Parkinson's Disease Psychosis – Disease State Overview

Prevalence[1,2]

~1 million individuals with PD in the US

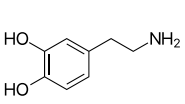
~50% of individuals with PD may experience hallucinations and/or delusions over the course of their disease

Risk Factors Associated with PD Psychosis[2,3]

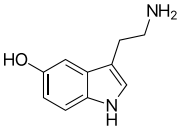
- Duration of PD
- Age at PD onset
- Severe cognitive disorder
- Daytime somnolence
- REM sleep behavior disorder

Proposed PD Psychosis Pathophysiology: 5HT Dysregulation[4-11]

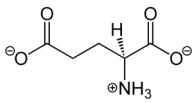
Three interconnected pathways hypothetically linked to psychosis:



Dopamine theory
Psychotic symptoms are the result of hyperactivity in the mesolimbic pathway which projects from the VTA to the ventral striatum



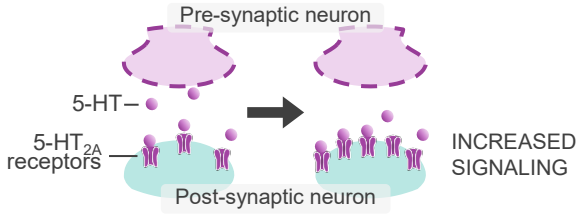
Serotonin theory
Hyperactivation of 5-HTA$_{2A}$ receptors on glutamate neurons in the cortex can result in glutamate release in the VTA, activating the mesolimbic pathway



Glutamate theory
Hypofunctional NMDA receptors on GABA interneurons in the cerebral cortex may lead to overactivation of downstream glutamate signaling to the VTA, leading to overactivation of the mesolimbic pathway

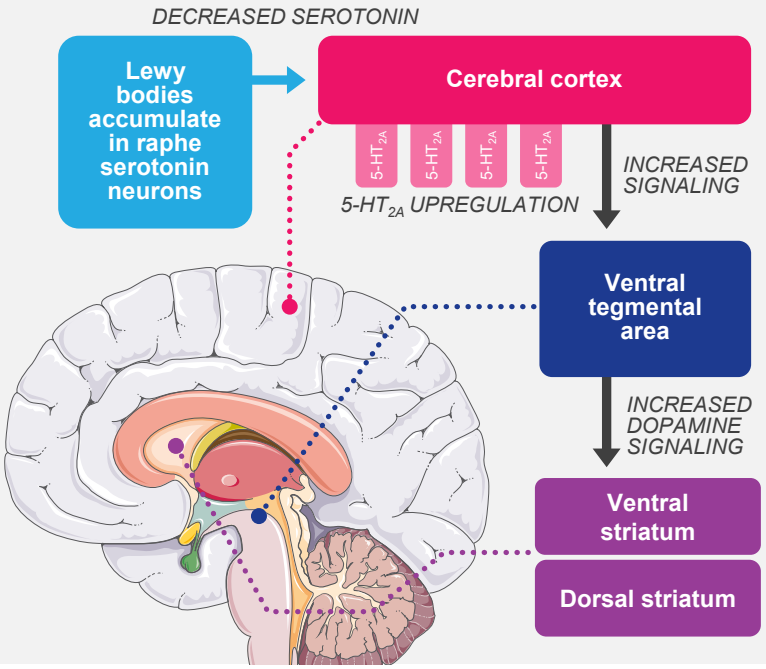
In PD, degeneration of raphe serotonergic neurons can lead to **upregulation of 5-HT$_{2A}$ receptors** in the cerebral cortex and may contribute to psychosis

Compensatory mechanism for low serotonin



Enhanced 5-HT$_{2A}$ activity in temporal cortex and in visual pathways may cause **hallucinations**

Enhanced 5-HT$_{2A}$ activity may induce downstream changes in neural pathways that indirectly increase dopamine release in the ventral striatum, **contributing to symptoms like hallucinations and delusions**



Characteristic Symptoms of PD Psychosis[12,13]

Psychosis is a **non-motor symptom** of PD psychosis, and it can be **progressive over time**

Many patients will have insight into their symptoms in the early phases of the disease, but **as the disease progresses, may lose insight** (the self recognition that what they are experiencing is not actually present)

Minor phenomena

- False sense of presence
- Passage hallucinations
- Illusions

Hallucinations

The perception of an object or event in the absence of an external stimulus

- Visual
- Auditory
- Tactile
- Olfactory
- Gustatory

Delusions

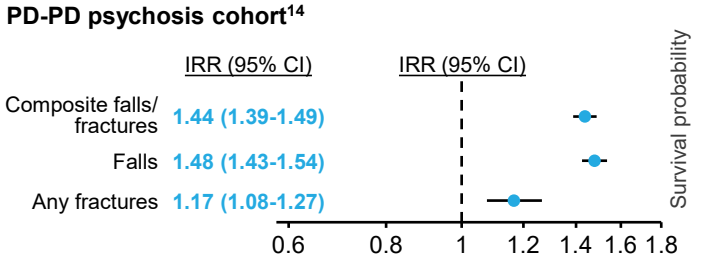
False, fixed, idiosyncratic beliefs that are maintained despite evidence to the contrary

- Jealousy
- Persecutory
- Reference

Burden and Consequences of PD Psychosis

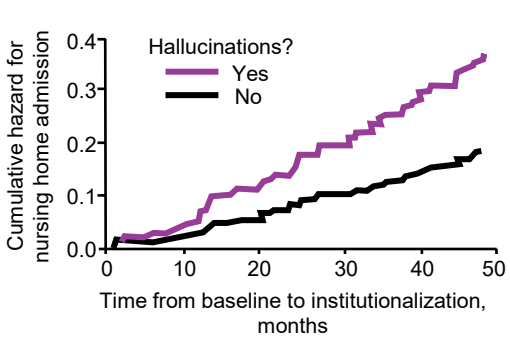
Results should be interpreted with consideration of the various study designs used, as each design may impact the findings and their generalizability. Please refer to each publication for a complete list of limitations.

