PFNCA SYMPOSIUM 2019
"Getting the most out of your Parkinson disease medications"

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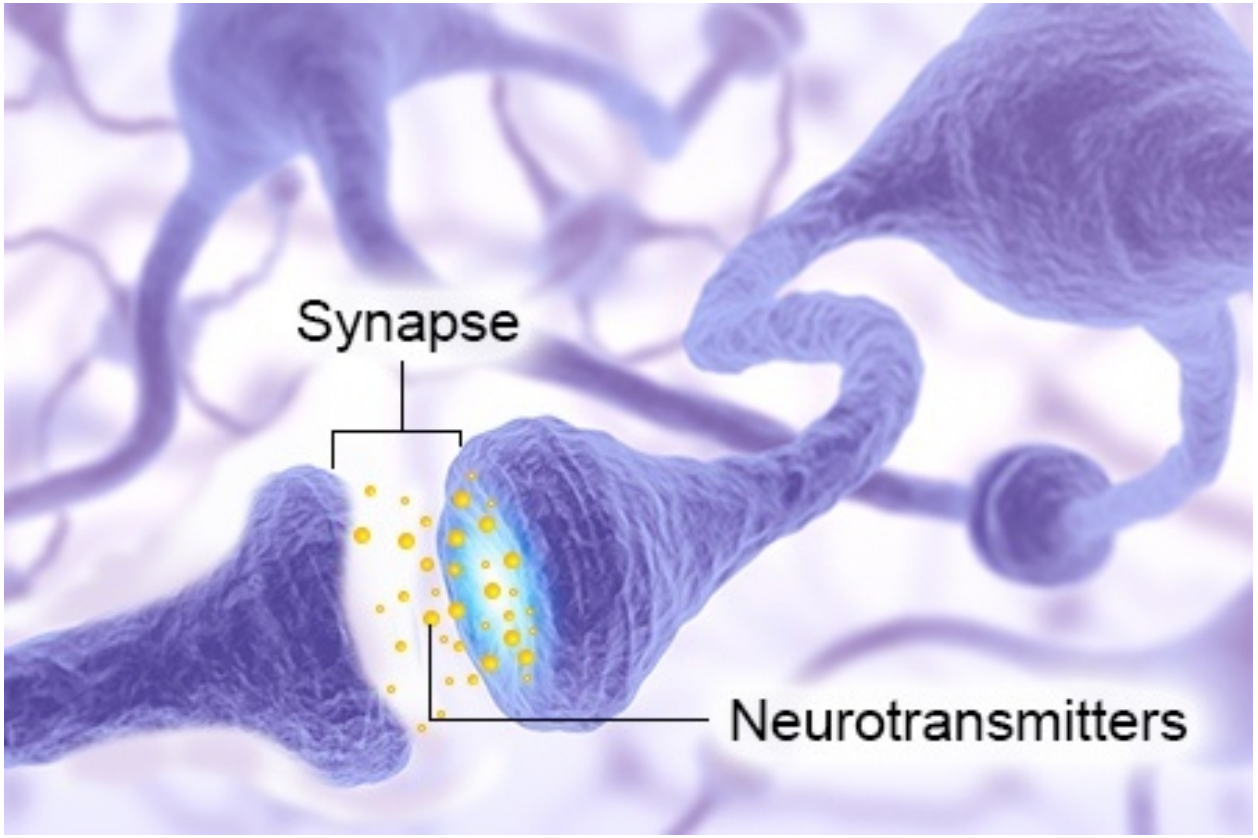
Disclosures and conflicts of interest: none

How do **medications** to reduce the **motor symptoms** of PD actually work ?

How do nerve cells communicate with each other?

"chemical messengers"

"neurotransmitters"



Neurotransmitter research:

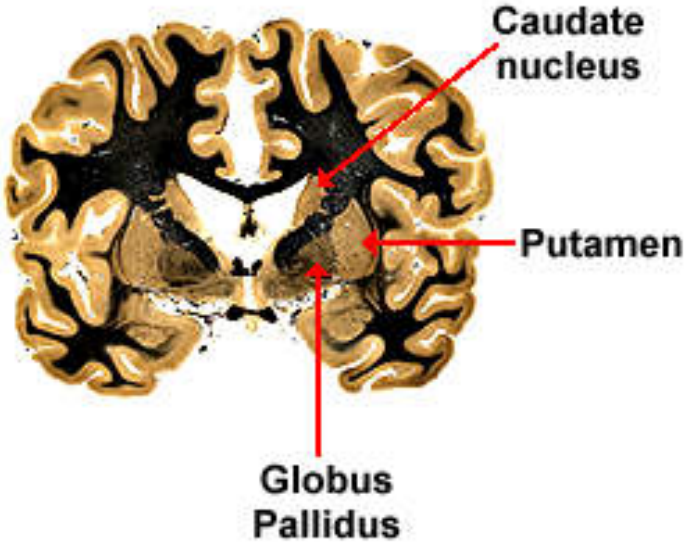
In 1959 Carlsson discovered that

DOPAMINE

is a **neurotransmitter**

and that dopamine was highly concentrated in the

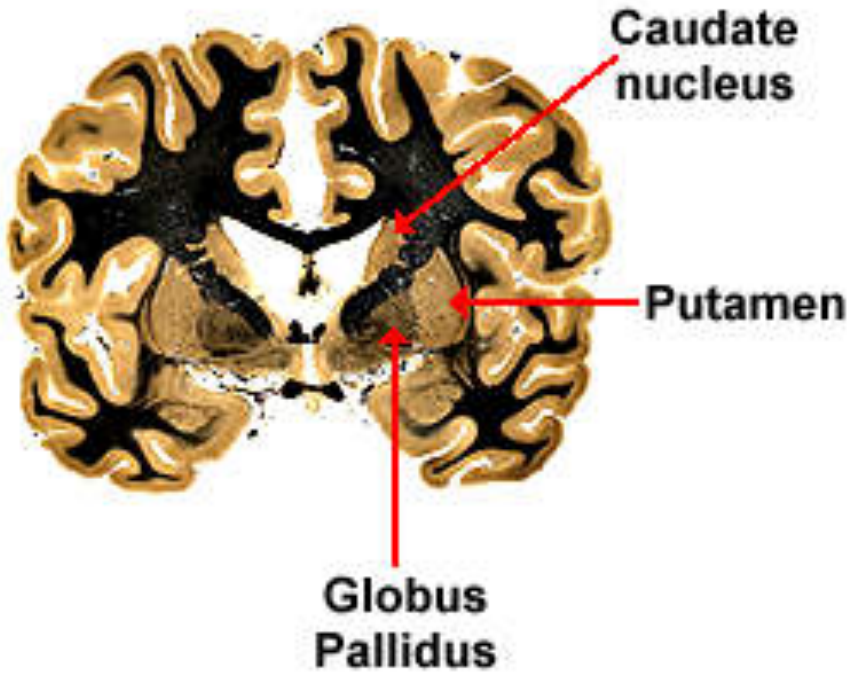
"striatum" (caudate and putamen)



What is a major function of the striatum ?

