

## **Pills, Patches, Pumps and Puffers for Parkinson's Disease.**

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To begin, I extend my gratitude to the Davis Phinney Foundation for organizing this Summit and inviting me to be a part of it.

### **Take home messages:**

My primary goal, even if it doesn't particularly relate to my chosen topic on medications, is that everyone here today leaves motivated to exercise. One can definitely say that for Parkinson's disease, exercise is "the best medicine". To date this seems to be the only way of slowing the progression of this disease.

You should leave motivated to develop a good relationship with your doctor or make plans to get a new one. You should be seen by a specialist in Parkinson's disease in addition to your regular doctor. With any medication trial, be informed about why it was chosen for you, what the alternatives are and what the most likely side effects will be.

Be aware of the time of day your medication should be taken and if you need to base the timing relative to meals. The relationship with your MD doesn't mean you can't research info on the internet, but remember your doctor can advise you regarding information that is pertinent to you as an individual; the internet cannot come close to doing this. Be cautious. There is a lot of false information on the internet. There are far too many snake oil salesmen out there who may seem to care and be knowledgeable, but their main motivation is to make money.

Try to stick with new medications for long enough to be sure of their effect. Many people become anxious with any new medication trial and the worry itself can worsen Parkinson symptoms. This makes it seem the medication failed or caused a worsening of Parkinson's when it wasn't at fault.

If you are convinced a change in medication is needed, check with your doctor before making changes on your own.

### **The disease:**

Parkinson's disease is a progressive, degenerative, neurologic disease triggered by environmental exposures in genetically predisposed people. The hallmark of the disease is nerve cell loss in the dopamine producing cell region at the base of the brain (Substantia Nigra). This Dopamine loss causes stiffness, slowness and tremor that lead to the diagnosis. Dopamine cells die during normal aging in everyone. Something occurs to cause them to die more quickly in the 2% of the population that have Parkinson's disease by age 80. We know exercise can slow down this nerve cell loss and thus slow down the speed of worsening of the disease. Avoid watching life go by from the couch.

### **What treatment to start and when?:**

“Pre-habilitation” by exercising to prevent loss of function works much easier than rehabilitation directed to regain functions once they have been lost. Both are important. Multiple animal and human studies support this notion and the current recommendation is 3 hours/week of cardiovascular fitness – (some huffing and puffing required). You want to be the shiny mouse.

Almost all people living with Parkinson’s disease have constipation and often for years prior to the diagnosis of Parkinson’s. This is aggravated by an equally common loss of thirst making people prone to dehydration and this further aggravated in those with a sedentary lifestyle. Pills work poorly in the situation of anxiety, stress, depression and poor sleep. To optimize benefit from medications for Parkinson’s disease, bowel habits need to be regulated and constipation controlled. Adequate fluid intake is the first step (8-10 glasses or servings / day) combined with a regular exercise schedule, a diet with fruit and fiber, and, if necessary, by laxatives (stool softeners and/or bowel stimulants) as recommended by your doctor.

Stress aggravates everything and can cancel out benefit from medications. This needs to be looked after. Management sometimes is as simple as talking to family or friends, learning how to say “no”, and advising the key people in your life that you have Parkinson’s so you don’t feel you need to hide it from others. Treating Parkinson’s motor symptoms rarely helps mood but fixing one’s mood often helps Parkinson’s motor symptoms. If there is anxiety or depression seek treatment for these.

There are no medications that have been proven to slow disease progression. As medication doesn’t slow the progression there is no hurry to start them. Having said that we know if you wait till you start to fall before starting them mortality increases. Medications can be expected to improve the speed of movement, reduce muscle stiffness and lessen tremor. The medications that I will discuss target these symptoms to improve function with the goal to improve quality of life. We do not aim to get rid of all symptoms or signs, we aim to allow one to carry on enjoying life at work and to maintain relationships at work, with friends and your social network.

By using medication to replace the effect of dopamine, it is like adding oil to a motor to get it to run smoother. There are numerous medications to attempt to accomplish this. We have the option of either providing dopamine directly by using levodopa or by using chemical mimics of dopamine (dopamine agonists). Indirectly we can improve the chemical balance in the brain by blocking acetyl-choline, as this makes the existing dopamine work better.

**Anticholinergics** (egs; Trihexiphenadyl (Artane), Benztropine (Cogentin)) are not used very often anymore due to prominent side effects including worsening constipation, dry mouth and memory loss. They will sometimes be added for stubborn tremor or excess saliva or resistant muscle cramping.

**Levodopa** after absorption from the small bowel is converted in the blood stream to dopamine effectively replacing exactly what is missing in the brain. This is the gold standard medication. It is the most likely to work and the least likely to cause side effects. With initiation, as it can cause nausea, it is usually started 3 x/day after meals but with time should be moved to 1 hour prior to meals or 2 hours after to improve absorption. Early on it lasts 4-6 hours but with progression of

the disease and further inability of the brain to produce its own dopamine, doses need to be increased and more frequent doses are needed to try to maintain an even response. The currently available long acting form of this medication (Sinemet CR) is often erratically absorbed and as a result is not commonly recommended except for overnight use. Levodopa is sold as a combination pill that includes an anti-nauseant called carbidopa under the names Levocarb or Sinemet, or benserizide under the name Prolopa. Side effects may include nausea and low blood pressure and later on, uncontrolled movements (Dyskinesia), especially, in young patients, memory problems, confusion and hallucinations can occur. All of these side effects increase with higher doses.

