

**Progress in Behavioral and Non-Motor Therapies in
Parkinson's Disease**
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Parkinson's disease and mental health

Objectives:

1. To become familiar with neuropsychiatric and other non-motor disturbances in Parkinson's disease (PD)
2. Learn evidence-based interventions for managing these symptoms in PD
3. Discuss gaps in knowledge and therapeutic priorities for future development

I. Neuropsychiatric symptoms in Parkinson's disease

II. Other non-motor symptoms in Parkinson's disease

Non-motor symptoms of Parkinson's disease

Neuropsychiatric symptoms: anxiety, apathy, depression, ICDs, psychosis, cognitive impairment and dementia

Autonomic dysfunction: drooling, ED, excessive sweating, OH, gastrointestinal and urinary dysfunction

Disorders of sleep and wakefulness: excessive daytime somnolence, sleep fragmentation and insomnia, RBD

Others: fatigue, olfactory and ophthalmologic dysfunction

Non-motor symptoms lacking evidence-based treatments

- Anxiety disorders
- Excessive sweating
- Olfactory dysfunction
- Ophthalmologic dysfunction
- REM sleep behavior disorder

Seppi et al 2019

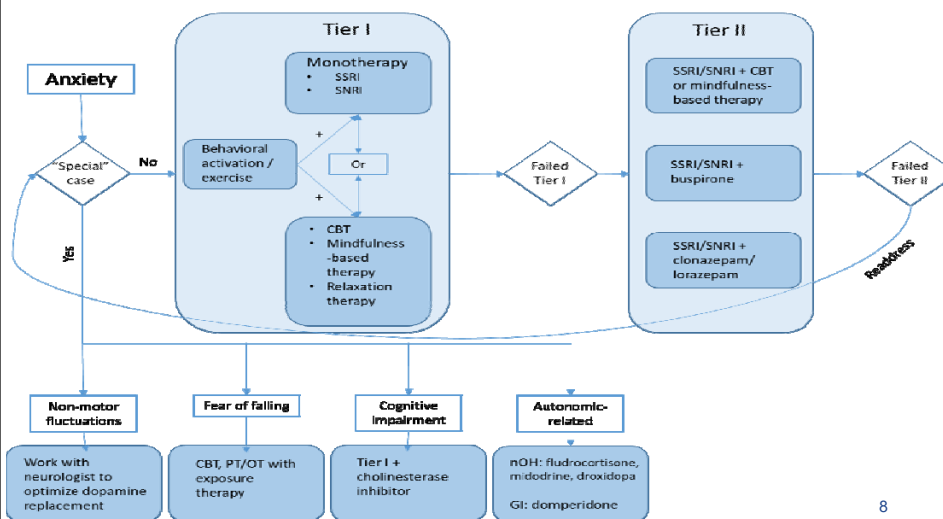
Anxiety in Parkinson's disease



Prevalence of anxiety and anxiety disorders in PD

- Up to 55% have clinically significant anxiety symptoms
- 31% have an anxiety disorder

PD anxiety treatment algorithm



Depression in Parkinson's disease



Parkinson Foundation



- Parkinson's Outcomes Project, a longitudinal look at which treatments produce the best health outcomes in PD n=12,000+
- The impact of depression on quality of life is almost twice that of the motor impairments

From NET-PD: depressive symptoms predict

- Increased need for symptomatic PD therapy (HR 1.86; 95% CI 1.29-2.68)
- Increased impairment in ADLs ($p < 0.0001$)

Parkinson's disease symptoms that could mimic symptoms of major depressive disorder



Core depressive symptoms in Major Depressive Disorder	Parkinson's symptoms that may mimic depressive symptoms
Depressed mood	Masked facies, adjustment disorder to diagnosis
Lack of interest of participation in usual activities	PD-related apathy
Weight loss or decrease in or increase in appetite	Wasting of advanced PD, levodopa-induced nausea, dysphagia
Insomnia or hypersomnia	Sleep fragmentation, medication-induced somnolence
Psychomotor agitation or retardation	Levodopa-induced dyskinesia, bradykinesia
Low energy	PD-related fatigue
Diminished ability to think or concentrate	PD-related cognitive impairment with prominent executive deficits
Feelings of inappropriate guilt or worthlessness or hopelessness	Core depressive symptom, no PD mimic
Suicidal ideation or plan	Core depressive symptom, no PD mimic