"facilitating complex sequences of movements"

(much as the conductor facilitates the harmonious music from an orchestra)



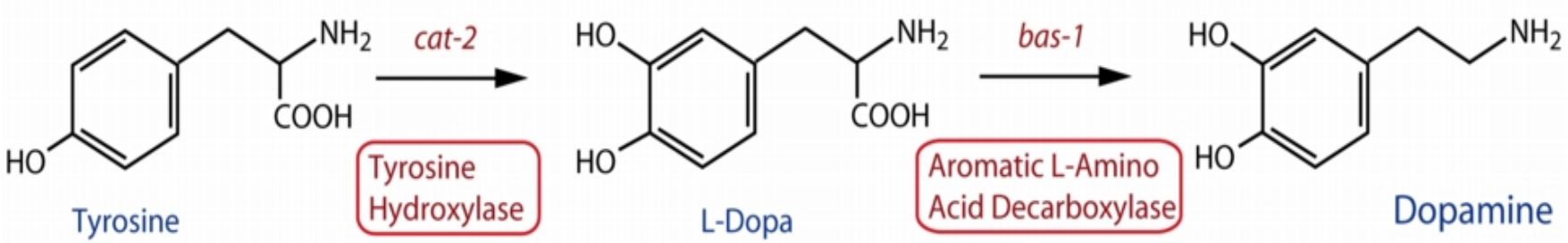
Post-mortem neurochemistry of PD

- In 1960 Dr. Hornykiewicz found **severe lack of dopamine in the striatum of PD patients**, but **not** in patients who had other neurologic disorders

He speculated:

"Might lack of dopamine in the striatum correlate with the severity of the motor symptoms in PD?"

How does the brain produce dopamine ?



- The amino acid **tyrosine** (which is prevalent in the diet and also manufactured from other dietary amino acids) is converted to **levodopa**
- **Levodopa is converted to dopamine**

Could anything be done to help?

L-dopa (levodopa) in the treatment of Parkinson disease:

- L-dopa was shown to be effective in treating the motor symptoms of Parkinson disease

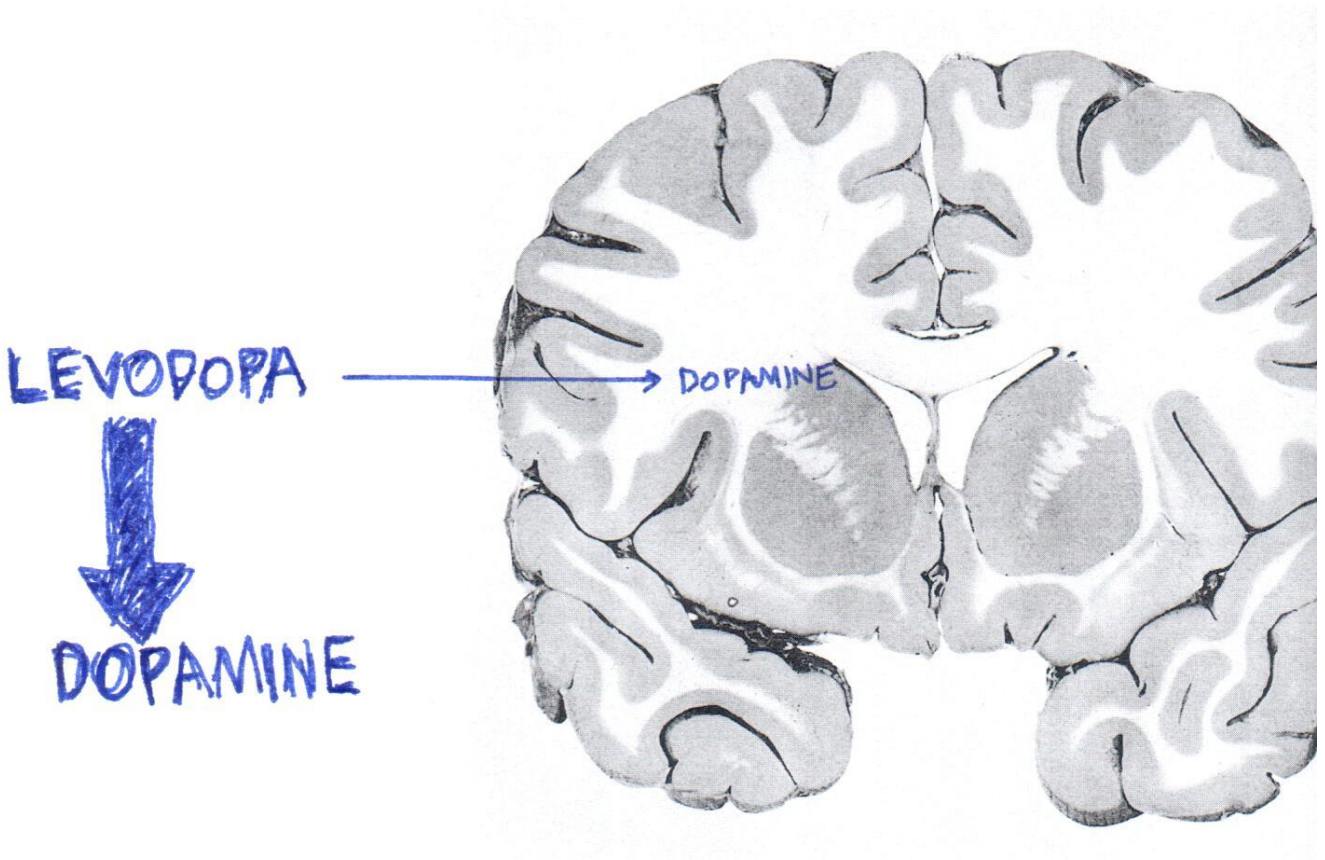
  George Cotzias et. al.

  NEJM 1969; 280: 337-345

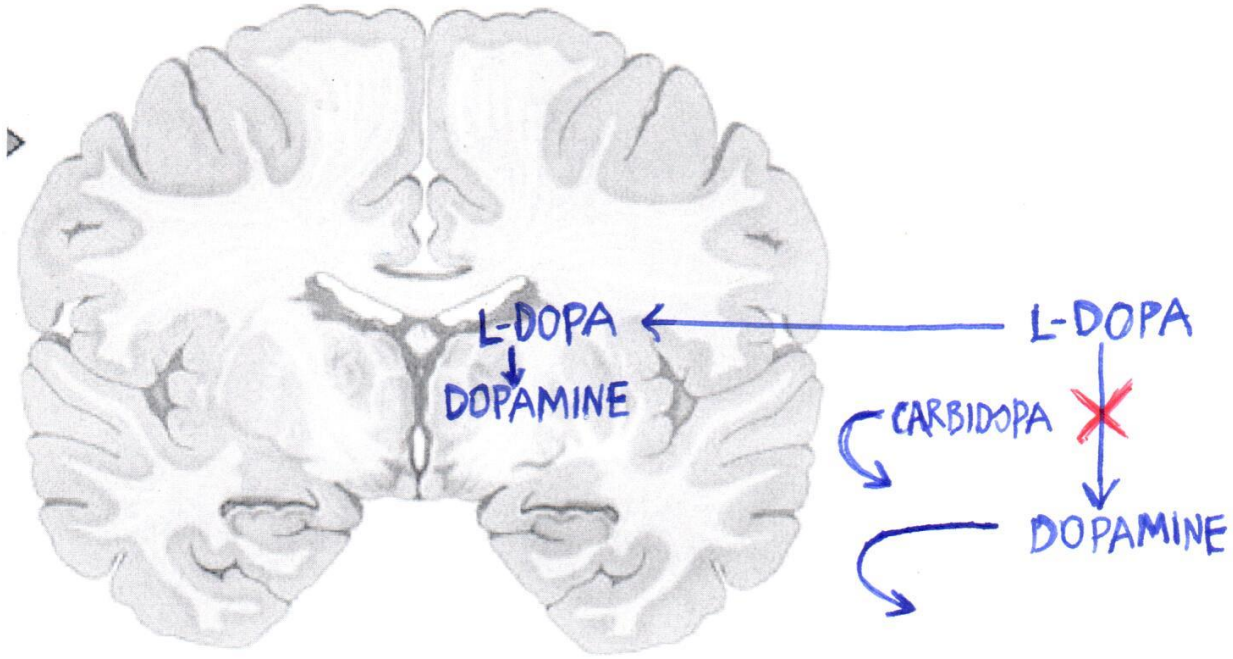
- An "**amazing breakthrough**": the first effective treatment for a neurodegenerative disease

  "resurrectamine"

What happens when you take levodopa ?



