



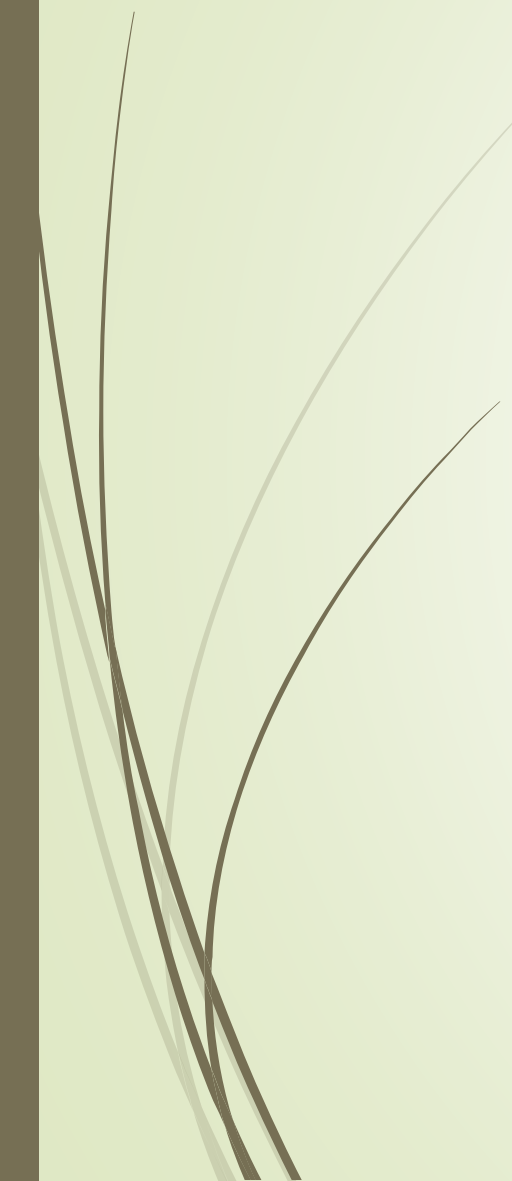


Nonmotor Symptoms in Parkinson disease

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Movement Disorders Fellowship

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- Common
 - Could be as prodromal
 - pain, anosmia and depressions' impact on quality of life more than motor symptoms
 - misdiagnosed initially

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- **Medications** to treat the motor symptoms of PD **can cause nonmotor** symptoms, including impulse control problems, confusion, hallucinations, and paranoid psychosis.
 - DBS could lead to behavioral, mood, and cognitive problems



Frequency of nonmotor symptoms in Parkinson disease

Symptom	Frequency (%)
Depression	36
Anxiety	33
Fatigue	40
Sleep disturbances	47
Sensory symptoms	63
No nonmotor symptoms	12



Sensory symptoms in Parkinson disease



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- Pain
 - Paresthesias
 - Numbness
 - Burning
 - Akathisia
 - Restless legs syndrome
 - Hyposmia
 - Urgency to urinate



Pain




- Boring pain in the initially affected limb may be the first complaint.
- Aching in the shoulder and arm is also a common earlier symptom in PD and may be incorrectly attributed to a bursitis or a frozen shoulder.
- When pain occurs in the hip or leg, it is often attributed to arthritis.
- Particularly in younger patients, may be painful dystonic foot cramps, especially on walking. Rarely, similar painful cramps may occur in the hands.
- Early morning painful cramps.
- More generalized excruciating pain during “off” periods, often a deep-seated aching, but sometimes accompanied by a superficial burning quality.

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- ▶ Once adequate dosing is achieved, whether or not mobility is restored, such pain may improve.
 - ▶ An “off-period” pain may be an indication for the use of rapidly acting water-soluble preparations of levodopa or apomorphine rescue injections.