### **Dopamine Agonists:**

This group of medications was designed to stimulate dopamine receptors. They do this in a more artificial way than dopamine and as a result can trigger abnormal behaviors not usually seen with levodopa. These include the drugs bromocriptine (Parlodel) (now rarely used due to heart valve side effects), Ropinirole (Requip) and Pramipexole (Mirapex). The hope that these medications could reduce the chance of causing dyskinesia (excessive involuntary squirming movements) was confirmed in clinical trials and led to them being approved, but once they were in common use, the side effects of excessive sleepiness (in 12%) and impulse control disorders in 13 % (gambling, hypersexuality, eating binges, excessive shopping) has limited their use. This group of medications is also more likely to cause low blood pressure, confusion and hallucinations than levodopa and this limits their use in older patients.

### **Patches:**

Late in 2017, Manitoba Pharmacare added a 24-hour dopamine agonist patch to the Provincial Pharmacare Formulary. It can have the same side effects of the other agonists mentioned above, but is the only current non-surgical option that uses a treatment method that lasts 24 hours and avoids the need for intestinal absorption as it is absorbed through the skin directly into the blood stream.

### **Enzyme Blockers:**

The body normally gets rid of dopamine through natural enzyme pathways of breakdown. If we use medications to block these enzymes then dopamine levels are increased and the levodopa effect can be lengthened. This helps maintain a more even response.

Medications in this group include the selective Monamine Oxidase inhibitors (MAO-B) Selegiline (Deprenyl), and Rasagiline (Azilect), as well as the Catecholamine Methyl Transferase (COMT) inhibitor Entacapone (Comtan). Most of the side effects of these medications are due to increasing levodopa levels in the blood.

Of note, Selegiline was an approved antidepressant in Europe prior to its use for Parkinson's disease. There is a potential additional benefit of improved energy and mood. As it is a stimulant that can result in a disturbance of sleep, it is not to be used later in the day. There are a lot of theoretical interactions with other medications and certain foods (old cheese and other tyramine

containing food), which is often a cause for concern for pharmacists. These issues are indeed rare as unlike older MOA-A inhibitors, MAO-B only targets the brain enzyme so the concerns with more systemically active MOA-A inhibitors are avoided.

### **Amantadine (Symmetryl):**

This is a medication that has been available since before levodopa. It has the unique ability to improve Parkinson's while also reducing the dyskinesic movements (70% of the time). It has anticholinergic effects so can also cause confusion, dry mouth and constipation so needs to be used cautiously as people age. It can also trigger low blood pressure, leg swelling and a mottled discoloration of the skin.

### **Fluctuations:**

Early on in Parkinson's, although the brain doesn't produce enough dopamine, it still produces some. This is particularly true over night, during sleep. As a result, Parkinson's disease is usually better in the morning. This has been called the honeymoon period.

At this stage, if the dopamine provided by medications doesn't last until the next dose starts to work, there is still a significant amount of dopamine in storage that is available to maintain function. This means that the pills don't seem to run out between doses and easier to maintain levels of dopamine in the "therapeutic window" (the level where the medication is working well without side effects). Thus the medications provide an even response through the day.

Over time, the dopamine storage ability fails. This results in the response becoming more dependent on the ability of medications to maintain stable blood levels of dopamine. As the illness worsens over time, a higher blood level is required and it becomes harder to maintain a good functioning state ("ON") with medications given 3 x/day. This leads to the need to take medications more frequently. From a symptom point of view the changing blood level results in "fluctuations" in response. Fluctuations are subdivided as to type and include: "Wearing OFF" which is a failure of symptom control occurring as the last dose runs out; "Peak dose dyskinesia" implying the excessive movements that occur due to levels of a medication that are too high and acts to speed up movement. Eventually these fluctuations become unpredictable.

The latter situation has been used by clinics to track the stages of a patient's response to medications as follows; 1) Stable all day, 2) Wearing off prior to supper, 3) Wearing off in the AM, 4) Predictable wearing off prior to every dose and 5) Unpredictable offs.

The management of these fluctuations is a major challenge for patients and doctors. The first step is to make sure the medications are being taken according to a schedule at the same times every day. This may require input from a reliable family member, or a pill timer (see [www.E-Pill.com](http://www.E-Pill.com)). One way of assisting management is for the patient to track symptoms with a daily diary to help sort out the pattern of their response and provide this information for the clinic to use to appropriately decide how to adjust the type of medication needed or to adjust the timing of meds.

Levodopa, like dopamine, is an amino acid. Amino acids are the building blocks for proteins. There is a limited capacity of the small bowel wall to absorb amino acids. If a levodopa tablet is taken at the same time as a large protein meal, it will not get absorbed as well and thus will not be as effective. As you need protein to remain healthy, the recommendation when absorption is a concern is to consult a dietician to sort out how best to adjust your dietary protein intake.