How does carbidopa/levodopa work?



Carbidopa blocks the conversion of levodopa to dopamine outside of the brain (reducing side effects such as nausea), allowing more levodopa to enter the brain where it can be converted to dopamine.

carbidopa/levodopa was marketed as **sinemet**:

"*sin*" (*sans*) = without "*emet*" (*emesis*) = vomiting

Levodopa in Parkinson disease

Now 50 years later:

Carbidopa / levodopa is still the <u>most effective</u> symptomatic drug treatment for PD

It is the *gold standard* against which new therapies must be measured

Wait a minute!
I read that carbidopa/levodopa is a dangerous medication with major side effects.

Unfortunately, many patients and physicians have fallen prey to an erroneous malady:

“levodopa-phobia”

Potential side effects of dopaminergic therapy

- **There are potential side effects** nausea, lightheadedness, sleepiness, dyskinesias, hallucinations, impulse control disorders, psychosis

However

- **Most people tolerate carbidopa/levodopa with few or no side effects**
- **It is <u>not</u> "dangerous"**

Warning Labels Can Be Hazardous to Your Health

Nov 18, 2008 1:59 PM CST

How much carbidopa/levodopa should I take ?

Many carbidopa/levodopa dosages are available

- 10/100
- 25/100
- 25/250
- CR 25/100
- CR 50/200
- ER 23.75/95 (rytary)
- ER 36.25/145 (rytary)
- ER 48.75/195 (rytary)
- ER 62.25/245 (rytary)

One size does not fit all !

Initial therapy is usually with the 25/100 strength and the dose is titrated according to the person's response.

Patients may need as little as 150mg of levodopa/day to over 1000mg/day to control symptoms.

Titrating carbidopa/levodopa

There is a wide range of effective doses:

“One size does NOT fit all”

Doses must be titrated according to improvement of the “target symptom” (e.g. rigidity, bradykinesia, gait) -

Tremor is not always an ideal “target symptom”.

The “do’s” and “don’ts” of treating Parkinson disease

Do not over-medicate patients!

Find the lowest dose that controls the target symptoms.

Over-medication can lead to serious side effects

The “do’s” and “don’ts” of treating Parkinson disease

Do not under-medicate patients!

Under-medication leads to increased disability.

Doses should be **individualized** and **titrated** according to the patient’s response.

The optimal dose and optimal time interval between doses needs to be identified for each patient.

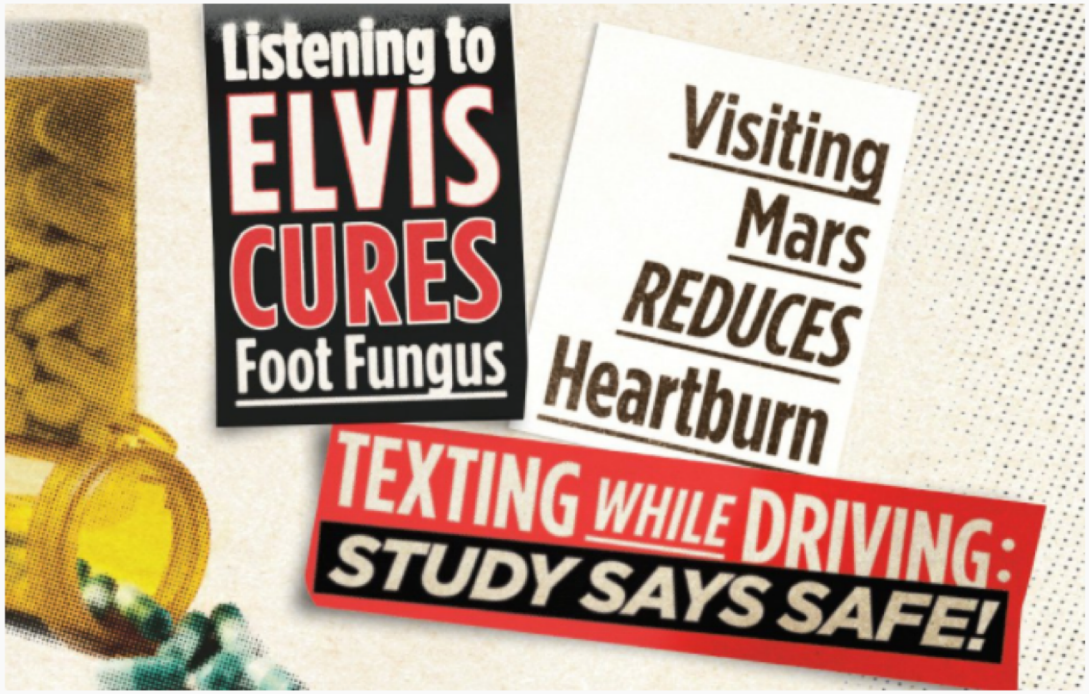
I read that levodopa “stops working” after several years: maybe I shouldn’t take it until my symptoms are much worse.

There is more fake and misleading news in medicine than in politics.

6 Tips That Will Help You Spot Fake

Don’t fall for any B.S.

BY TRACY MIDDLETON March 27, 2017



WOMEN'S HEALTH/GETTY

Initiating treatment for Parkinson disease

- Find the dose of carbidopa/levodopa that works best
- Arbitrarily delaying or restricting the dose has no long term benefit:

“you cannot save the best response for later”

- Initial therapy should be with regular carbidopa/levodopa

What is the goal for treating the motor symptoms in Parkinson disease?:

- **To completely eliminate tremor and all other motor symptoms at all times**

(this would be nice,

but is seldom possible)

or

- **To keep people functioning in the mainstream of life**

(a realistic goal)

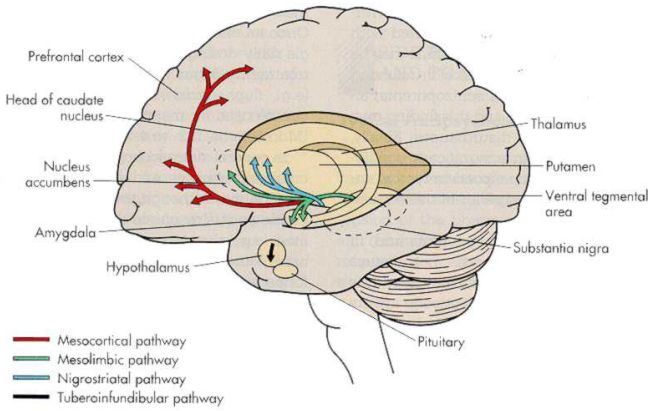
How often should I take carbidopa/levodopa ?

How is dopamine normally released in the striatum?

"phasic" bursts of dopamine ?

or

"tonic" (continuous) release of dopamine within the striatum ?



"**continuous release** of dopamine keeps the motor system ***en garde***"

- The loss of "tonic" rather than "phasic" dopamine release is most responsible for motor symptoms in Parkinson disease

Idealizing treatment with levodopa

With treatment we are trying to reproduce the normal state of

“continuous dopaminergic stimulation”

(which is why carbidopa/levodopa is best taken in **multiple divided doses**)

Movement Disorders 2017; 32: 1280

I heard that levodopa can cause dyskinesias? What are dyskinesias ?

