MEDICATION MANAGEMENT OF PARKINSON'S DISEASE

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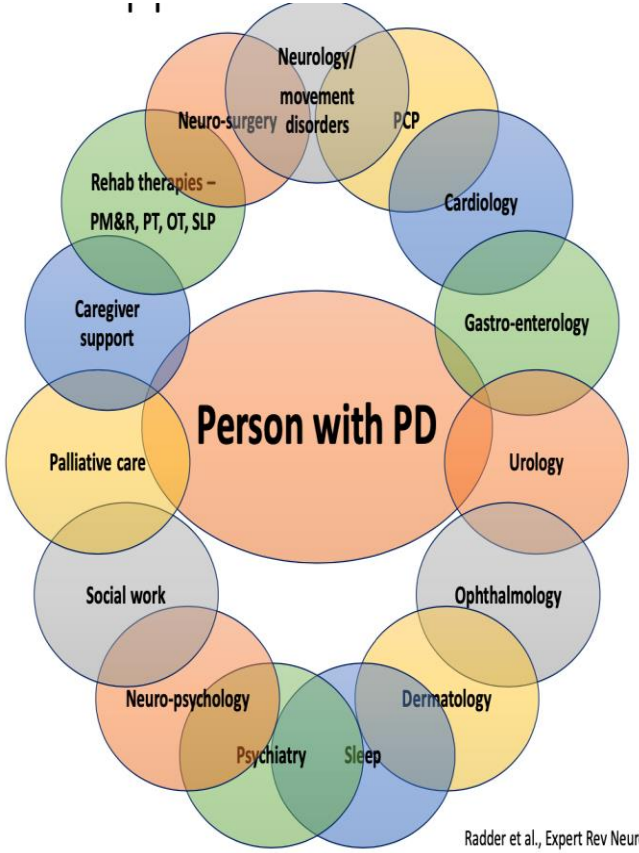
From Newcastle. For the world.

INTRODUCTION

The management of PD is multidisciplinary and involves doctors, nurses, physical therapists, occupational and speech therapists
Management must be individualized and takes into consideration: age of px, stage of dz, presence of comorbidities, accessibility of medications (including affordability)

Assessment and treatment of motor and nonmotor symptoms by a multidisciplinary team is advised.
All newly diagnosed patients should be screened for depression and treated as needed
An exercise program and in-person and online support groups may be extremely helpful.

Nonpharmacologic treatment, such as physical therapy and occupational therapy, can be extremely helpful in alleviating symptoms of stiffness and may improve gait.



Radder et al., Expert Rev Neurother 2019; Jrl Parkinson Dis 2020

INTRODUCTION

The mainstay of drug treatment is to boost dopaminergic activity in the nigrostriatal pathway, either by giving levodopa which can be turned into dopamine within the remaining neurones in the substantia nigra or by giving dopamine agonists which mimic the effect of dopamine in the striatum

Less potent benefits can be obtained from drugs which inhibit the metabolism of dopamine by monoamine oxidase type B and catechol-*O*-methyl transferase, and from drugs that modify other neurotransmitters in the striatum such as amantadine and anticholinergics.

MEDICAL MANAGEMENT OF PD

There are a variety of medications used in the management of PD
LEVODOPA in combination with decarboxylase inhibitor(carbidopa)
DOPAMINE AGONISTS EG ropinirole, pramipexole, carbegoline, bromocriptine
MAO INHIBITORS EG rasagiline, selegiline
COMT INHIBITORS: entacapone
GLUTAMATE ANTAGONIST: amantadine
ANTICHOLINERGICS : trihexyphenidyl
CHOLINERGICS : donepezil, rivastigmine
ANTIDEPRESSANTS : TCA, SSRI, SNRIs
ATYPICAL ANTIPSYCHOTICS : clozapine, pimavanserin, quetiapine

LEVODOPA

Initial therapy for older patients

Also indicated in medically fragile patients

Used in cognitively impaired and those with behavioral issues

Advantages of Levodopa: easier to use, most effective medications, most available, well tolerated
Disadvantage: Treatment emergent side effects, fluctuations and dyskinesias

Carbidopa-levodopa is available in standard preparations that contain a fixed ratio of each drug,
10 mg carbidopa to 100 mg levodopa (10/100)
25 mg carbidopa to 100 mg levodopa(25/100)
25 mg carbidopa to 250 mg levodopa(25/250)
A controlled-release formulation is available in ratios of 25 mg carbidopa to 100 mg levodopa (25/100) or 50 mg carbidopa to 200 mg levodopa (50/200).