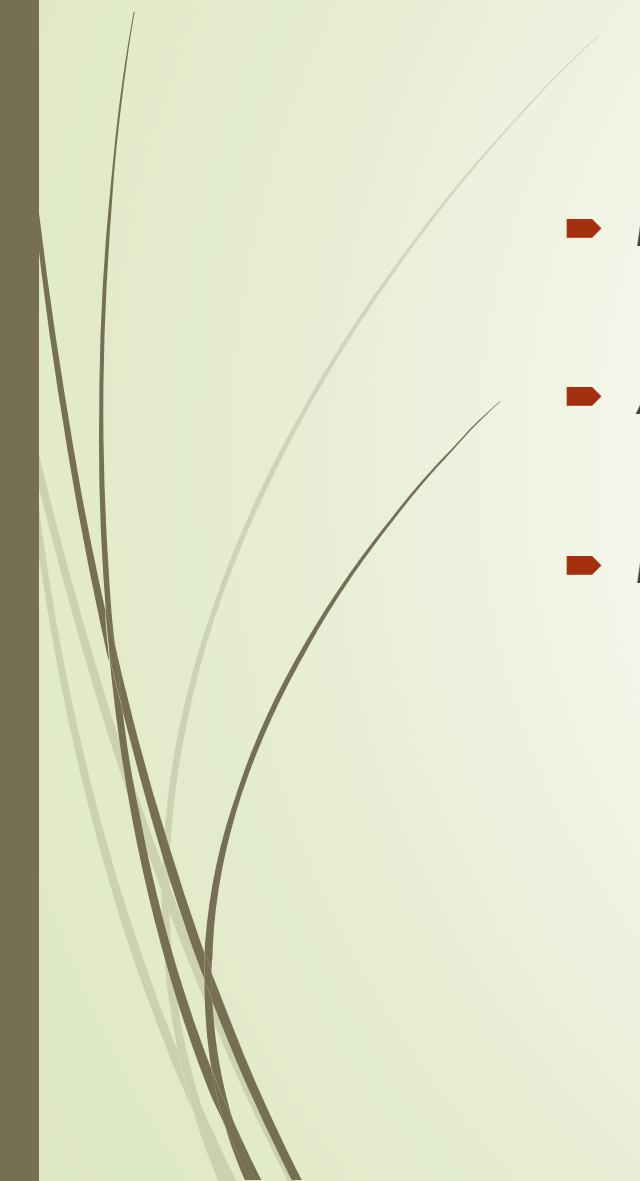


Burning, numbness, and paresthesia

- ▶ Less common
 - ▶ Treatment: dopaminergic drugs, opioids, nonopioid analgesics, anticonvulsives, antidepressants, and cannabinoids.
 - ▶ May be resistant to many of these therapies.
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Akathisia

- May be a presenting feature of PD.
 - Akathisia may also occur during the “off” period.
 - May respond to dopamine replacement therapy.
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Restless legs syndrome

- ▶ Sporadic and familial RLS respond to **dopamine agonists** and levodopa, but these drugs can cause **augmentation**, a worsening of the restless legs symptoms—more severe unpleasant sensations, occurring earlier in the day, and spread to involve other body parts.
- ▶ **Opioids** are effective in treating RLS and periodic movements in sleep: Propoxyphene, Oxycodone, tramadol, methadone
- ▶ Pregabalin and Gabapentin

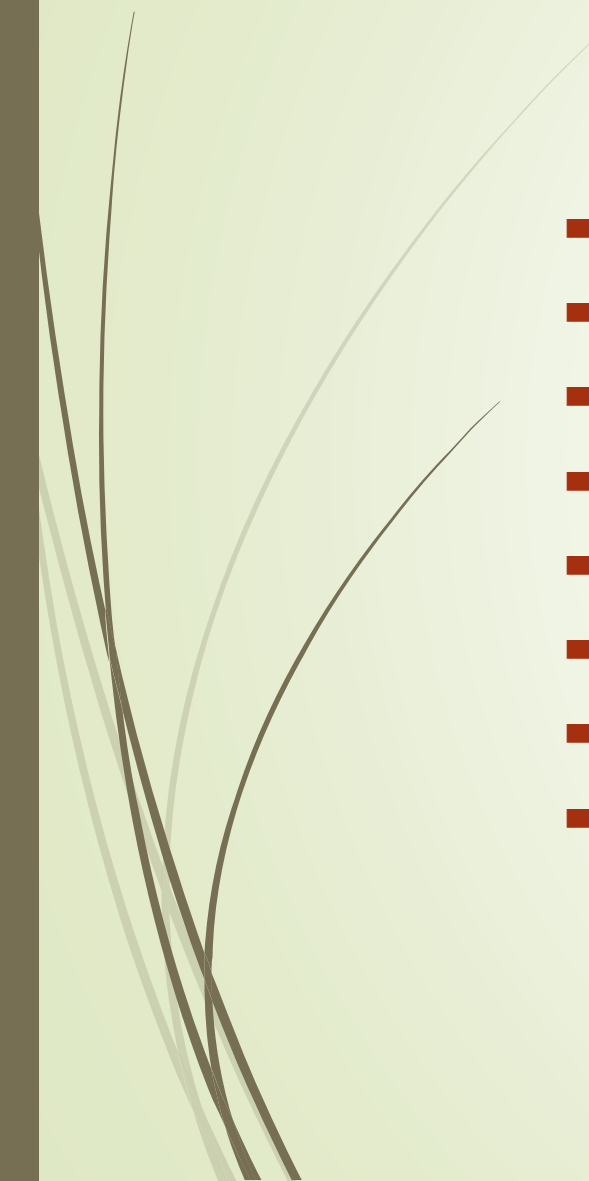




Hyposmia


- ▶ More predictive than executive dysfunction
- ▶ Also is seen in other neurodegenerative disorders, including CBD and some others



Autonomic dysfunctions: bladder and sexual

- Bladder problems
 - Sexual dysfunction
 - Hypotension
 - Gastrointestinal problems
 - Seborrhea
 - Sweating
 - Rhinorrhea
 - Abdominal bloating
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- ▶ The diagnosis of significant prostate enlargement in PD is difficult, and prostatectomy may not improve the symptoms and may in some cases lead to worsening.
 - ▶ Prostatectomy should be considered only in those with proven outflow obstruction.
 - ▶ A simple screening test in patients with PD is noninvasive ultrasonic estimation of **postmicturition residual volume (>100 ml)** and decrease in **urinary flow rate**.