Dyskinesias are involuntary movements induced by levodopa in patients who have had PD for a number of years:

Management of dyskinesias

- In most cases dyskinesias are mild and no change in treatment is needed:

  (patients prefer to be dyskinetic rather than bradykinetic or rigid)

However, if dyskinesias are troubling:

- Reduced levodopa doses should diminish dyskinesia:

Management of dyskinesias

Decreasing the levodopa dose may not be tolerated if there is worsening of parkinsonian motor symptoms:

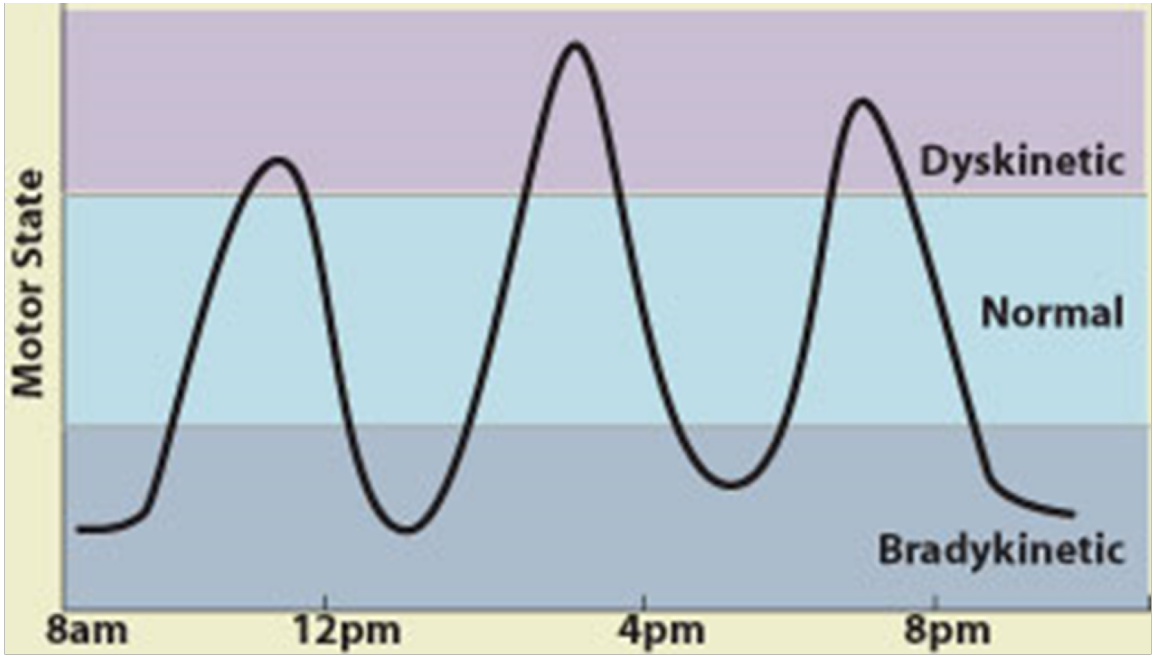
In this situation:

- Continue the previous levodopa dose and add **amantadine** to reduce dyskinesia

or

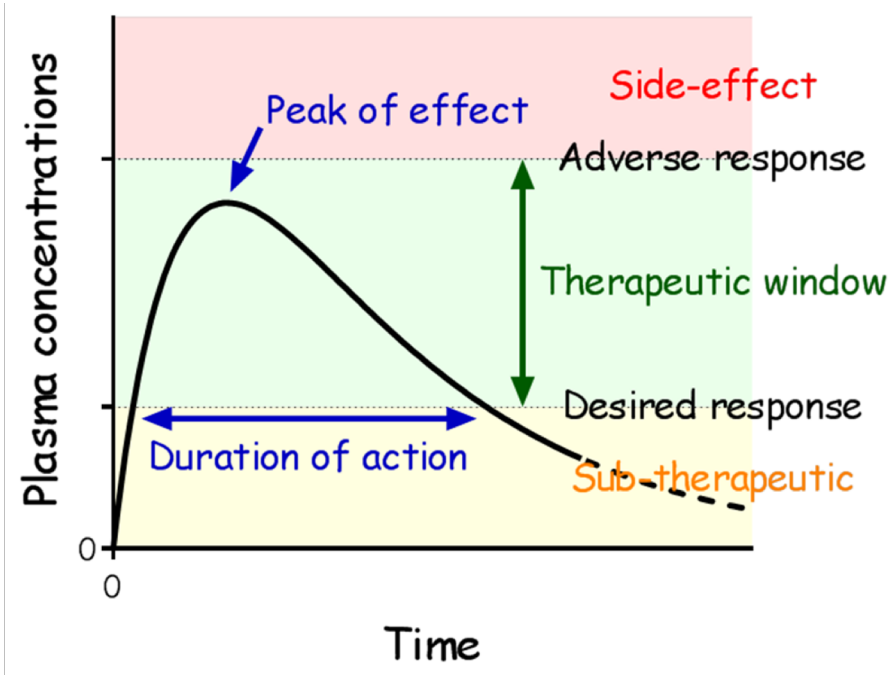
- Continue lower doses of levodopa and add a **"dopamine agonist"** to improve motor function

What causes symptoms to fluctuate in some persons who have had PD for many years?



Pharmacokinetics of carbidopa/levodopa

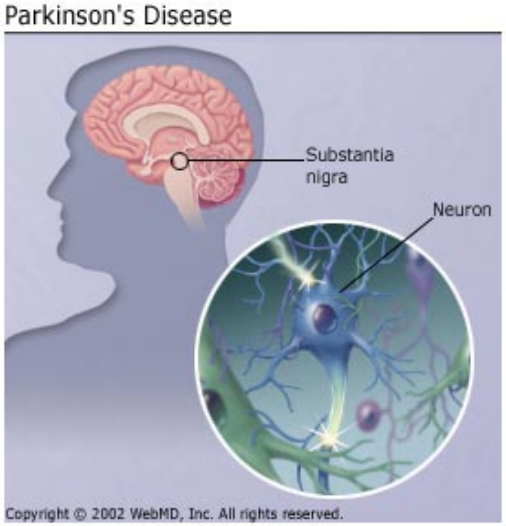
- Doses taken on an empty stomach reach peak blood levels in 30-45 minutes
- Blood levels drop to baseline in ~3 hours
- Higher doses result in higher peak blood levels, but do not last longer



Pharmacodynamics of carbidopa/levodopa

"Long duration response":

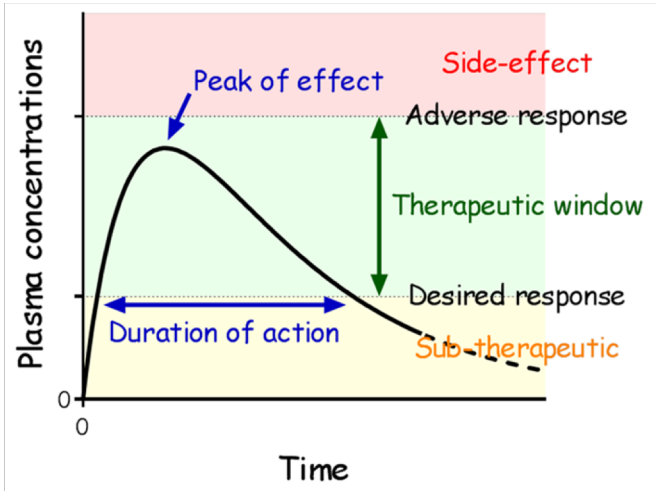
- During the first years of PD the response to levodopa is stable and not prone to fluctuation
- Patients can be late or even miss doses without noticing a change in motor symptoms
- If a patient with early PD discontinues carbidopa/levodopa it takes about a week for symptoms to decline to baseline



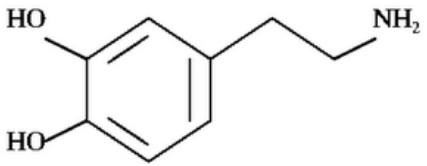
Pharmacodynamics of carbidopa/levodopa

"Short duration response":