HOW TO TAKE LEVODOPA

Best on an empty stomach
30 minutes after a meal, or wait an hour after meals
Protein interferes with absorption

As PD becomes more advanced drug schedules become more complicated
Writing down dosages and medications in a chart or aided by a nurse are helpful to patient and caregivers

WHAT TO EXPECT WHEN ON LEVODOPA

Most patients initially respond brilliantly to levodopa therapy and this is often termed " The Honeymoon period"

There are three subsequent problems:

Wearing off: the **response becomes shorter and is less dramatic**

Dyskinesia**: each dose produces involuntary choreiform movements**

On–off effect: the **transition between lack of response(off)and response (on) becomes rapid.**

HOW DO WE MANAGE THESE

Selegiline and entacapone prolong the duration of action of levodopa, and have a limited role in smoothing fluctuations.

Amantadine can be very helpful in suppressing dyskinesia

To managed very refractory fluctuation or dyskinesia:

- ***Apomorphine infusion*****: this parenteral dopamine agonist can be infused subcutaneously to achieve stable control. This requires specialist medical and nursing care.**
- ***Surgical treatments*****: these are aimed at inhibiting overactive parts of the basal ganglia circuitry, either with a stereotactic lesion or by implanting an electrode with an impulse generator.**

SIDE EFFECTS OF LEVODOPA

Nausea
Hypotension
Constipation
Confusion
Hallucinations
NO IV FOURMULATION BUT FOR NGT FEEDING CAN BE CRUSHED OR DISSOLVED IN WATER

Management of levodopa induced side effects

NAUSEA and VOMITING
Add more carbidopa
Try CR version
Add antinausea medication like ondansetron
Take with a carbohydrate meal

DOPAMINE AGONISTS

After levodopa, 2nd most effective medications
Usually used for mild PD alone OR can be used as an ADD ON
Dopamine agonists are synthetic compounds that stimulate striatal dopamine receptors.
Elderly patients(especially >70) are more likely to develop confusion, sleepiness, and psychosis from DA
EG :Ropinirole, Pramipexole
Thought to delay motor complications
Advantage is most have once a day dosing
Disadvantage is cost, availability and increased side effects especially Impulse control Disorders
In 70% of pxs rarely able to control symptoms after 3 years of treatment

SIDE EFFECTS OF DOPAMINE AGONISTS

Impulse control disorders(gambling, shopping)
Sleep attacks
Nausea
Vomiting
Sleep attacks including when driving
Orthostatic hypotension
Illusions, hallucinations and mania
DOSING: started at very low doses , titrated upwards slowly, individual response varies, may switch and try another if not tolerated

APOMORPHINE

Apomorphine is a nonergot dopamine agonist that is available for subcutaneous injection to rapidly treat sudden, severe, disabling off periods

Dosing must be titrated slowly and under the supervision of a physician

Side effects include severe nausea, profound hypotension, dyskinesias, and hallucinations

Because severe nausea and vomiting occur at recommended doses of apomorphine, an antiemetic such as must be used in conjunction with this medication.

SELEGILINE (MAO B INHBITORS)

Initial therapy in patients with very mild symptoms or as add-on therapy, especially in patients with prominent gait difficulties such as freezing.

The dosing of selegiline is 5–10 mg every day.

Dosing should not exceed 10 mg/day because of risks associated with MAO enzyme inhibitors and ingestion of foods containing tyramine.

