Neuropsychiatry of Movement Disorders: Practical Considerations

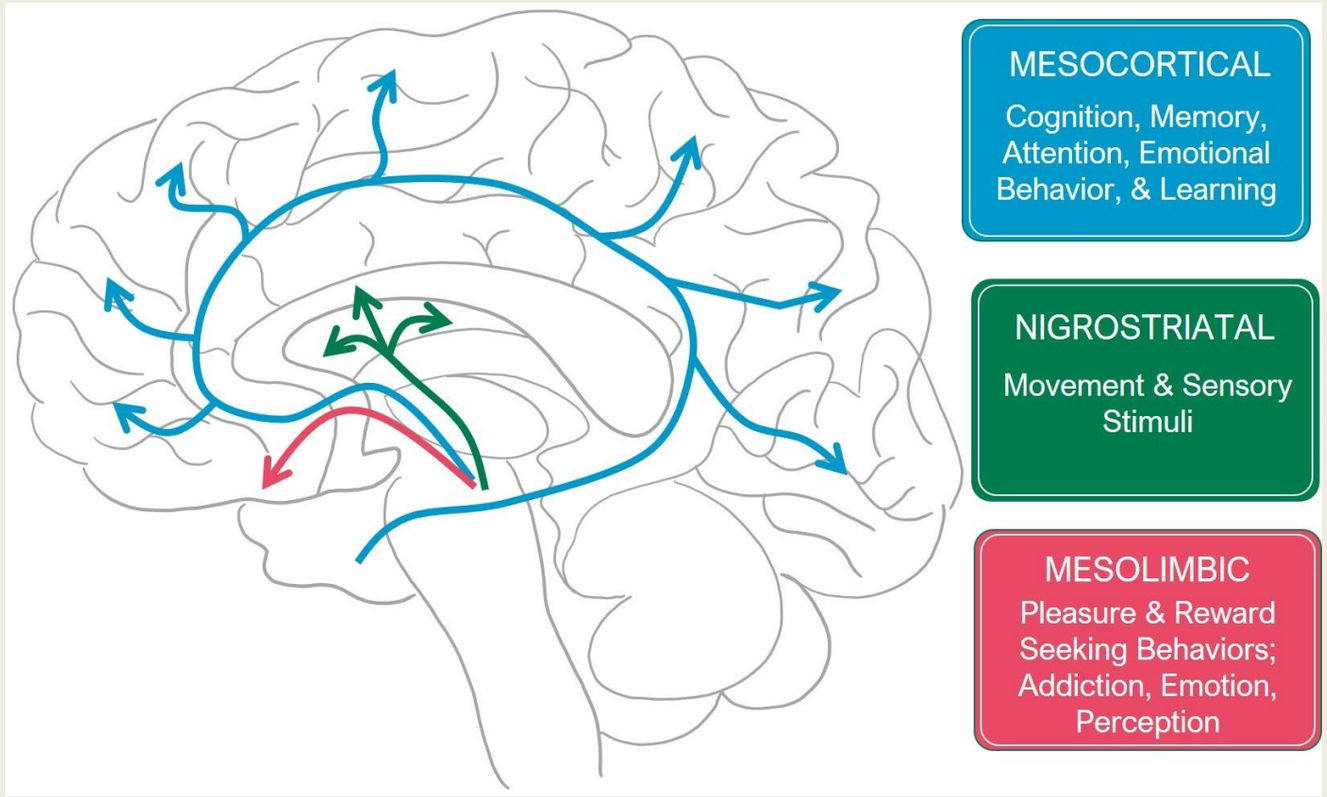
Stanley Lyndon, MD

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)

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