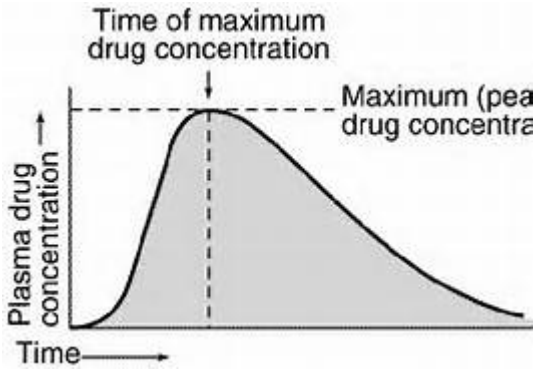
- As the disease progresses the "long duration response" declines
- Levodopa still "works", but the benefits wax and wane:
  patients note improvement 20-40 minutes after each dose, only to see the effect decline after a few hours

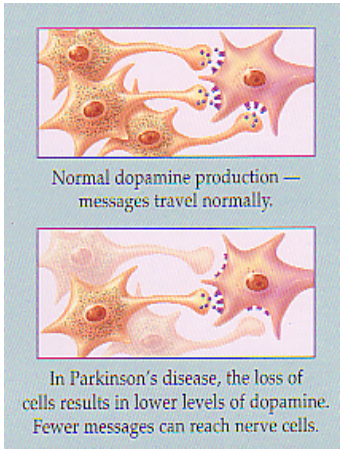


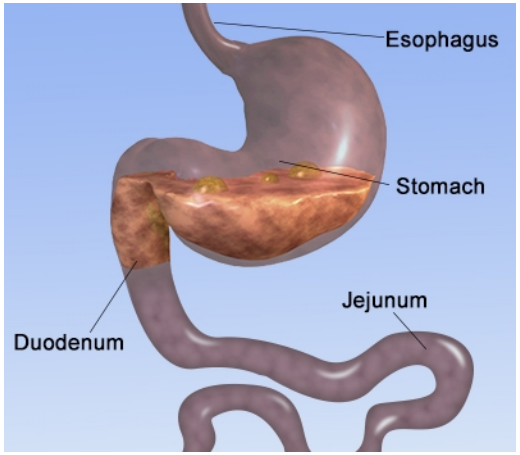
More Dopamine, Please!



Why do symptoms fluctuate ?

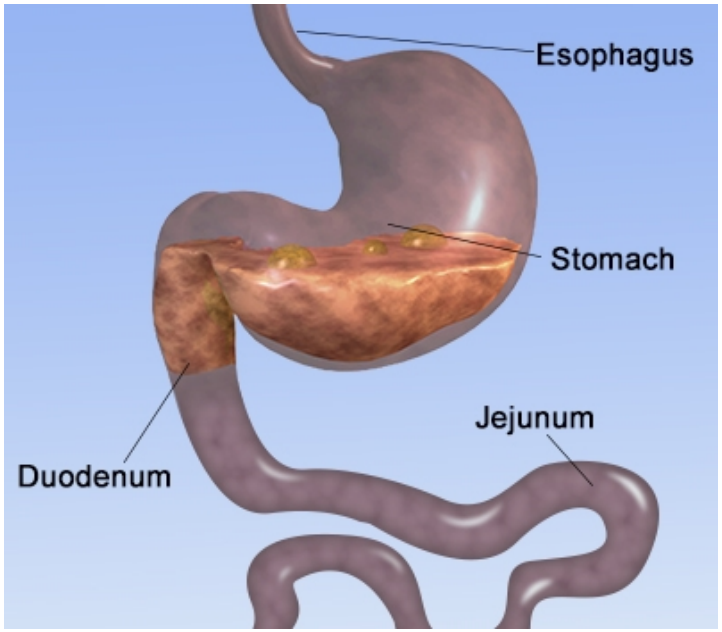






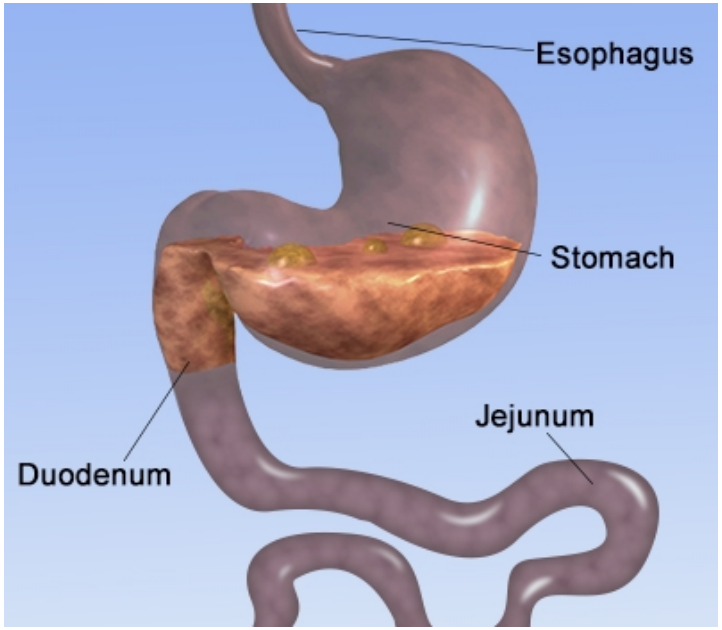
- Short half-life of carbidopa/levodopa (2-3 hours)
- Progressive loss of nerve cell reduces the capacity to buffer fluctuating levodopa levels
- Delayed gastric emptying
- Levodopa is absorbed in the jejunum, competing with amino acids from protein in the diet

Should I take carbidopa/levodopa with food or on an empty stomach ?



Effect of meals and protein on levodopa levels

- Meals reduce peak plasma levodopa concentrations by approximately 25-30%
- Meals delay absorption of levodopa by ~30 minutes
- High protein meals reduce the therapeutic effect of levodopa: **amino acids in the diet compete with levodopa**



"protein redistribution diet" for PD

Patients with significant fluctuations may benefit from avoiding protein containing foods with breakfast and lunch:

low or no protein foods:

muffins, breads, jams, salads, fruit

high protein foods:

dairy products, fish, eggs, meat, nuts

- Protein containing foods can be consumed with dinner or at night when the patient is planning to be less active

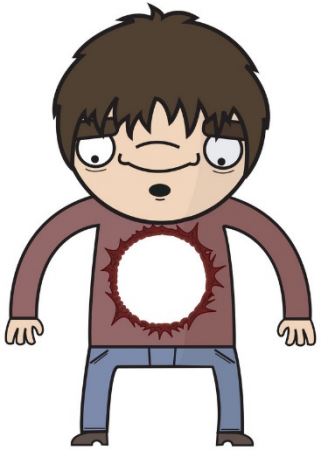
Do all PD patients with fluctuations require a “protein redistribution diet”?

NO! But for best effect try to take levodopa on an empty stomach:

- At least 30- 45 minutes before meals

  or

- About 2 hours after meals

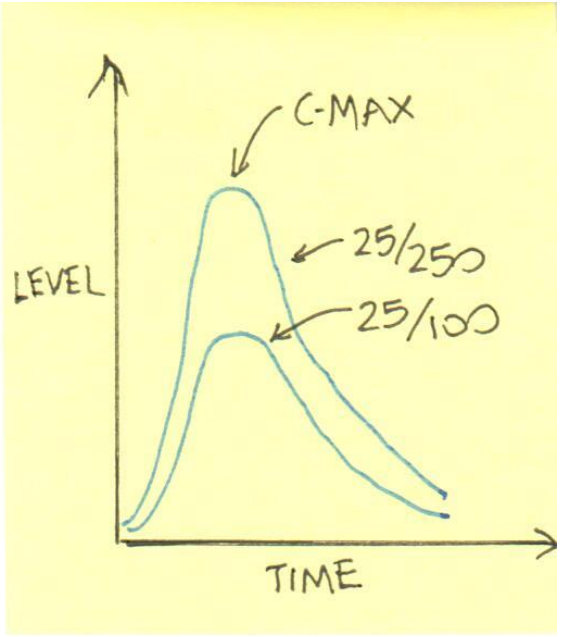


What else can be done to reduce fluctuating symptoms?