If there is no significant residual volume or reduction of flow rate:

- ▶ urinary frequency and urgency may be helped by a peripheral antimuscarinic drug such as oxybutynin or TCAs.
- ▶ Intranasal desmopressin (DDAVP) at night also may reduce nocturia

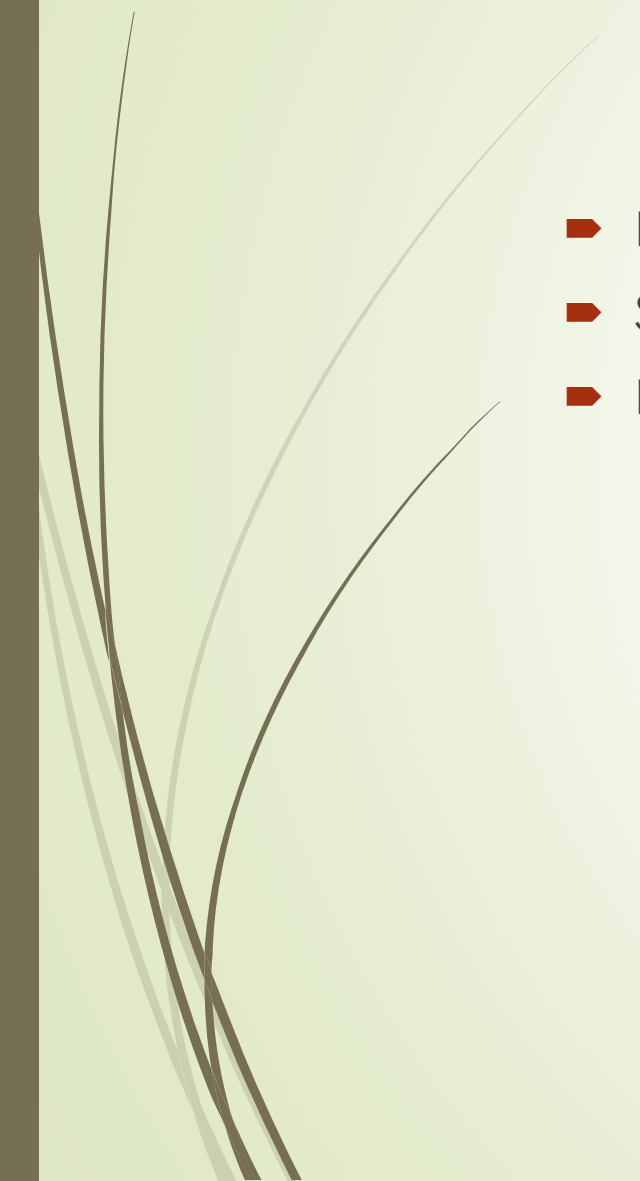


Sexual dysfunction

- ▶ Sildenafil can be efficacious in the treatment of erectile dysfunction in both PD however, it can unmask or exacerbate hypotension.
- ▶ Parkinsonian symptoms are not affected, but a side benefit of **reduced dyskinesias has been reported**.
- ▶ Hypersexuality, particularly in males, is a rare and unacceptable side effect of dopamine replacement therapy in PD.
- ▶ Usually requires reduction of antiparkinsonian medication.



Orthostasis

- ▶ Pathogenesis of PD
 - ▶ Side effect of Levodopa and dopamine agonists
 - ▶ Postprandially because of gastrointestinal vasodilatation
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Orthostasis management

- Domperidone
- Increasing fluid and salt intake,
- Head-up tilt at night, which may reduce nocturnal polyuria
- Intranasal DDAVP reduces nocturnal polyuria but can cause hyponatremia.
- Fludrocortisone
- Midodrine
- Pyridostigmine



Parasympathetic failure

- ▶ Delay in esophageal and gastric motility.
- ▶ Sense of bloating, indigestion, and gastric reflux are all common in PD.
- ▶ Levodopa is absorbed in the upper small bowel, so gastric stasis may slow or prevent levodopa assimilation, leading to “**delayed-ons**” and “**no-ons**” (dose failures) after single oral doses.



