Treating psychiatric symptoms in patients with Parkinson's Disease.

Leonard S Richards DO

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What are psychiatric symptoms?

- Depression
- Anxiety
- Psychosis
- impulse control disorders
- Agitation
- obsessive compulsive disorder
- Apathy
- Cognitive impairment

Today’s Focus

- Depression
- Anxiety
- Psychosis

Today's questions

- Do Parkinson's patients get depressed , anxious, or psychotic?
- How often?
- How does this compare with other people?
- What are the best ways to treat these conditions?

Major Depressive Disorder

Depressed mood or anhedonia

and : decreased appetite
insomnia or hypersomnia
Psychomotor agitation or psychomotor retardation
fatigue or loss of energy
feelings of hopelessness helplessness or worthlessness
Diminished ability to remember, concentrate, or make decisions
recurrent thoughts of death or suicide

Must have 5 of the above 9 symptoms every day or nearly every day for two weeks.

Diagnostic and statistic manual 5th edition; American Psychiatric Association; 2013

The prevalence of Depression.

- Parkinson's disease-40% (or 2.7%-90%)
- General population; men 5%-12%, women 10 %-25%

- multiple sclerosis 40%
- stroke 10%-27%
- diabetes mellitus 25%
- Cancer 25%

- Erndt, et al., A systematic review of prevalence of depression studies in Parkinson’s disease. ; Movement Disorders, 25 January 2008

Treatment

- Medication
- Psychotherapy
- Exercise
- ECT
- TMS
- alternative therapies

SSRIs

- Fluoxetine-(Prozac)
- Sertraline-(Zoloft)
- Paroxetine-(Paxil)
- Fluvoxamine-(Luvox)
- Citalopram-(Celexa)
- Escitalopram-(Lexapro)

Selective Serotonin Reuptake Inhibitors (SSRI's)

- Block serotonin reuptake " pump", thereby increasing serotonin concentration in the synaptic cleft.
- Increased levels of serotonin postulated to lead to desensitization of serotonin 1A receptors.
- Considered first-line for depression and anxiety

Selective Serotonin Reuptake Inhibitors (SSRI's)

- Safest
- Fewest side effects
- Also indicated for anxiety
- Most frequently used in all depression including depression in Parkinson's disease patients

Ryan et al., Drug treatment strategies for treating depression in Parkinson's patients. ;

The Journal of Expert Opinion of Pharmacological Therapy

SSRIs
side effects

- G.I. upset, diarrhea (especially sertraline)
- Insomnia
- sedation
- Headache
- Restless , nervousness, akathisia
- Weight gain

Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRI's)

- Venlafaxine (Effexor)
- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)
- Levomilnacipran (Fetzima)

SNRIs-mechanism of action

- Inhibit serotonin reuptake by blocking the “pump” the draw serotonin back into the presynaptic membrane where it is broken down by monoamine oxidase.
- Increased levels of serotonin desensitizes serotonin receptors particularly 1A auto receptors

- Also inhibits norepinephrine reuptake by blocking the norepinephrine “ pump”
- Increase norepinephrine/noradrenaline concentrations desensitize beta noradranergic receptors

SNRIs-mechanism of action

- Also a weak inhibitor of dopamine reuptake “ pump”

- This increases dopamine transmission in the frontal cortex, which lacks dopamine transporters.
- Whether or not this contributes to antidepressant effects is controversial
- Whether or not this improves motor symptoms in Parkinson's disease is also controversial.

Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRI's)

- Same side effects as SSRIs but higher frequency. Usually GI distress, tachycardia, or hypertension.
- Still very well tolerated, but because of these side effects titration schedule is longer.
- Possible improvement in motor functioning but results are mixed and inconclusive.

Pontone and Mills, Optimum Treatment of Depression and Anxiety in Parkinson's Disease.

American Journal of Geriatric Psychiatry; June 6th 2021.

Bupropion-Wellbutrin

- Novel mechanism of action – norepinephrine/dopamine reuptake inhibitor
- Blocks the “ pump” that transport these non-serotonin monoamine’s across the presynaptic membrane where they are broken down by monoamine oxidase
- This increases norepinephrine/dopamine concentrations in the synaptic cleft. The delayed antidepressant effect probably has something to do with down regulation of auto receptors.