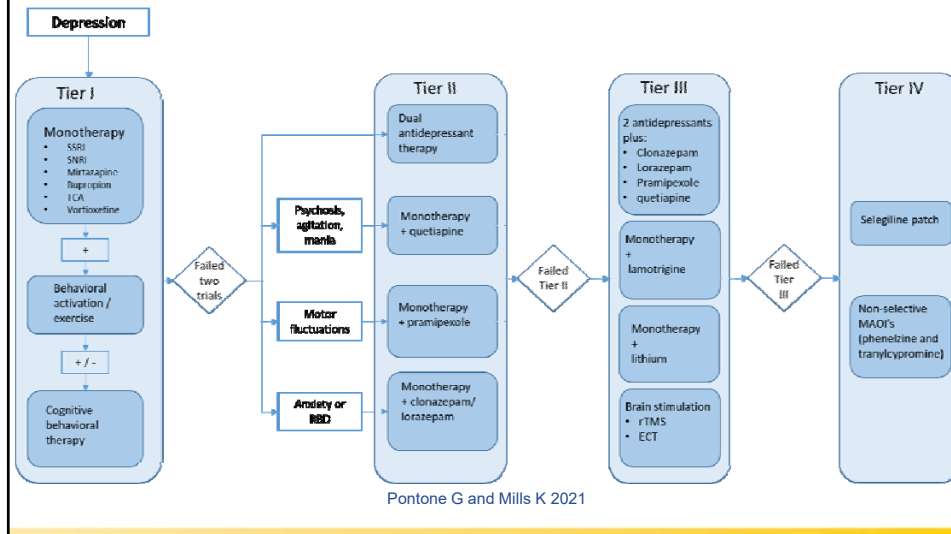
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Antidepressant treatment for PD (Seppi K et al 2019)



Intervention		Efficacy	Safety	Practice implications
Drug class/ intervention strategy	Drug/intervention			
Dopamine Agonists	Pramipexole	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
	Pergolide	Insufficient evidence	Acceptable risk with specialized monitoring	Not useful
	Rotigotine	<i>Unlikely efficacious</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
Monoamine oxidase B (MAO-B) inhibitors	Rasagiline	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
	Selegeline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Moclobemide	Insufficient evidence	Acceptable risk with specialized monitoring ^a	Investigational
Tricyclic antidepressants	Nortriptyline	Likely efficacious	Acceptable risk without specialized monitoring ^b	Possibly useful
	Desipramine	Likely efficacious	Acceptable risk without specialized monitoring ^b	Possibly useful
	Amitriptyline	Insufficient evidence	Acceptable risk without specialized monitoring ^b	<i>Possibly useful^f</i>
Selective serotonin reuptake inhibitors/selective serotonin norepinephrine reuptake inhibitors	Citalopram	Insufficient evidence	Acceptable risk without specialized monitoring ^a	<i>Possibly useful^f</i>
	Sertraline	Insufficient evidence	Acceptable risk without specialized monitoring ^a	<i>Possibly useful^f</i>
	Paroxetine	Insufficient evidence	Acceptable risk without specialized monitoring ^a	<i>Possibly useful^f</i>
	Fluoxetine	Insufficient evidence	Acceptable risk without specialized monitoring ^a	<i>Possibly useful^f</i>
	Venlafaxine	<i>Efficacious</i>	<i>Acceptable risk without specialized monitoring^a</i>	<i>Clinically useful</i>
Other antidepressants	Atomoxetine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Nefazodone	Insufficient evidence	Unacceptable risk	Not useful
Alternative therapies	^c Ω-3 fatty acids	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Nonpharmacological interventions	rTMS	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring^f</i>	<i>Possibly useful (short term)</i>
	CBT	<i>Likely efficacious</i>	<i>Insufficient evidence^g</i>	<i>Possibly useful</i>

PD depression treatment algorithm



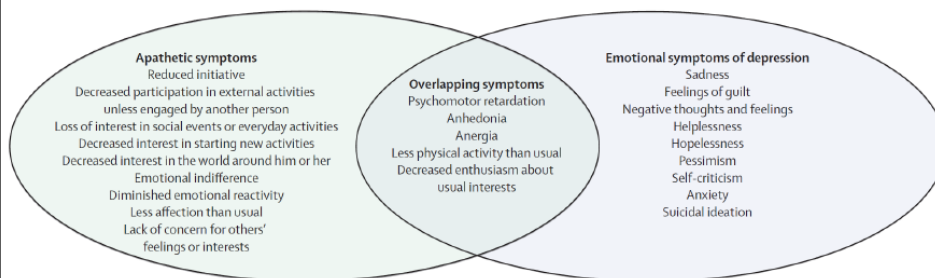
Future directions

- No established treatment algorithm or augmentation strategies
- No long term treatment studies
- Arguments for comparative efficacy are lacking
- Treatment of bipolar illness in PD has been neglected