Incidence rate ratios of falls and fractures for a matched PD-PD psychosis cohort[14]



- Retrospective claims analysis of US Medicare patients with PD (2008–2018) with (n=12,082) and without (n=24,164) psychosis
- Matched PD psychosis patients had **higher incidence of falls and fractures** than PD patients without psychosis

Four-year cumulative risk for nursing home admission[15]



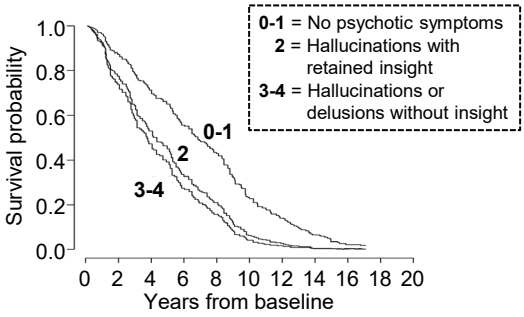
- Four-year, population-based study in Norway in 178 community-dwelling subjects with PD
- PD patients with hallucinations were 2.5x **more likely to be admitted into a nursing home**

Study of the association between neuropsychiatric variables* and current and future diagnosis of dementia in 696 patients with PD[16]

Hallucinations were associated with a shortened time to diagnosis of PD dementia in participants without dementia at baseline.

*Study partners completed a baseline NPI or NPI-Q, providing yes/no responses to regarding the presence of delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, nighttime behaviors, and eating abnormalities.

Survival according to baseline severity in psychotic symptoms[17]



- Population-based study in Norway in 230 community-dwelling subjects with PD followed prospectively (1993–2005) to identify mortality risk factors
- Patients with psychotic symptoms with (p=0.007) or without (p=0.004) preserved insight at baseline had **shorter survival time** as compared to participants not exhibiting psychotic symptoms

Validated Screener for PD Psychosis[18]

Oftentimes, information regarding psychosis symptoms are not volunteered by the patient during the clinic visit due to embarrassment or lack of insight. If the patient or caregiver responds positively to a screening question and other causes of psychosis have been ruled out**, further evaluation, diagnosis, and intervention by a clinician may be necessary.**

Self-Administered Screening Questionnaire for Psychosis in PD (SASPAP)

Question 1

In the past month, have you misinterpreted something that you saw or heard; for example, thought a lamp was a person?

___Yes. ___No.
___Not now, but I have experienced this before.

Question 2

In the past month, have you sensed that someone or something was around you, but nothing was actually there?

___Yes. ___No.
___Not now, but I have experienced this before.

Question 3

In the past month, have you ___seen, ___heard, ___smelled, or ___physically felt things that you or other people around you did not think were real?

___Yes. ___No.
___Not now, but I have experienced this before.

Question 4

In the past month, have you had thoughts or believed things that others did not think or believe to be true; for example, someone was cheating or harming you, or being unfaithful to you?

___Yes. ___No.
___Not now, but I have experienced this before.

Who completed this questionnaire?

___Patient in person
___Patient via telemedicine
___Caregiver in person
___Caregiver via telemedicine

Each SASPAP question identifies a potential symptom of PD psychosis: 1. Illusion, 2. False sense of presence, 3. Hallucinations, 4. Delusions.

CI=confidence interval; GABA=gamma-aminobutyric acid; IRR=incidence rate ratio; NMDA=N-methyl-D-aspartate; NPI=Neuropsychiatric Inventory; NPI-Q= Neuropsychiatric Inventory Questionnaire; PD=Parkinson's disease; REM=rapid eye movement; VTA=ventral tegmental area.

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References: 1. Marras C, et al. *NPJ Parkinsons Dis.* 2018:10;4:21. **2.** Forsaa EB, et al. *Arch Neurol.* 2010;67:996-1001. **3.** Fénelon G, et al. *Brain.* 2000;123:733-745. **4.** Stahl SM. *CNS Spectr.* 2016;21(5):355-359. **5.** Ballanger B, et al. *Arch Neurol.* 2010;67(4):416-421. **6.** Braak H, et al. *Neurobiol Aging.* 2003;24(2):197-211. **7.** Huot P, et al. *Mov Disord.* 2010;25(10):1399-1408. **8.** Joutsa J, et al. *J Nucl Med.* 2015;56(7):1036-1041. **9.** Kometer M, et al. *J Neurosci.* 2013;33(25):10544-10551. **10.** Sadzot B, et al. *Psychopharmacology (Berl).* 1989;98(4):495-499. **11.** Stahl SM. *CNS Spectr.* 2018;23(3):187-191. **12.** Ravina B, et al. *Mov Disord.* 2007;22(8):1061-1068. **13.** Goetz C, et al. *Arch Neurol.* 2006;63(5):713-716. **14.** Forns J, et al. *PLoS ONE.* 2021;16(1):e0246121. **15.** Aarsland D, et al. *J Am Geriatr Soc.* 2000;48(8):938-942. **16.** Gryc W, et al. *J Parkinsons Dis.* 2020;10(4):1643-1648. **17.** Forsaa EB, et al. *Neurology.* 2010;75:1270-1276. **18.** Koneru V, et al. *Mov Disord.* 2023;38(11):1982-1987.