Dosing of rasagiline is 0.5–1 mg once a day

ENTACAPONE

This drug is used in conjunction with levodopa to extend the "on time" (duration of action of each dose of levodopa) by inhibiting the enzymatic conversion of levodopa to its metabolite.

This results in increased synaptic levels of dopamine.

Side effects include diarrhea, dyskinesia, and orange discoloration of urine.

Entacapone comes in a 200-mg tablet and is taken simultaneously with levodopa

ANTICHOLINERGICS

Often used to treat tremor
Little or no effect on other symptoms of PD
Associated with memory problems and hallucinations
Caution in the elderly!!!

AMANTADINE

In mild PD, amantadine can reduce symptoms of PD, especially tremor.
In advanced PD, amantadine is a useful adjunct to therapy with levodopa and dopamine agonists.

It is also effective in decreasing levodopa-induced dyskinesias.

Side effects include peripheral edema, confusion, livedo reticularis, rash, and visual hallucinations.

The usual dosage is 100 mg twice a day; doses up to 400 mg/day can be used.

ADVANCED PD

Lack of stable response to levodopa
Motor complications
Fluctuations
Dyskinesias
Gait freezing and falls
WHAT TO DO?
Increase dosing
Add other medications: amantadine (dyskinesias)

NONMOTOR FEATURES MANAGEMENT

- **Behavior**
  - **Mood**
  - **Cognition and dementia**
  - **Hallucinations and psychosis**
  - **Impulse control disorders**
  - **Fatigue**
  - **Apathy**
- **Sleep**
  - **Insomnia**
  - **REM behavior disorder**
  - **Excessive daytime somnolence**

- **Autonomic function**
  - Gastrointestinal
  - Genitourinary
  - Cardiovascular
  - Thermoregulatory
  - Dysphagia
  - Drooling
- **Sensory/musculoskeletal function**
  - Olfaction
  - Visual system
  - Pain
  - Posture

Skin

MANAGING NON MOTOR FEATURES

DEPRESSION:

•TCAs – likely efficacious, but side effects

•SSRI/SNRIs

• Nortriptyline

•paroxetine CR vs. placebo

• citalopram vs. placebo

venlafaxine

CAN ALSO USE THE FOLLOWING MEDICATIONS

MAO-inhibitors

DA agonists (rotigotine - negative; pramipexole - positive)

NON PHARMACOLOGICAL

- Cognitive Behavioral Therapy
- Exercise and physical activity
- Neuromodulation

NONMOTOR FEATURES

ANXIETY

Common in PD and under recognized...

- **Prevalence range: 5-40%**
- **Contexts:**
- **Depression**
- **Generalized anxiety disorder**
- **Panic disorder**
- **Phobias (social, agoraphobia)**

Obsessive-compulsive disorder *and as...*

Non-motor fluctuations, particularly "off" state

Non-pharmacological treatment

- Psychotherapy, relaxation/biofeedback, behavioral therapy
- If anxiety/panic symptoms relate to:
- "Off" periods→modify dopaminergic regimen
- Underlying depression→use antidepressants

Medications for depression

- Benzodiazepines with short half life - watch for sedation, falls, confusion
- SSRIs - frequently used

