrabenazine has some evidence also
- THC has a small effect (Cochrane review)

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

McKeith I, Mintzer J, Aarsland D, et al. Dementia with Lewy bodies. Lancet Neurol 2004;3:19–28

Parkinson J. An Essay on the Shaking Palsy. Sherwood, Neely,and Jhones 1817.

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