Re-timing carbidopa/levodopa doses is the first step in reducing motor fluctuations

- **Larger carbidopa/levodopa doses do not last longer**, (but will raise the peak blood levels which increases the potential for side effects)

1. Find the lowest dose that "works",
2. The duration of benefit, and then
3. Take the doses at the proper time interval (around the clock if necessary)



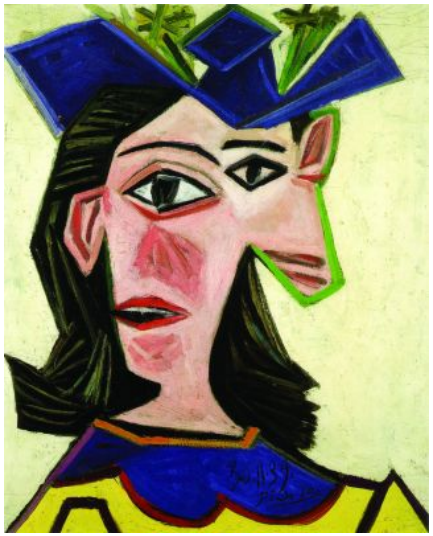
"medical treatment" of motor fluctuations

- Shorten interval between carbidopa/levodopa doses
- Take levodopa on empty stomach
- Protein redistribution diet
- Extended release carb/levodopa
- Medications to lengthen duration of levodopa effect:
  - COMT inhibitors
  - MAOb inhibitors
- Add a dopamine agonist

Caution: risk of over-medication !

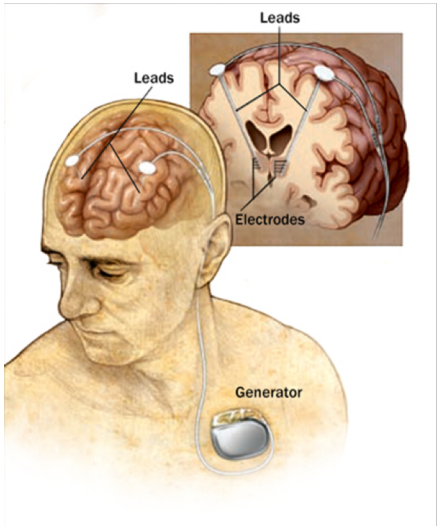
Aggressive adjustment of levodopa and use of polypharmacy to eliminate “off” time can result in **over-medication** and **serious side effects**:

- Intolerable dyskinesias
- Hallucinations
- Psychosis
- Impulse control disorders
- “Dopamine addiction”

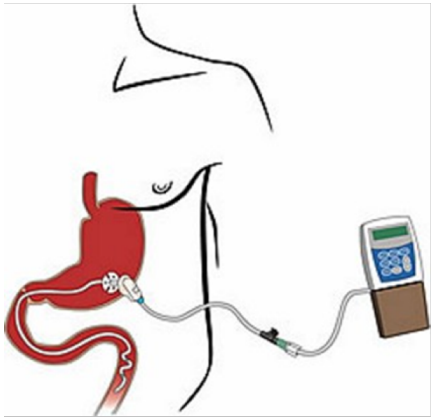


Surgical treatments to reduce fluctuating symptoms in PD

- "deep brain stimulation" (DBS)

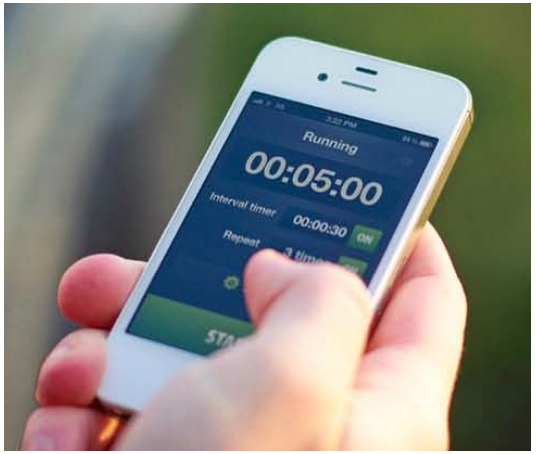


- Continuous infusion of levodopa (duopa)



Adjusting the timing and doses of levodopa is helpful but COMPLIANCE is CRUCIAL !

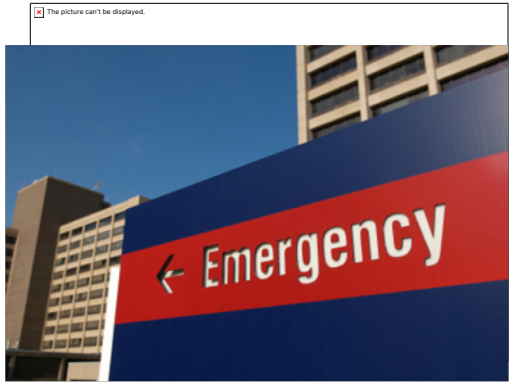
- Patients with fluctuations must adhere to a very reliable time schedule for dosing of levodopa
- Doses should be taken on an empty stomach when possible
- Use of a "timer" (e.g. on a "smart phone") helps improve compliance
- The physician's recommendations will not be helpful if the patient is unreliable or not compliant !



Avoiding problems in the hospitalized Parkinson disease patient :

- Patients should bring their PD medications with them to the hospital (some medications may be “non-formulary” and not immediately available)
- An accurate list of the doses and timing of medications should be provided to the staff caring for the patient
- The physicians, nurses, and pharmacy must be educated regarding “fluctuations” and why **precise timing** of medications is important to prevent these problems:

doses must be given **ON TIME EVERY TIME!**



(the usual hospital policy of allowing a 1 or 2 hour time window for medication administration is NOT appropriate for patients with Parkinson disease who are experiencing motor or non-motor fluctuations)

I hope this information will help you better understand some of the nuances that will help you get the most benefit from you Parkinson disease medications !

There have been misconceptions about levodopa

such as:

"Levodopa is toxic"

or

"Levodopa stops working after 'x' number of years"

These misleading ideas have made some physicians hesitant to recommend and many patients reluctant to take carbidopa/levodopa:

What gave rise to these erroneous concepts?

Unfortunately, many patients and physicians have fallen prey to an erroneous malady:

“levodopa-phobia”

Levodopa: sooner or later ?

Fluctuating responses to levodopa therapy is related to the duration and progression of disease rather than the duration of levodopa treatment

“you can’t save the best for later”

Levodopa: sooner or later ?