Bupropion

- FDA indicated for Major Depression, Seasonal Affective Disorder, and nicotine addiction
- No indication for anxiety
- not efficacious for anxiety
- Minimal drug interactions

Bupropion– side effects

- Dry mouth, constipation, nausea, anorexia, weight loss
- Insomnia, dizziness, headache, agitation, anxiety, tremor, abdominal pain, tinnitus
- Myalgia, sweating, rash
- Hypertension

- Of these side effects only nausea is common
- Typically given in the morning with food to minimize insomnia and nausea

Tricyclic Antidepressants

- No longer considered first line treatment
- Not because of poor efficacy(may even work better for depressed men than SSRIs)
- Because of significant side effects , and lethality in overdose

Tricyclic side effects

- Dry mouth
- blurred vision
- Constipation
- urinary retention
- Potentiates many antihypertensives
- Sedation
- Drowsiness
- Weight Gain
- Potentiates central nervous system depressants
- Orthostatic hypotension
- Reflex tachycardia

Regarding Medication

- At this time there are no medications specifically indicated for depression in Parkinson’s Disease.
- There are multiple studies but no clear consensus regarding the efficacy of these medications in Parkinson's patients with depression or anxiety.
- Our treatment strategies are largely extrapolated based on our experience in treating patients without Parkinson’s Disease.
- The same can be said for TMS or ECT.

Transcranial Magnetic Stimulation

- Safer than ECT
- Not as effective as ECT
- Has been used in Parkinson's with mixed results
- should be considered if medication and adjunctive therapies have failed or if medications are contraindicated.

Zung et al., The efficacy of repetitive TMS in Parkinson's disease.

The Lancet; July 29th 2022

Electoral Convulsive Therapy

- Up to 70% of Parkinson's patients show improvement in psychiatric disturbance following ECT
- Indicated for treatment resistant depression, which is defined as failure of three adequate medication trials
- May show improvement in motor functioning

But……

Frisina et al., Depression in Parkinson's disease: Health risks, etiology, and treatment options

Neuropsychiatric Disease and Treatment: 2008: 4(1) 81-89

ECT

- Improvement in motor functioning is temporary
- Significant side effects and risk related to repeated general anesthetic
- Usually requires two to three weeks of hospitalization
- Expensive

Psychotherapy

- Strong evidence that the combination of psychotherapy along with medications is the best treatment for depression and anxiety.
- Mixed but generally positive evidence that this is also true for patients with Parkinson's disease.
- Most evidence supports the effectiveness of cognitive behavioral therapy.

- Egan etal., Cognitive Behavioral Therapy for depression and anxiety in Parkinson's disease.; The journal of Parkinson's disease: 2015 5(3)

Adjunctive treatment

- Significant evidence that the addition of exercise to a treatment regimen improves outcomes in depression and anxiety in Parkinson's patients.
- Anecdotal evidence for nontraditional modalities such as yoga, meditation, acupuncture, and massage.

These interventions are low risk and worth trying but are not a substitute for medication and psychotherapy.

- Pei etal., The effectiveness of physical activation on patients with depression and Parkinson's disease. PLOS ONE, July 27th 2017

What is an anxiety disorder?

Fear or anxiety that is excessive and related behavioral disturbances.

- Fear is an emotional response to a real or perceived imminent threat
- Anxiety is an uncomfortable anticipation of a future threat

- Anxiety disorders include Generalized Anxiety Disorder, panic attacks, and phobias.
- Today's focus is specifically on generalized anxiety and panic.

Anxiety prevalence

• general population	19.1%
• Parkinson's disease	20%-40%
• Cancer	6%-30%
• Diabetes	9%-65%
• Stroke	42%

- Upneja et al., Anxiety in Parkinsons Disease; correlation with depression and quality of life. Journal of Neuroscience Rural Practice. March 24,2021
- Romanazzo et al. Anxiety in the medically ill: a systematic review. Front Psychiatry; June 3rd 2022

FDA indications for Anxiety Disorders

	GAD	OCD	Panic	PTSD	Social anxiety	
clomipramine		X				
fluoxetine		X	X			
Sertraline		X	X	X	X	
Paroxetine	X	X	X	X	X	
Paroxetine CR			X			
Citalopram	(none)	(none)	(none)	(none)	(none)	
Escitalopram	X					
Fluvoxamine			X			
Venlafaxine	X		X		X	
Duloxetine	X					

Anxiety treatment

- there are no randomized placebo controlled trials published regarding the use of medications for anxiety in Parkinson's disease patients.
- However, there is anecdotal evidence of the effectiveness of SSRI's and SNRI’s
- It may also be appropriate to use Buspirone and Hydroxyzine
- In severe cases resistant to other treatments, benzodiazepines may be appropriate

Weintraub, Daniel; Management of psychiatric disorders and Parkinson's disease. The American Society for Experimental Neurotherapeutics. June 8th 2020

Anxiety treatment

- cognitive behavioral psychotherapy should be considered as an addition to pharmacological treatment
- There is evidence that exercise may be effective
- Nontraditional therapies also have some anecdotal support but should not be used in place of traditional medications and psychotherapy

Weintraub, Daniel; Management of psychiatric disorders and Parkinson's disease. The American Society for Experimental Neurotherapeutics. June 8th 2020

Three Tiered Approach- Tier 1

(treatment of *anxiety and depression* in PD)

- Monotherapy with SSRI, SNRI, Mirtazapine, or vortioxetine; combined with exercise and cognitive behavioral psychotherapy.