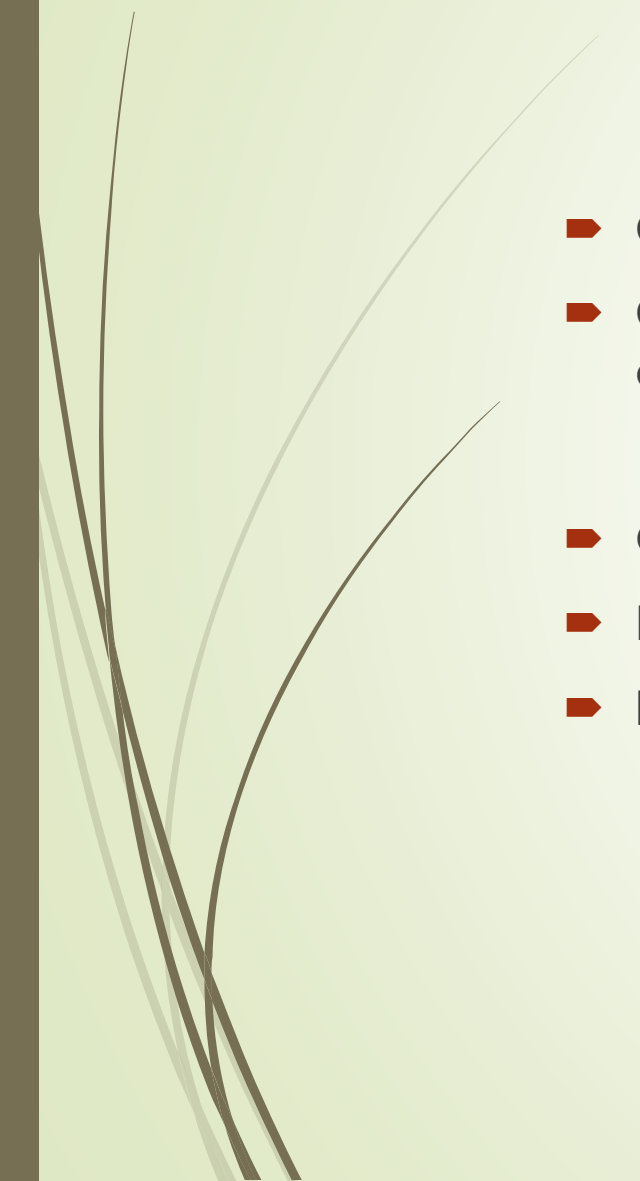
Constipation

- ▶ The role of **levodopa** in causing or in treating constipation is **uncertain**.
- ▶ Adequate fluid intake, fruit, vegetables, fiber, and lactulose
- ▶ Refractory constipation may be helped by **apomorphine** injections
- ▶ **Pyridostigmine** is also another option by enhancing parasympathetic tone



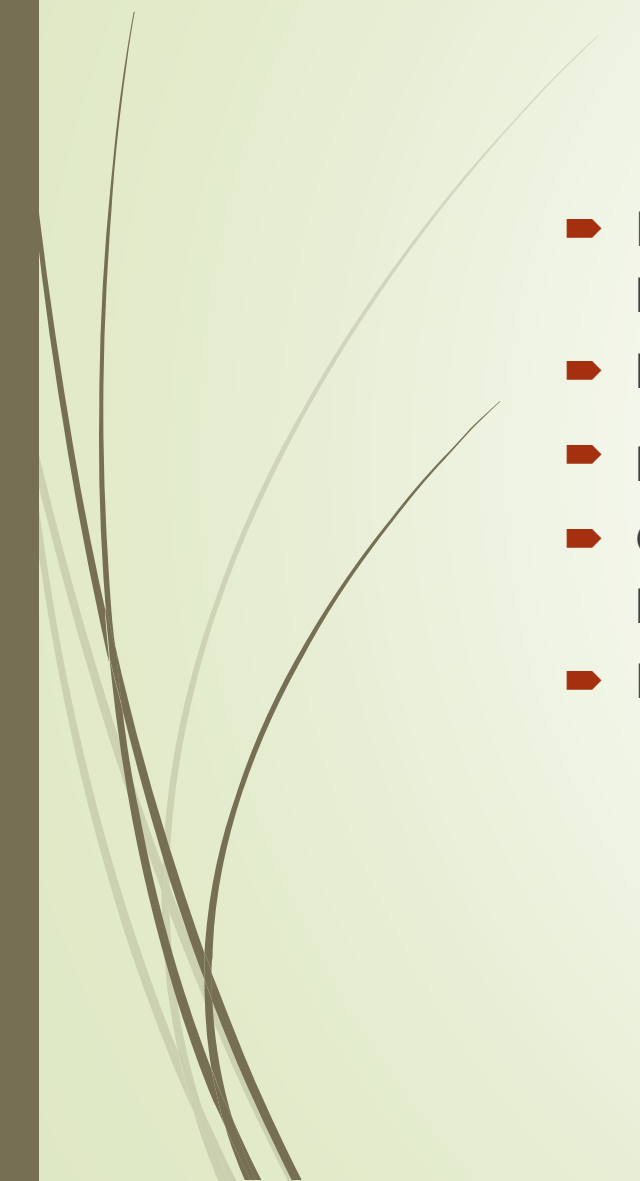
Sialorrhea


- ▶ Chewing gum (which also helps with dry mouth).
 - ▶ Chewing gum has also been found useful to increase swallow frequency and decreases the latency of swallowing in PD.

 - ▶ Glycopyrrolate
 - ▶ Propantheline
 - ▶ If these are unsuccessful, intraparotid injections of botulinum toxin B
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Respiratory distress