Options to control fluctuations include; taking doses more frequently, take pills 1 hour before or 2 hours after meals, using enzyme blockers to keep the dopamine around longer (Selegiline, Entacapone, Rasagiline), adding an agonist, including, the 24 hour Rotigotine patch, adding in Amantadine, having Deep Brain Stimulation (DBS) surgery, and, finally, having a surgically implanted levodopa suspension pump system (duodopa).

### **Pumps:**

The Duodopa pump system requires the surgical implantation of a tube through the skin (percutaneous) into the stomach and the tip of the tube is advanced into the small bowel. The tube is attached to a portable pump worn on a belt. The system requires regular filling and the pump infuses the medication steadily through the day. This system is costly but is covered in Manitoba for those who cannot control fluctuations and who are not candidates for DBS surgery. Currently Dr. Julius Anang, a movement disorder neurologist at the St Boniface Clinic, is offering the treatment.

### **Making Treatment Choices:**

At many stages of Parkinson management there are multiple options or choices to be made as to what to consider next to optimize function, while avoiding unnecessarily creating side effects.

Choices will depend on the importance of trying to improve today's problems while minimizing the risk of aggravating future control. Nuisance symptoms have a lower priority to chase than disabling ones. There can be many simultaneous issues and one has to establish priorities, as generally it is wise not to introduce multiple simultaneous changes. One change at a time is always wise. Any change in treatment needs to consider the potential good effects but also potential adverse effects. The "I'm willing to try anything" approach is frequently regretted. It remains important that, although, there are many options for treatment for the host of complaints that can arise in Parkinson's management, some symptoms have no treatment and some treatments are too risky to consider in some patients. This leads to the important need for patients to adapt over time to their condition, emphasizing their remaining abilities and not spending too much time dwelling on aspects of life that are no longer possible or are so frustrating to no longer provide enjoyment. In a word, 'recalibration' is needed to grow old gracefully with this illness.

### **Other issues/other medications/Allied health:**

Depending on the stage of the illness and the problematic areas, there are many other medications that are provided or recommended in a Parkinson clinic. These are often to address "non-motor" concerns. These areas include, but are not limited to, **Low blood pressure**

(increase fluid and salt intake, domperidone, Midodrine, Florinef), **Depression and Anxiety** (Counselling, antidepressants), **Sexual dysfunction** (Viagra, Cialis), **Bladder control** (Ditropan), **Confusion** (treat other medical issues), **Constipation** (fluids, fiber, fruit, exercise, appropriate laxatives), **Sleep fragmentation** (sleep study to investigate apnea, manage bladder complaints, consider Melatonin, Trazodone), **Nightmares** (quetiapine), **Fatigue**, including while driving (Stop driving, Caffeine, Modafinil), Memory loss (General medical work up, Donepezil, Rivastigmine, Galantamine), **Action tremor** (Propranolol), and **Hallucinations** (Quetiapine, Clozapine).

Despite the best medications available problems can develop that we do not have medications to help. Examples would include falling, swallowing problems, quiet speech, financial consequences of the disease and more. This is the reason a specialty clinic will provide care from allied health professionals. **Physiotherapy** for fall avoidance and general fitness and strategies to slow progression, **Occupational therapy** to create better strategies, environments or equipment to improve function and safety, **Social Worker** to help with emotional issues, personal and family interactions and life decisions, **Speech therapy** for assistance with speech or swallowing difficulty, **Genetic Counselling** to assist in sorting out issues relating to forms of Parkinson's that run in families (16%), **Dietician** for advice regarding diet modifications, and a **Clinic Coordinator** to help organize this interdisciplinary care.

### **Recent / New Medication Ideas:**

#### **Pokes:**

**Apomorphine** (Movapro) is a dopamine agonist (which is neither a generic drug produced by Apotex or a pain medication related to morphine) now approved in Canada and coming to clinics likely during 2018. It is an injectable product provided in prefilled syringes with retractable needles attached that works similarly to levodopa but will start to work within 5 to 10 minutes and last ~ 1 hour. It will be used as a rescue drug for patients with severe wearing off in the morning or unpredictable offs. The same drug will be coming to Canada within a few years in an under the skin infusion system to be provided over 24 hours.

#### **Patch/Film:**

An under the tongue film that releases apomorphine is also coming to Canada. After placement under the tongue for 2 minutes this will work within 12 to 15 minutes and last 90 minutes. It will be another rescue treatment option.

#### **Puffers:**

A Levocarb puffer (inhaler) has been studied in clinical trials and should be arriving for use in Canada within a few years. This is a capsule form of the drug in a specially designed inhaler. The system, when activated, breaks and spins a capsule of levodopa in the inhaler and the patient then breathes the created powder into their lungs. The effects begins within 5 minutes and last 1 hour.

If further information is needed I recommend going to [www.cmdg.org](http://www.cmdg.org) and following treatment links on the main page to treatment, or the links to other Parkinson websites including the Davis Phinney Foundation.