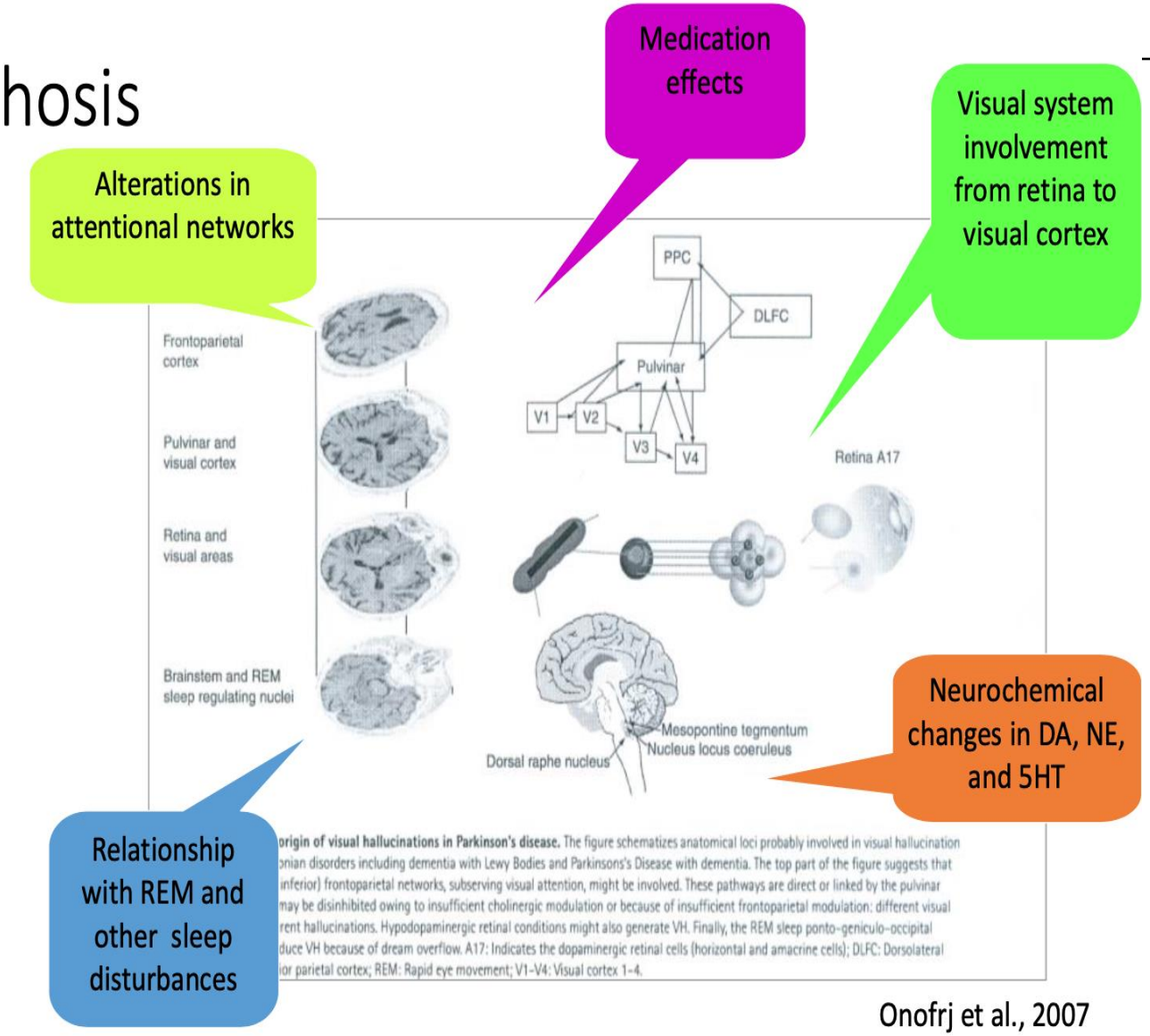
– Citalopram - if depression also presented

- SNRIs - may be well tolerated

– Venlafaxine - can cause initial increase in anxiety symptoms

– Mirtazapine - can help with sleep, weight gain; elderly

Psychosis



Onofrj et al., 2007

DIFFERENTIAL DIAGNOSIS IN PD PSYCHOSIS

Parkinsons disease medications
Systemic illness
Centrally acting medications
Hepatic renal or other organ dysfunction
Overdose of medications or intoxications
Sensory deprivation
Infection
Structural lesions: stroke, subdural, intracranial hemorrhage, trauma

PSYCHOSIS

Treat underlying medical illness
Reduce or discontinue PD medications
Discontinue medications that may exacerbate hallucinations(anticholinergics)
Nonpharmacological strategies
Pharmacological:
Pimavanserin
Clozapine
Quetiapine