- Respiratory distress such as dyspnea can occur as a symptom of PD in some patients, including during the “off” period
 - In peak-dose dystonia
 - pergolide
 - Off” period dyspnea is difficult to treat, other than attempting to keep the patient “on.”
 - Despite the sensation of dyspnea, oxygen saturation is not affected
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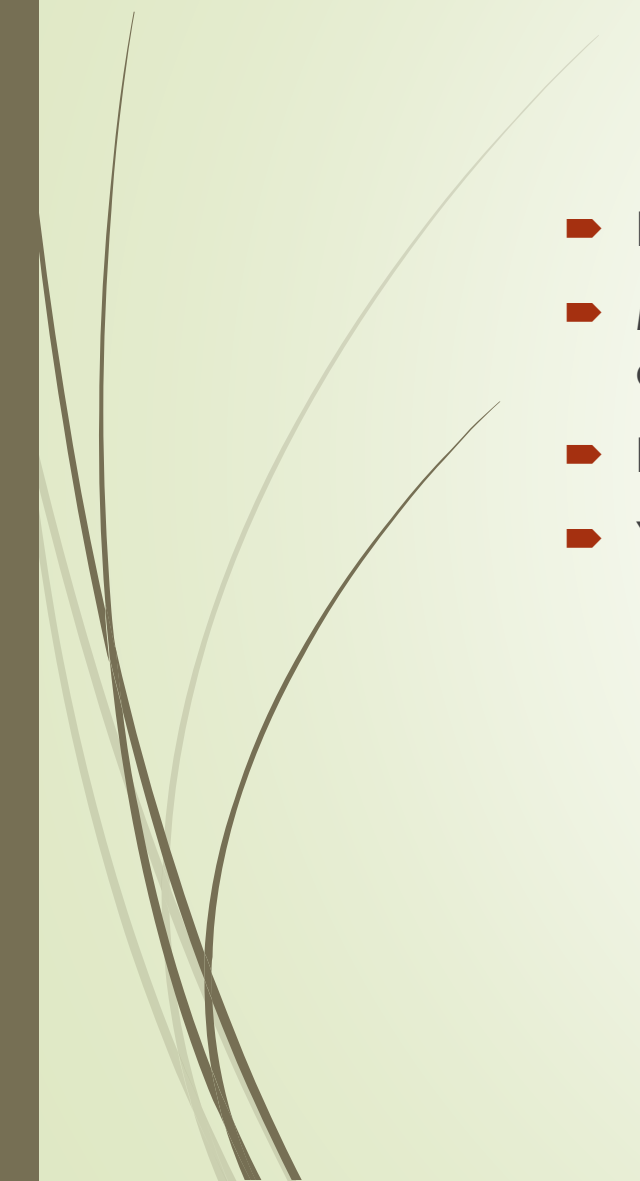


Difficulties at night and daytime sleepiness

- Sleep fragmentation
- Periodic leg movements in sleep
- Fragmentary nocturnal myoclonus
- Sleep apnea
- RBD
- Intense dream-like motor and behavioral problems
- Parasomnias (nocturnal hallucinations and nocturnal wandering with disruptive behavior)
- Reversal of the sleep rhythm with sundowning



Sleep benefit

- Reduces the severity of daytime parkinsonism
 - Might not require antiparkinsonian medication for some hours after they awaken
 - Daytime nap “charges the batteries
 - Young onset PD patients with mutations in the parkin gene
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Levodopa induced drowsiness

- ▶ Levodopa administered at night may provoke excessive dreaming and disrupted sleep in some patients
- ▶ Drowsy after each dose of medication, this may possibly be a sign of overdose.
- ▶ Reducing the dosage can in some cases improve this problem.
- ▶ Substituting Sinemet CR for standard Sinemet will help



Sleep problem management


- ▶ Avoiding alcohol, caffeine, nicotine, and excessive fluid intake at night
- ▶ **Selegiline** which is metabolized to methamphetamine and amphetamine, should not be given at night.
- ▶ A **sedative antidepressant**, such as **amitriptyline** (10–25 mg at night), **mirtazapine**, or **trazodone**, can be very useful, not only to induce and maintain sleep, but also to reduce urinary frequency.

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- ▶ A dose of a long-acting levodopa preparation before bed may improve nocturnal akinesia
 - ▶ Drugs such as methylphenidate and amphetamine are usually well tolerated by patients with PD.
 - ▶ RBD: clonazepam



Sleep attacks



- ▶ Falling asleep while driving and without warning is a **serious problem** that has been encountered with dopaminergic agents
- ▶ More likely to occur with **pramipexole** and **ropinirole**
- ▶ Once sleep attacks have occurred, the patient **should not drive** or the **medication should be changed**.
- ▶ **Modafinil** has been reported to be helpful in preventing some sleep attacks; however, over the years it has **not** been shown to be universally efficacious



Sleep and DBS of pedunculo pontine (PPN)

- ▶ To treat parkinsonian gait disorders
- ▶ Low-frequency stimulation increase alertness
- ▶ High-frequency stimulation induced non-REM sleep

Fatigue



➤ 44%

➤ Fatigue is often a complaint during the **earliest** phase of the disease, before motor symptoms.

Management of Fatigue

- ▶ Treating **depression and daytime sleepiness** would be helpful, but when fatigue is an independent symptom, no treatment has been found satisfactory
- ▶ **No significant** effect from **Amantadine**, **Selegiline** and **Modafenil**
- ▶ **Methylphenidate** 30 mg/day has been reported to reduce fatigue in a controlled clinical trial
- ▶ **Oxybate** at bedtime also has been reported to help but may lead to confusion in PD.
- ▶ A small study showed that **rasagiline** may improve fatigue in PD, but a larger randomized study will be needed to confirm this result.



Depression

- There also have been **concerns** over the use of selective serotonin reuptake inhibitors (**SSRIs**), which in a few cases have been reported to interact with levodopa to induce the “**serotonin**” **syndrome** (confusion, myoclonus, rigidity, and restlessness) and to **worsen PD** symptom.
- **ECT** in refractory cases can be used and can temporarily improve mobility in PD.
- Both **paroxetine** and **venlafaxine** XR significantly improved depression in subjects with PD.
- Both medications were generally **safe** and **well tolerated** and did not worsen motor function.