- **Later stage complications** (such a dysphagia, dysphonia, cognitive decline, retropulsion, and "freezing gait") **are not due to lack of dopamine, and will occur whether or not levodopa is used early or later.**

"you can't save the best for later"

Reducing side effects from carbidopa/levodopa

- **Find the dose that "works"**
- **Many side effects are related to the peak blood level of each dose:**

Thus if either 1 ½ or 2 tablets of carbidopa/levodopa 25/100 will control the patients motor symptoms:

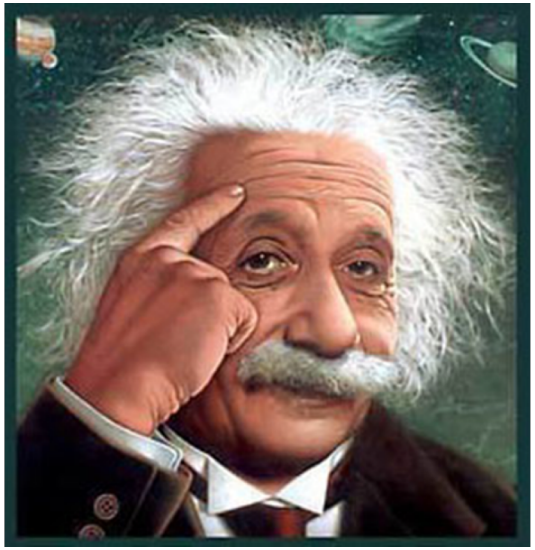
1 ½ tablets 3 or 4 times/day (doses 4 hours apart)

Would be less likely to cause dyskinesia, somnolence, orthostatic hypotension, or nausea than

2 tablets 3 times/day (doses 4-6 hours apart)

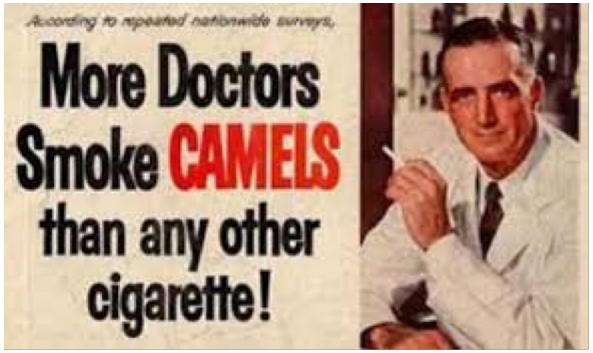
Research indicates that

scientists and doctors *don't have all the answers!*



Food for thought:

"Are the opinions of two people who do not know what they are talking about more valuable than the opinion of one person who does not know what he is talking about?"



KNOWLEDGE versus WISDOM

KNOWLEDGE is knowing that a tomato is a fruit

WISDOM is not putting it into a fruit salad!

Why do some people still have tremor despite taking carbidopa/levodopa?

TREMORS will be intensified by

- **Stress**
- **Anxiety**
- **Excitement**
- **Anger**
- **Fatigue**
- **Mental activity**
- **Self-consciousness**

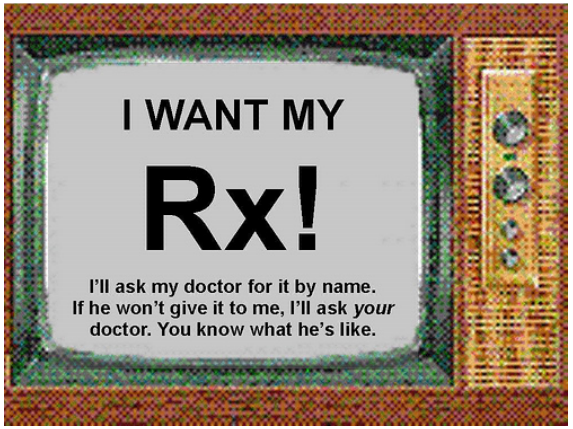
Tremor may respond less robustly to levodopa

- Unlike rigidity and bradykinesia, **tremor does not directly correlate with the degree of dopamine depletion**
- Other networks besides dopamine affect tremor severity
- **Tremor progresses more slowly than other motor symptoms, and while potentially embarrassing is seldom disabling.**

Movement Disorders 2016; 7: 957-961

Assessing new treatments in medicine:

"In many instances the widespread use of new treatments reflects "***the miracle of medical marketing***" rather than "***the miracle of medical science***."



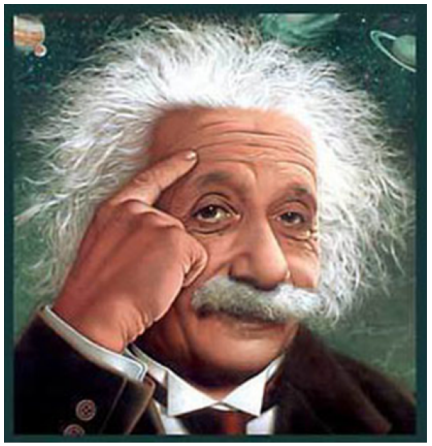
The “Max Planck chauffeur syndrome”

Professor Planck’s chauffeur heard lectures about ***quantum mechanics*** so many times that he could repeat the lectures verbatim (but he understood

absolutely nothing

about the subject matter).

Max Planck
(1858-1947)



Two types of patient:

The patient who answers

"yes or no"

versus

the patient who answers

"not yet"

Two types of patient:

When asking a patient whether they have a particular symptom, I expect them to answer:

"yes" or "no"

Two types of patient:

However, some patients respond:

"not yet !"

Which patient has better mental health ?

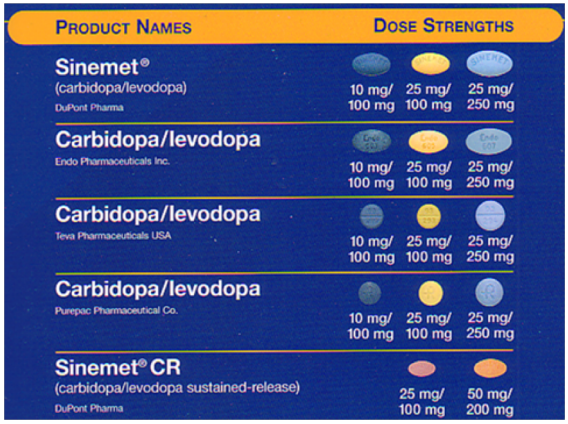
Human nature 201:

“Pessimists and optimists develop the same illnesses but lead very different lives!”

How to initiate carbidopa/levodopa: start with the 25/100 strength

Why 25/100 instead of 10/100?

75 to 100mg (or more) of carbidopa is needed to inhibit peripheral dopa decarboxylase:



The 25/100 strength (not 10/100) will achieve adequate amounts of carbidopa to block the “peripheral” conversion of levodopa to dopamine, thereby reducing nausea and making more levodopa available to enter the brain where it is needed.

How to initiate carbidopa/levodopa 25/100

- **Start with a low dose** such as

  ½ tablet 3 times/day before meals

- **Titrate the dose upward** slowly by ½ tablet weekly:

