Thinking outside the Dopamine box

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October 26, 2019
Progressive loss of neurons in the substantia nigra

Lost neurons produce a NT called dopamine (DA)

DA is responsible for motor control and movements

Symptoms do not appear until DA levels decline by at least 70–80%.
**Presymptomatic phase**

- Onset
- Sleep
- Olfactory
- Mood
- Autonomic system

**Early nonmotor symptoms**

Dopaminergic neuron loss in PD

**Specific symptoms**

- Diagnosis
- Motor

% Remaining Dopaminergic Neurons

*Olfactory dysfunction may predate clinical PD by at least 4 years.*


Multiple Sites of Neurodegeneration in PD

• **Dopamine** (DA) – red

• **Norepinephrine** – green
  (May precede loss of DA: Associated with brain functions such as: sleep, memory, learning and mood)

• **Serotonin** – orange
  (May precede loss of DA: Associated with mood, anxiety, appetite, GI function and pain)

• **Acetylcholine** – blue
  (Associated with memory and learning)

*Lang & Lozano (1998)*
Neurotransmitters involved in Parkinson’s Disease (PD)

- Dopamine
- Acetylcholine
- Serotonin
- Glutamate
- Adenosine
- GABA
- Norepinephrine
Criteria That Define a Neurotransmitter

1. Neurotransmitter present
2. Presynaptic terminal

1. Action potential
2. Neurotransmitter released
3. Application of transmitter, agonists, or antagonists
4. Postsynaptic cell
5. Neurotransmitter receptors activated
Neurotransmitter imbalance in Basal Ganglia in PD

- Dopamine and GABA deficiency
- Acetylcholine and glutamate surplus
PD is primarily related to deficiency of dopamine: Gold standard of treatment is L-DOPA (Sinemet)

- The neurotransmitter imbalance in PD suggest multimodal pharmacology is helpful in managing non-motor and motor symptoms
Excess activity of cholinergic neurons leads to bradykinesia, rigidity, tremor

Anti–cholinergic medications – Restrict action of acetylcholine (artane, cogentin)
  – Used for more than 100 years and is effective for dystonia and tremor.
  – Side effects include Dry mouth, urinary retention, memory loss, and sleepiness
  – Typically avoided in older patients since it increases risk of dementia
Acetylcholine (Ach)

- There is loss of cholinergic neurons in nucleus basalis of Meynert (AD) and brainstem pedunculopontine nucleus.

- The degeneration seen with progression results in dementia with instability and fall.

- Postural instability and gait disorder (PIGD) subtype of PD typically responds less to dopaminergic medications.
Inhibits acetylcholinesterase enzyme from breaking down acetylcholine which increases levels in the brain

Acetylcholinesterase Inhibitors:
- Rivastigmine is FDA approved for Parkinson’s Disease with Dementia (PDD). Oral or patch delivery
- Donepezil, Galantamine

Glutamate: primary excitatory NT in basal ganglia

Increased glutamatergic activity seen in PD has been implicated in the development and maintenance of levodopa induced dyskinesias (LID)

Glutamate antagonist (amantadine): effective for LID

Glutamate/NMDA receptor antagonist

Enhances dopamine release:
- Only medication available to reduce dyskinesia which improves ON time
- Side effects include leg edema, confusion, insomnia, orthostatic hypotension and psychosis, livedo reticularis, etc
- Patients frequently do not tolerate evening doses due to insomnia and RBD
Gocovri is a high-dose, extended release amantadine

Product design

Gocovri was designed to be taken once-daily at bedtime

Delayed release coating and extended release layer allow for gradual rise in plasma concentrations during night

NOTE: Colors are for illustration purposes only and not actual color of product

Extended release coating
Seal coating
Amantadine HCl
Inert core

Capsule

ER Coated Pellets in Capsule
Gocovri

- GOCOVRI® is FDA approved for LID
- High dose amantadine, dosed QHS (bedtime)
  - Only drug FDA approved for dyskinesia with a secondary benefit of reducing OFF time
  - High amantadine plasma concentrations upon waking and throughout the day (~1500 ng/mL) and is lower at night (avoids insomnia, RBD)
- Side effects include hallucination, dry mouth, leg edema, constipation, and orthostatic hypotension
EASE LID 2: Open-label study

Long-term durability of effect

<table>
<thead>
<tr>
<th>Double-Blind</th>
<th>Open-Label Baseline</th>
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<tbody>
<tr>
<td>n = 60 67 72 68</td>
<td>n = 58 57 55 52</td>
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<tr>
<td>n = 60 61 55 54</td>
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<td>Placebo</td>
<td>DBS Previous Placebo</td>
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<tr>
<td>Gocovri</td>
<td>Previous Amantadine IR**</td>
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<tr>
<td></td>
<td>Continuing Gocovri</td>
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Double-Blind: BSL 2 8 12/24 BSL**
Open-Label: 8 16 28 40 52 64 76 88 100