Anxiety



- **Often** can be relieved by effective **antiparkinsonian** drug therapy
- If **uncontrolled** and pervasive, it might require an **antidepressant**
- If **dysphoria** is present, a **benzodiazepine** (e.g., lorazepam 0.52 mg three times a day) or buspirone.
- Anxiety and stress **worsen tremor**, and **alprazolam** 0.25 mg during those periods can provide relief.
- Recent interest in cannabinoids as treatments for pain, sleep and anxiety (PSA)



Sensory and Behavioral “off”

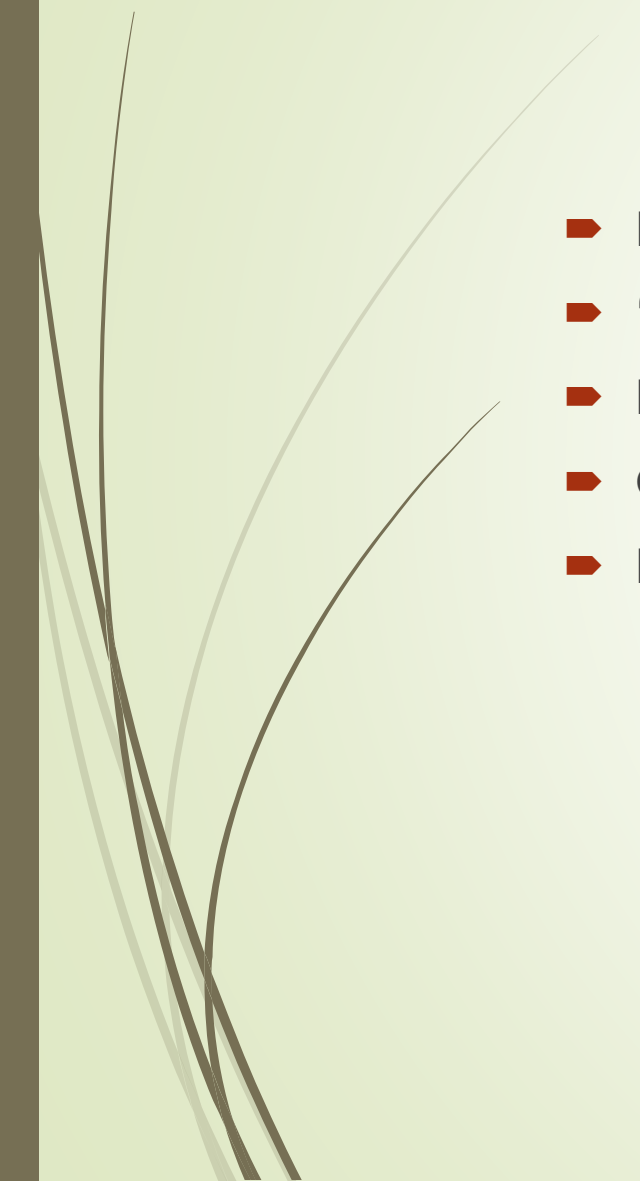
- **Behavioral** “off”: Depression, anxiety, dysphoria, and panic
- **Sensory** “off”: pain or akathisia.
- Most distressing to the patient.

- Motor “offs”: insufficient dopaminergic tone in the **neostriatum**
- Behavioral and sensory “offs”: Insufficient dopaminergic tone in the **limbic** dopaminergic areas of the brain, such as the nucleus accumbens, amygdala, and cingulate cortex.

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- ▶ Keeping the patient “on” all the time would prevent these sensory “offs,” but this is a difficult task.
 - ▶ It is not clear that DBS can overcome sensory “offs.”




Cognitive problems

- Bradyphrenia: slowness of thinking
 - “Tip of the tongue phenomenon”: trouble finding words
 - Problems in handling multiple task
 - Confusion
 - Dementia
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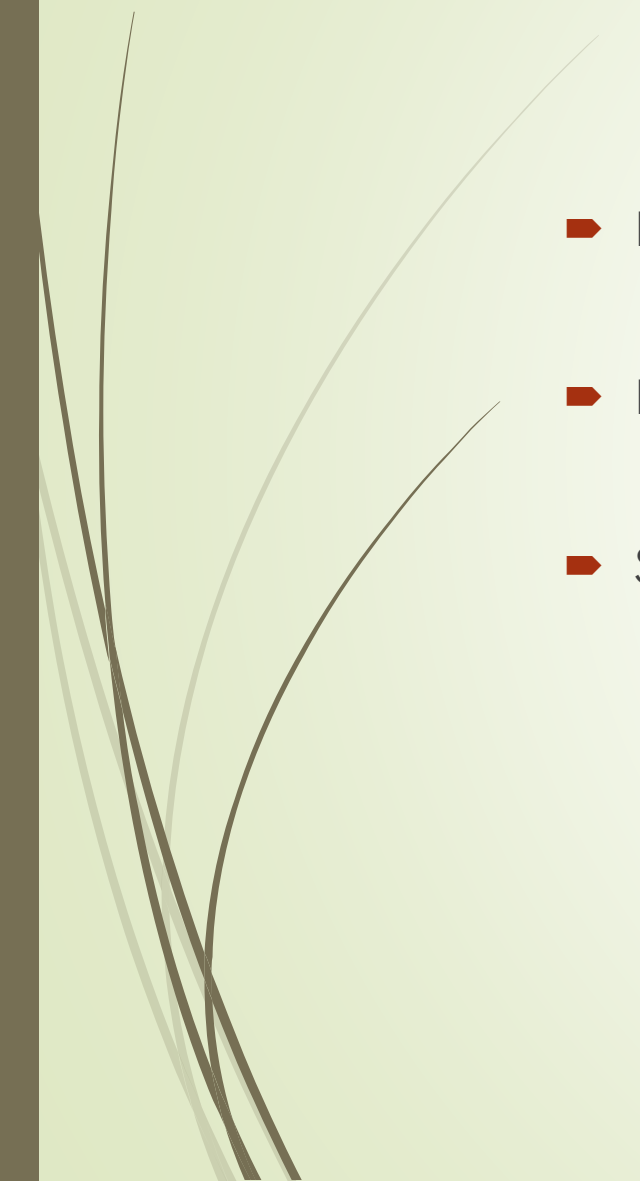