Visual aids and techniques

- Night lights
- Redirection
- Reassurance
- Verification
- Art therapy
- Humor

IMPULSE CONTROL DISORDERS

- Education, prevention, surveillance
- Adjustment of PD medications
- Reduce oral DA agonist, etc
- Monitor for dopamine withdrawal syndrome
- Psychiatric management
- Antidepressants, atypical neuroleptics (antipsychotics)
- Cognitive behavioral therapy (likely efficacious, insufficient evidence, Seppi et al., 2019)
- DBS
- Research (opioid, cannibinoid, and nicotinic or other dopamine systems; naltrexone)

DEMENTIA

•Acetylcholinesterase inhibitors

• Donepezil(Aricept) 5-10 mg/d

• Rivastigmine (Exelon) :1.5-6 mg/BID oral or 4.6 or 9.5/24h patch

• Galantamine(Razadyne,priorReminyl) : 4-12 mg/BID

•NMDA antagonists

Memantine(Namenda) :5-20 mg/d

- Neuromodulation and DBS
- Non-pharmacological

• Objective assessments (baseline, serial)
• Exclude other causes, especially if acute (infections, mood, etc)
• Review medications (both PD and non-PD)
• Consider medications for dementia
• Non-pharmacological strategies
• Assess safety at home, driving, etc
• Discuss work, if appropriate
• Address adjustments and psychosocial impact for patient and caregiver

SLEEP

REM SLEEP BEHAVIOR DISORDER

- **Safe environment**
- **Counseling**
- **Exclude mimics and minimize exacerbating factors**
- **Medications**
- **Melatonin3-12mgbeforebedtime**
- **Clonazepam 0.25-2 mg before bedtime**
- **Bed alarm system?**

INTRINSIC SLEEP PROBLEMS

RLS PLMS: Dopamine agonists, Gabapentin

Sleep apnea: CPAP

Good sleep hygiene

Sedatives/hypnotics:Eszopiclone

NOCTURNAL PD SYMPTOMS

Extended release levodopa/carbidopa
Entacapone
Additional doses

MEDICATION EFFECTS AT NIGHT
Avoid amantadine or selegiline at night

DAYTIME SLEEPINESS
Reduce levodopa dose and other sedating medications
Power naps
Treat OSA
Modafinil
Caffeine

AUTONOMIC SYMPTOMS

Nonpharmacological

- Elevation of head of bed by
- 30 degrees
- Increase salt and fluid intake
- High pressure thigh/waist high compression stockings
- Abdominal binders
- Small frequent meals

PHARMACOLOGICAL

- Reduce antihypertensives and/or dopaminergic drugs as able • Agents to increase blood pressure
- First line
- Fludrocortisone, doses 0.1-0.5 mg/day • Midodrine, doses 5-10 mg TID
- Droxidopa (prodrug of NE, crosses BBB)
- Pyridostigmine, domperidone, indomethacin

GI SYMPTOMS and GENITOURINARY

Nausea/vomiting

Take meds with light snack, add extra carbidopa

Avoid DA blocking meds (metoclopramide, prochlorperazine)

Consider domperidone, trimethobenzamide, ondansetron

Constipation

Exercise

Maximize dietary factors (water, fiber)

Medications:

•Psyllium husks, Colace, Senna, Bisacodyl, Magnesium sulfate, lactulose, Lubiprostone

•Probiotics

•Enemas

- Standard agents for neurogenic bladder dysfunction
- Anticholinergics: oxybutynin, tolterodine, solifenacin, etc
- Monitor for side effects (hypotension, constipation, cognition)
- Muscarinic agonists (bethanechol)
- B3 adrenergic agonist (mirabegron)
- Catheterization
- Pelvic floor physical therapy
- Behavioral therapies
- Botulinum toxin: Onabotulinum toxin A

•Drooling and Dsyphagia

•Oral medications :Amitriptyline ,Glycopyrrolate,Sublingual atropine ,Ipratropium spray ,Botulinum toxin

•Speech therapy

CONCLUSION

Management of PD requires a multidisciplinary and individualized approach

As the disease advances, medication adjustments become necessary and require detailed explanations and guidance

Nonpharmacological methods of management should be considered when appropriate

THANKYOU FOR LISTENING