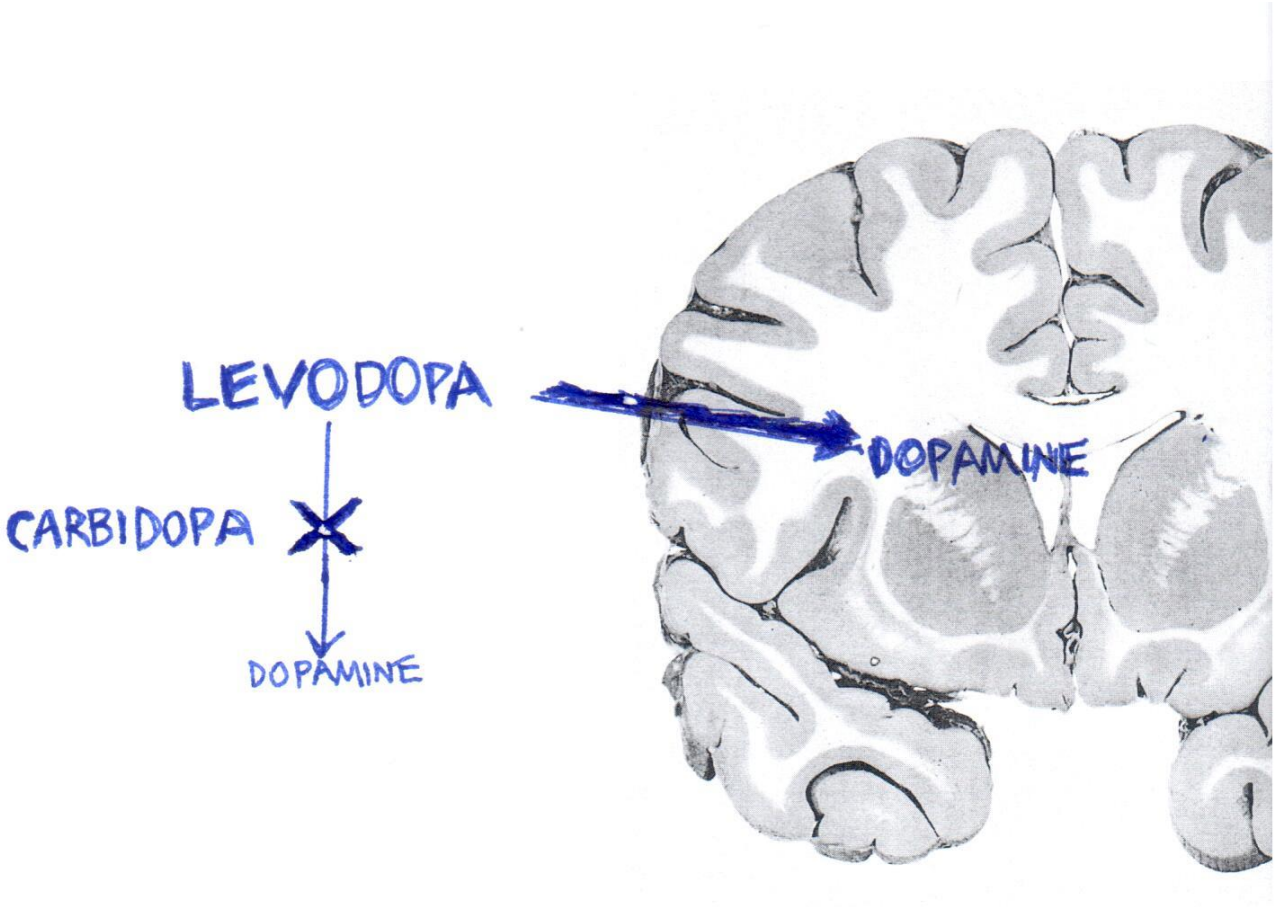
  1 tablet 3 times/day for 1 week

  1 ½ tabs 3 times/day for 1 week

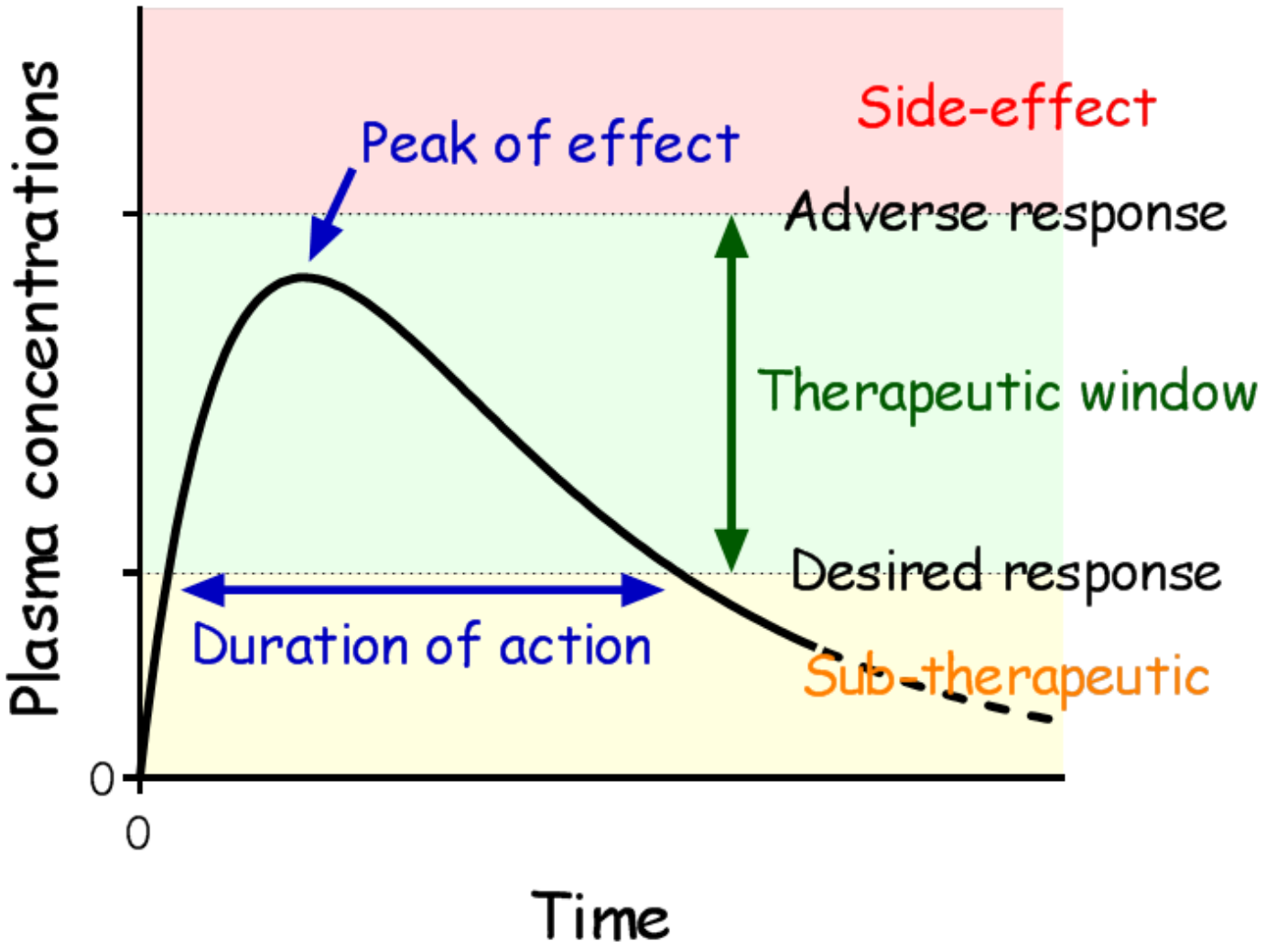
  2 tabs 3 times/day etc

In most cases the target symptoms will improve with 1 ½ to 2 tablets 3 times/day, but some patients will require higher doses (1000mg of levodopa/day or more) and some patients will be more sensitive and only require a total of 150 to 300mg/day.

What happens when you take carbidopa /levodopa ?



Levodopa pharmacokinetics



“pearls” in optimizing treatment with carbidopa/levodopa”

- Find the levodopa dose that “works”
- Find the proper time interval between doses
- Smaller doses given frequently have fewer side effects than larger doses less often
- Larger doses of levodopa do not last longer than smaller doses
- Compliance with schedule is important
- Levodopa is absorbed more quickly and completely on an empty stomach
- Re-distributing dietary protein to evening can reduce “off” time during the day
- Bedtime doses and middle of night are helpful if PD symptoms interfere with sleep
- Monitor closely for side effects:

  dyskinesias, hallucinations, psychosis

Additional measures to reduce fluctuating symptoms in Parkinson disease

- Carbidopa/levodopa CR
- Extended release CD/LD (rytary)
- Dopamine agonists

"levodopa extenders"

- MAOb inhibitors
- COMT inhibitors

DBS

Intestinal infusion (duopa)