APATHY IN PARKINSON'S DISEASE



Apathy vs depression in PD



Treatment of apathy in PD

- **Acetylcholinesterase inhibitors**
 - rivastigmine, efficacious, possibly useful
- **Dopamine agonists**
 - piribedil, likely efficacious, possibly useful following STN DBS
 - rotigotine, unlikely efficacious, investigational

Psychosis in Parkinson's disease



Treatment of psychosis in PD

Drug	Efficacy	Safety	Practice implications
Clozapine	Efficacious	Acceptable, with specialized monitoring	Clinically useful
Pimavanserin	Efficacious	Acceptable, without specialized monitoring	Clinically useful
Quetiapine	Insufficient evidence	Acceptable, without specialized monitoring	Possibly useful

Seppi K et al 2019

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Impulse control disorders in Parkinson's disease



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Treatment of ICDs in PD

Drug	Efficacy	Safety	Practice Implications
Amantadine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Naltrexone	Insufficient evidence	Insufficient evidence	Investigational
CBT	Likely efficacious	Insufficient evidence	Possibly useful

Seppi K et al 2019, Papay K et al 2014,
Okai D et al 2013, Thomas et al 2010

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Cognitive impairment in PD: Dementia and non-dementia



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Pathological comorbidity



Primary Pathological Diagnosis	Primary Clinical-Pathological Diagnosis	Associated Pathological Findings	n
Lewy Body Disease (n = 176)	Parkinson's Disease (PD) (n = 62, 35%)	None	42
		PART	2
		Low-level AD pathology	13
		Non-AD Tauopathy	1
		PSP and Low-level AD pathology	1
		Neurofibrillary Degeneration	3
		None	34
	Parkinson's Disease with Dementia (PDD) (n = 110, 63%)	PART	2
		Low-level AD pathology	16
		Moderate-level AD pathology	32
		High-level AD pathology	14
		PSP	1
		FTLD	1
		Neurofibrillary Degeneration	1
		CVD	5
		CVD, Moderate-level AD pathology	1
		CVD, High-level AD pathology	2
Dementia with Lewy Bodies (DLB) (n = 4, 2%)	Low-level MSA pathology, Moderate-level AD pathology	1	
	None	1	
	Moderate-level AD pathology	2	
	High-level AD pathology	1	

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Treatments for dementia in Parkinson's disease



Drug	Efficacy	Safety	Practice implications
Rivastigmine	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
Donepezil	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Galantamine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Memantine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational

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Non-dementia cognitive impairment in Parkinson's disease



- Diagnosis of Parkinson's disease
- Gradual decline in cognitive ability
- Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities
- Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

Treatments for non-dementia cognitive impairment in PD



Drug	Efficacy	Safety	Practice implications
Rivastigmine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Rasagiline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Transcranial direct current stimulation	Insufficient evidence	Insufficient evidence	Investigational
Cognitive rehabilitation	Insufficient evidence	Insufficient evidence	Investigational

I. Neuropsychiatric symptoms in Parkinson's disease

II. Other non-motor symptoms in Parkinson's disease

Autonomic dysfunction

Symptom	Drug	Efficacy	Safety	Implications
Orthostatic hypotension	droxidopa	efficacious	acceptable	possibly useful
Anorexia, nausea, vomiting	domperidone	likely efficacious	acceptable with QT monitoring	possibly useful
Constipation	probiotics and prebiotic fiber	efficacious	acceptable	clinically useful
Drooling	Botulinum toxin B and A; glycopyrrolate	efficacious	Acceptable; insufficient evidence	clinically useful; possibly useful
Sexual dysfunction	sildenafil	efficacious	acceptable	clinically useful

Disorders of sleep and wakefulness and fatigue

Symptom	Drug	Efficacy	Safety	Implications
Insomnia	Rotigotine	Likely efficacious	acceptable	Possibly useful
	CPAP	Likely efficacious	acceptable	Possibly useful
Excessive daytime somnolence	CPAP	Likely efficacious	acceptable	Possibly useful
Fatigue	rasagiline	efficacious	acceptable	Possibly useful
RBD	clonazepam; melatonin; environment modification	None with proven efficacy	n/a	investigational

Questions?