- If this fails after an adequate trial (adequate medication dose for at least six weeks), *switch classes of antidepressant*.

- If two different medications fail; *move on to Tier 2*

Tier 2- combination pharmacotherapy

- Use two complementary antidepressants (Bupropion plus SSRI, SNRI plus mirtazapine)
- Consider augmentation with Quitiapine (Especially if psychosis is present)
- Consider augmentation with benzodiazepine (if anxiety is significant)

Weintraub, Daniel; management of psychiatric disorders and Parkinson's disease. The American Society for Experimental Neurotherapeutics. June 8th 2020

Tier 3

- Two antidepressants plus quetiapine or a benzodiazepine
- One antidepressant plus lithium
- One antidepressant plus TMS or ECT

Weintraub, Daniel; management of psychiatric disorders and Parkinson's disease. The American Society for Experimental Neurotherapeutics. June 8th 2020

Psychosis

- Up to 60% of patients with Parkinson's disease suffer from hallucinations or delusions
- Hallucinations are false sensory perceptions and are most commonly visual or auditory.
- Delusions are strongly held false beliefs that caused distress or dysfunction
- Symptoms can be the result of the illness or side effect of dopaminergic medications.

Fenelon and Alves; Epidemiology of psychosis in Parkinson's disease.; Journal of Neuroscience 2009 289:12-17

Treatment of psychosis; Antipsychotics

Three atypical antipsychotics that have low or no affinity for dopamine receptors.

Quetiapine

Clozapine

Pimvanserin

Black box warning

- all atypical antipsychotics have a black box warning in the PDR
- this comes from a 10 week study that showed 4.5% of elderly dementia patients that we're taking an atypical antipsychotic died.
- This study also showed 2.6% of the patients that were not taking an atypical antipsychotic died.
- Death usually related to cardiovascular events

Relative versus actual risk

- 4.5% versus 2.6%
- “nearly doubled”
- “73% increase in mortality”

- 1/40 vs 1/22

Documenting Risk Versus Benefit

- In order to prescribe antipsychotics for elderly patients we must establish that the potential benefit is worth the risk and *document this in the medical record.*
- We must discuss it with patient and or decision makers and *document this in the medical record.*
- In order to establish risk versus benefit we must determine the risk of any dangerous behaviors related to the psychosis (usually falls or assaults), and *document this in the medical record.*
- We must also attempt nonpharmacological management and *document this in the medical record*.

Non pharmacological interventions

- reorient patient
- reassure patient
- manage the environment
- fall precautions
- closer supervision

Attempt these alternative interventions and document the results in the chart prior to starting any antipsychotic.

Antipsychotics

- Quetiapine – (Seroquel, SeroquelXR)
- Also indicated for augmentation of antidepressant efficacy
- start low 12.5-25 2-3 times a day or prn
- Increase gradually until resolution of symptoms or adverse effects

Antipsychotics

- Clozapine- (Clozaril)
- No significant binding with dopamine receptors
- gold standard of all antipsychotics, *nothing works better*.

- Significant side effects complicate treatment

Clozapine-adverse effects

- **Severe agranulocytosis**
- 5– 10% seizure risk particularly at doses above 600mg daily
- Myocarditis, paralytic ileus, pulmonary embolism

Common side effects include;

- Weight gain, sedation, constipation, tachycardia, orthostasis, and *sialorrhea*

clozapine

- Weekly blood draws for ANC (absolute neutrophil count) for first six months
- Biweekly blood draws from 6 – 12 months
- After a year, monthly blood draws

- If ANC drops below 1000 µL, stop treatment and redraw daily until levels are above 1000 µL, then three times a week until levels are above 1500 µL . Consider hematology consultation
- If levels drop below 500 µL, stop treatment, consult hematology, and monitor as above

Clozapine

- Starting dose 25 mg at night, then titrate by 25 – 50 mg daily increasing every 2 to 3 days
- Target dose is 200 mg (Perhaps lower in Parkinson’s)
- Trough levels available with target 350 ng/mL – 700 ng/mL
- Doses above 500 mg daily are usually divided

Pimvanserin (Nuplazid)

- 37% reduction in hallucinations and delusions (compared to 14% in the placebo control group)

- Atypical antipsychotic but only indicated for use in patients with Parkinson's disease
- Black box warning
- may cause QTC prolongation
- other side effects include nausea, confusion, peripheral edema

Nuplazid package insert; Acadia Pharmacueticals

Pimavanserin

- Dose is 34 milligrams daily
- No titration schedule(start at 34 mg once daily)
- Higher dose is not recommended

- But? The pills are 17 milligrams?