Frontostriatal cognitive syndrome

- ▶ 60% with early PD will show abnormalities of cognitive function on formal neuropsychological testing sensitive to frontal lobe dysfunction such as MOCA.
 - ▶ Absence of any major defects in language, episodic memory, or visuospatial functions.
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Risk factors for developing dementia

- ▶ Low serum epidermal growth factor (Chen-Plotkin et al., 2011)
 - ▶ Low CSF amyloid-beta (Siderowf et al., 2010)
 - ▶ Severity of olfactory impairment
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Cognitive problem management in PD

- ▶ Do **not seem** to respond to **dopamine** replacement therapy.
- ▶ These issues may **not** respond to **antidepressants**, unless depression is present and is itself the cause of the slowness of thinking.
- ▶ Review current drug therapy: anticholinergics, amantadine, dopamine agonists, and even levodopa in excess may also possibly impair cognitive function.

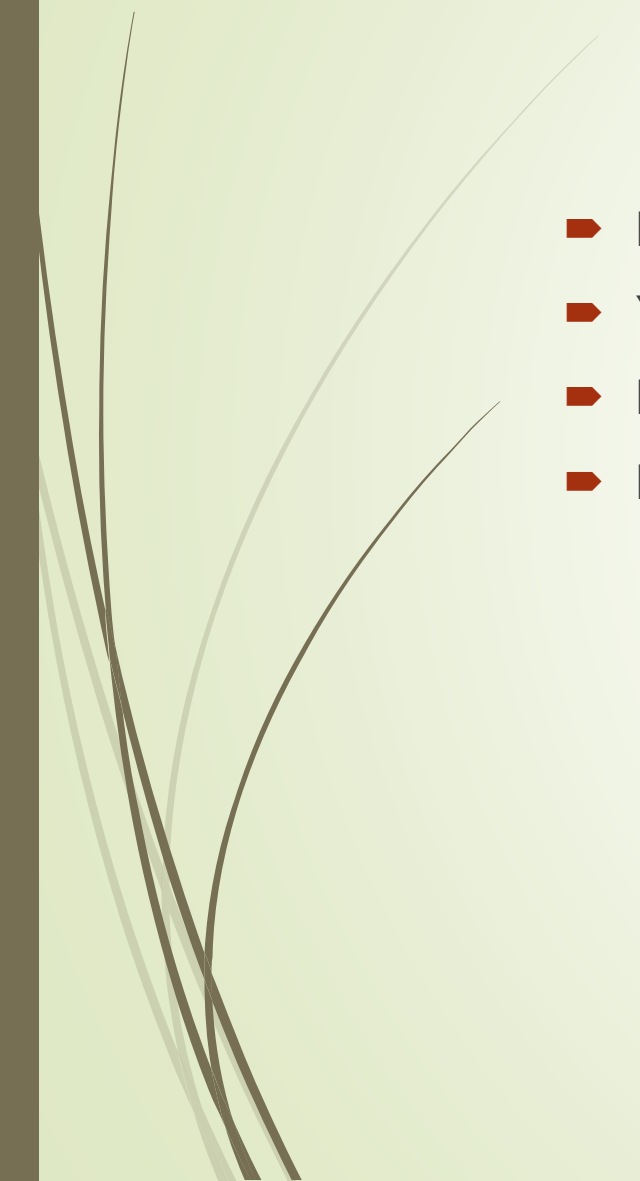


Impulse control disorders (ICDs)

- ▶ Pathologic gambling: 5.0%
 - ▶ Hypersexuality: 3.5%
 - ▶ Compulsive buying: 5.7%
 - ▶ Binge-eating: 4.3%, lead to wight gain that is in contrast to the typical weight loss often seen in patients with PD.
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- A screening questionnaire for ICDs (the QUIP) has been validated



ICD Risk Factors

- ▶ Dopamine agonist
 - ▶ Young individuals
 - ▶ Higher novelty seeking traits
 - ▶ Personal or family history of alcohol use disorders
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Punding