Number of weeks

Week 52
Change from Gocovri initiation

Week 100
Change from Gocovri initiation

*Data from weeks 12 and 18 of EASE LID are not shown here.
**For participants enrolling directly from a double-blind Gocovri trial, their final efficacy visit in EASE LID 3 or EASE LID 4 occurred 12 or 16 weeks after baseline MDS-UPDRS assessment for the prior treatment. For all patients, the baseline MDS-UPDRS assessment was performed between study days -14 and -1.
***The Previous Amantadine IR subgroup is not mutually exclusive with the pre-specified patient groups, and contains 32 patients. All patients within the DBS group, Bocovri group, and Previous Placebo group were randomized patients. At baseline, the patients in the group had a mean 233 mg/daily dose of amantadine (corresponding with 274 mg amantadine HCl), and a mean treatment duration of 2.5 years.
†Charts show change from Gocovri initiation (i.e., change from double-blind baseline for the Continuing Gocovri group, and change from open-label baseline for Previous Placebo and DBS groups).

DBS, deep brain stimulation; MDS-UPDRS, Movement Disorders Society-Unified Parkinson’s Disease Rating Scale; IR, immediate release

Adapted from Hauser et al. and Isaacson et al., posters presented at MDS, Hong Kong, 2018.
OSMOLEX ER has a unique pharmacokinetic profile that delivers amantadine throughout the day\(^2\)

- Amantadine plasma levels are higher during waking hours and lower during the night\(^2\)

- OSMOLEX ER is taken once daily, in the morning
Known as the “happy chemical” since it regulates mood, and low serotonin is associated with depression, anxiety, OCD, PTSD, phobias, etc.
Degeneration of the dorsal raphe nuclei seen in PD contributes to non-motor (mood, sleep, constipation) and motor (dyskinesia, tremors) symptoms. Recent study from King's College London reveals changes in the brain's serotonin were found to precede changes in dopamine, suggesting this may be the earliest sign of PD. It correlates with pre-motor symptom (depression, anxiety).
Depression in PD

- Depression is common and affects 50% of PD pts
- Serotonin, norepinephrine, and dopamine loss contribute to developing depression which can occur years before the Parkinson’s is diagnosed.
- Diagnosis is difficult since it overlaps PD symptoms
- Depression is often seen with fatigue, decreased appetite, sleep disturbance, loss of motivation
Selective serotonin reuptake inhibitors – Blocks reabsorption of serotonin and raises levels in brain.

Serotonin and norepinephrine reuptake inhibitors – Block the reabsorption of serotonin and norepinephrine.

Tricyclic antidepressants – serotonin reuptake inhibitor, noradrenaline, anticholinergic, alpha 1 adrenergic antagonist and antihistamine.
Serotonergic involvement in Psychosis

- Parkinson’s disease psychosis (PDP) causes patients to have hallucinations and/or delusions. Over half of patients develop PDP over the course of the disease.

- Effect of serotonergic drugs like LSD suggests 5-HTP plays a role in psychosis in other conditions.

- Cause of PDP is unknown: serotonin likely plays a role since studies reveals preservation of 5HT in PDP pts.
NUPLAZID® Is a Selective Serotonin Inverse Agonist (SSIA)

Response (%)

[Drug concentration]

Agonists:
Stimulate the receptor

Antagonists:
Block agonists
but permit basal activity

Inverse Agonists:
Suppress basal activity

2. NUPLAZID Prescribing Information.
Nuplazid

- Decreased psychosis compared to the placebo, including improvements in nighttime sleep, daytime wakefulness, and caregiver burden

- Possible side effects: nausea, leg edema, confusion; with no worsening in motor symptoms

- May prolong the QT interval and should be avoided in patients with known QT prolongation or in combination with other drugs that prolong QT
NUPLAZID SAPS-PD Change From Baseline Through 6 Weeks

NUPLAZID 34 mg showed a 37% improvement in SAPS-PD from baseline at Week 6 versus 14% for placebo (P=0.006)

The effect of NUPLAZID on SAPS-PD improved through the six-week trial period

LSM: least-squares mean; SE: standard error
1. NUPLAZID Prescribing Information.
Norepinephrine (NE) alerts brain and body for fight or flight response and increase HR/BP

- NE involved with mood, attention, memory
- NE loss results from degeneration of locus coeruleus and sympathetic ganglia
- Contributes to depression, orthostatic hypotension and fatigue.
NOH: drop in BP (>20pts) upon standing causing dizziness, fainting, falling
Norepinephrine maintains BP with change in posture
Treatment: Increase fluids/salt, sleep in elevated position, compression stocking, abdominal binder, small frequent meals
Droxidopa (Northera) is NE precursor

- FDA approved for nOH
  - Study reveals reduction in dizziness, and increased standing BP after week 1
    - Rates of falls reduced (0.38 vs 1.73/wk)
    - Most common side effects: headache, supine hypertension, nausea
Adenosine has an inhibitory effect in the central nervous system.