- ▶ Abnormal motor behavior in which there is an intense fascination with repetitive handling and examining of mechanical objects, such as picking at oneself, taking apart watches and radios, or sorting and arranging of common objects, such as lining up pebbles, rocks, or other small objects.
- ▶ A common form is repetitive cleaning/rearranging/ordering behaviors, which can be disabling, associated with hypomania, occur during motor “on” periods, and often occur nocturnally.
- ▶ These have Excessive use of the computer is a particular form of repetitive behavior reported to be caused by levodopa therapy (Fasano et al., 2006).
- ▶ Punding incidence is lower than other compulsive behaviors.
- ▶ Punding has been reported with levodopa and dopamine agonists





Punding cont


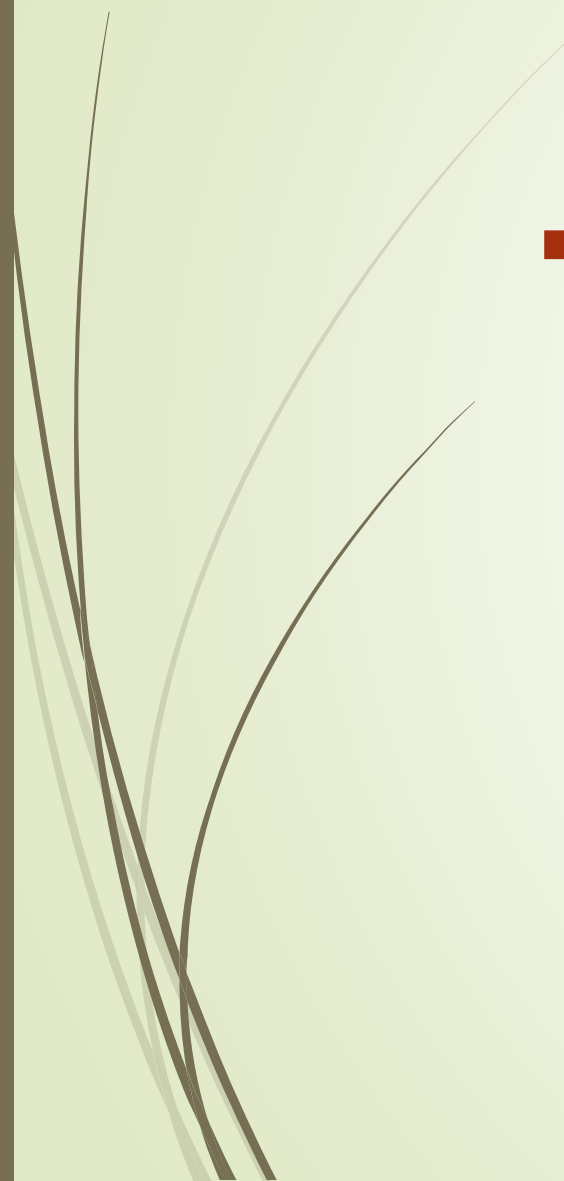
- ▶ The **repetitive behavior** responds poorly to serotonin reuptake inhibitors, but may benefit from **atypical antipsychotics**.
- ▶ In a small cross-over study, **amantadine** was found to reduce pathologic gambling (Thomas et al., 2010); however, two reviews of databases showed that pathologic gambling and other ICDs are more often associated with patients on amantadine (Weintraub et al., 2010c; Lee et al., 2011).
- ▶ Recently **naltrexone** was also tried as a therapy to address ICD but was not found to be efficacious (Papay, 2014).



Psychosis: hallucinations and paranoia

- ▶ 60% in 12 year follow up.
- ▶ **Risk factors** were higher age at onset, dopaminergic dose, and RBD at baseline.
- ▶ Isolated **visual hallucinations** are fairly common.
- ▶ Auditory hallucinations are very uncommon.

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- ▶ **Pseudohallucinations** : Visual hallucinations often take the form of familiar humans or animals, which the patients know are false.
 - ▶ **Benign hallucinations**: Visual images are friendly and not frightening.
 - ▶ These milder forms can worsen to a more malignant type of hallucination or delusional paranoid state or frank confusional state with impairment of attentiveness and disorientation.



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- ▶ When such symptoms occur, although antiparkinsonian drug therapy is the most likely cause, it is **wise** first to search for some **intercurrent illness**, such as a **stroke** or **intracranial mass lesion**, a **chest or urinary infection**, **disturbance of electrolytes**, **renal or hepatic dysfunction**, **anemia**, or **endocrine dysfunction**.





Psychosis treatment in PD

- Quetiapine
- Clozapine

- Anticholinesterase drugs that are used in the treatment of dementia.
- Anticholinesterase have similar efficacy on psychosis as quetiapine.

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- If psychosis continues without adequate benefit from the antipsychotics, selegiline, anticholinergics, and amantadine should be withdrawn.
 - The need for anxiolytics and antidepressants should be reconsidered.
 - If the symptoms persist, dopamine agonists should be reduced or stopped.
 - If necessary, the dose of levodopa should be tapered.
 - Drug holiday, withdrawing dopaminergic drugs for 1 to 2 days each week.
 - **keep in mind that intact mental function is more important than intact motor function.**

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- ▶ **Ondansetron** (serotonin 5HT₃-receptor antagonist blocks) reduce hallucinations, paranoia, and confusion in PD, without worsening of parkinsonism.
 - ▶ Pimavanserin (serotonin inverse agonist): effective in treatment of mild to moderate psychosis in PD and received FDA approval without worsening PD motor symptoms.