Caffeine stimulatory effects are primarily due to blocking adenosine (A2A) receptors.

Reduction in adenosine leads to increased activity of dopamine.
A2A antagonists (Blocks adenosine 2A receptor) Add on therapy for motor fluctuations

Istradefylline: Mild Positive results in Phase 3 Approved in Japan, FDA did not approve in 2008

Preladenant (SCH420814): Improved motor function and improved “on” time, but 3 trials neg.

Tozadenant (SYN115): Decrease off time (1.2 hr) and improved motor function. TOZ–PD Phase 3 trial halted due to side effect of agranulocytosis
Istradefylline (Nourianz)

- FDA recently approved on 8/27/19 for add-on therapy to levodopa for wearing off

- 4 different 12-week placebo-controlled clinical studies that included a total of 1,143 participants. Nourianz showed significant decrease from baseline in daily “off” time

- Side effects: dyskinesia, dizziness, insomnia, constipation, nausea, and hallucination.
Marijuana contains numerous cannabinoids: tetrahydrocannabinol (THC), which causes the "high" and cannabidiol (CBD), with no mind-altering effects and potential benefits.

Natural cannabinoids are used by our brain to control sleep, appetite, and mood:
- Cannabinoid receptors are found in high numbers in the basal ganglia.
Cannabinoids and PD

- Anecdotal reports on social media showing cannabis reducing tremors suggest benefit.

Research shows mixed results and no double blind placebo trials: insufficient evidence that medical marijuana is a treatment for PD.

- Research is limited due to:
  - Marijuana is Schedule I – illegal by federal law.
  - Lack of standardized or known doses, and variable CBD and THC concentrations.
Cannabinoids and PD

- Potential Tx: pain, insomnia, anxiety, nausea, appetite, RLS, cramps, agitation, RBD

- Side effects: dizziness, low blood pressure, apathy, imbalance, memory loss, dry mouth, fatigue, etc
  - THC more likely to cause side effects such as paranoia, anxiety, confusion, or psychosis

- Pure CBD product may have less potential side effects and consider a cream for focal pain or sore muscle
Physical exercise influences the dopaminergic, noradrenergic and serotonergic systems.

Exercise improves mental acuity, mood, well being
Continuous exercise can produce a transient state of euphoria with feelings of profound contentment, elation, and well-being

- Release of endogenous psychostimulant, endorphin, and cannabinoid
Exercise as a therapy

- Exercise is associated with a lower risk of developing neurodegenerative disorders.

- Regular aerobic exercise improves symptoms in CNS disorders and used as adjunct therapy

- Clear benefit seen in depression and ADHD

- AAN Clinical guidelines recommends exercise for Mild cognitive impairments and AD
Role of exercise in PD

- Studies suggest exercises slow progression:
  - PD outcomes projects: Earlier intervention of exercise (2.5 hrs/wk) – slower decline in qol

- Managing symptoms:
  - Improves balance and gait
  - Improves cognition, constipation, mood

- Avoids isolation:
  - Exercising as a group can be a social activity or support group
Types of Exercise
Choose an exercise program that you enjoy since it is important to exercise regularly.

Exercise program should include:
- Flexibility (stretching) exercises
- Aerobic activity
- Resistance training or strengthening exercises
- Agility
High Intensity Interval Training (HIIT)

- HIIT: 30–60 seconds of exercise at maximum limit, followed by recovery for a similar time. Exercises is repeated for 20–30 min workout

- Exercise can vary from walking, cycling, etc. Ex: 30 secs of running, then 30 secs of walking

- HIIT found more effective in treating heart disease, stroke, diabetes, etc.
128 Early PD patient randomized to high intensity treadmill (4 days/week at 80%–85% HR max), mod-intensity treadmill (4 days/week at 60%–65% HR max), or control x 6 months.

UPDRS at 6 months was ±0.3 in the high-intensity, ±2.0 in the mod-intensity, and ±3.2 in the control.

High intensity exercise may delay progression and a larger phase 3 trial is warranted.
Effectiveness of home–based and supervised aerobic exercise in PD: double-blind controlled trial

130 patients randomized to either aerobic or active control group and followed for 6 months.

Aerobic Group used stationary home–trainer (cycle w/virtual reality) vs control group (stretching) by a motivational app 3x/wk

The MDS–UPDRS motor score revealed a difference of 4.2 pts in favor of aerobic group
Conclusions

- Parkinson’s is secondary to neurodegeneration of multiple areas of the brain affecting dopamine, serotonin, acetylcholine, glutamate

- Multimodal pharmacology and exercise is vital for relief of motor and non-motor symptoms

- Exercise program should include a variety of activities for flexibility, strength, agility, and aerobic for ideal outcomes.