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Research Article

Biochemistry of Methylphenidate in Long-term Treatment of Parkinson's

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Abstract

Background: Discoveries in this study can significantly improve the health and quality of life of over ten million Parkinson's- affected people. Clinicians prescribe AntiParkinsonian medications to treat Parkinson's illnesses and Parkinsonism. AntiParkinsonian Carbidopa-Levodopa, Ropinirole, and Pramipexole commonly cause progressive neural damage (augmentation) and adverse reactions such as excessive sedation, sudden passing out, and slowed cognition. This study presents a neurobiochemistry analysis regarding the world's first long-term treatment of Parkinson's with Methylphenidate. The neurobiochemistry analysis in this study describes and explains how Methylphenidate adjunctive therapy counteracts the adverse effects of AntiParkinsonians and how Methylphenidate monotherapy controls motor and non-motor symptoms, strengthens neural tissues, sustains alertness and cognition, and slows progressive worsening.

Clinical uses of Methylphenidate rarely cause side effects and they are virtually always minor. Methylphenidate is prescribed to millions of children as young as 6 years.

Methods: This article analyzes the neurobiochemistry of Methylphenidate vs. AntiParkinsonian therapy based on a review of over 400 published articles and a 17-year treatment for severe Parkinson's/Parkinsonism with nine years of AntiParkinsonians followed by eight years of Methylphenidate. The recipient, Dr R, is a 66-year-old PhD American male who is a published Researcher. At age-55 he was documented as disabled and needing medications to function. At age- 58 his illness and the adverse effects of APs jointly caused total disability for which there was no medication or remedy. Thus he conceived and designed the world's first long-term Methylphenidate treatment of Parkinson's. He implemented it with the cooperation of a prescribing Physician.

Results: Initial experimentation found that 30 mg doses of Methylphenidate overcame the adverse effects of adjunctive AntiParkinsonians. Continued experimentation later found that 20 mg doses of Methylphenidate monotherapy controlled Parkinson's illness-symptoms better than AntiParkinsonians. An experimental 3-hour dosing schedule resulted in uninterrupted efficacy during transitions between doses. Efficacy duration was extended to 16 hours by adding sequential doses every three hours. A 25 mg dose upon waking overcame residual morning grogginess from high-dose AntiParkinsonians at bedtime that gave good sleep. Six years of gradual titration resulted in an optimally effective daily regimen of: [dose-1, 3-hour MPH-IR 25 mg], [dose-2, 6-hour MPH-ER 40 mg], [dose-3, 3-hour MPH-IR 20 mg], [dose-4, 3-hour MPH-IR 20 mg], [bedtime 2 tabs Carb-Levo 10/100 mg, 2 tabs Carb-Levo ER 25/100 mg, and 2 tabs Pramipexole 0.25 mg].

Conclusion: Clinicians can replace diurnal AntiParkinsonians with diurnal Methylphenidate in order to provide safer and more effective long-term treatment of Parkinson's illnesses and Parkinsonism.

Keywords: AntiParkinsonians; Dopamine; Methylphenidate; Narcolepsy; Parkinson's; Pramipexole

Abbreviations

ADD: Attention Deficit Disorder; ADHD: Attention Deficit and Hyperactivity Disorder; AP: AntiParkinsonian; b.i.d.: Two Times Per Day; DA: Dopamine Agonist; DBS: Deep Brain Stimulation; DRT: Dopamine Replacement Therapy; ER: Extended Release; IR: Immediate Release; mg: Milligrams; MPH: Methylphenidate; PD: Parkinson's Disease; PI: Parkinsonism Illness; qd: Once Per Day; q.i.d: Four Times Per Day; RLS: Restless Leg Syndrome; t.i.d.: Three Times Per Day; WED: Willis-Ekbom Disease

Introduction

This study found that Methylphenidate (MPH) is significantly more effective and significantly safer for treatment of diurnal Parkinson's symptoms than widely used AntiParkinsonians (APs) such as Carbidopa-Levodopa (Sinemet) and Pramipexole (Mirapex). This study analyzed the neurobiochemistry of MPH as a long-term diurnal monotherapy for controlling diurnal Parkinson's symptoms. The findings of the analysis were demonstrated and validated by in-vivo data from the world's first long-term MPH-treatment of Parkinson's. The in-vivo data was substantial and robust by virtue of the length (2014 through 2022), success, and safety of the MPH-treatment.

Treatment of Parkinson's symptoms with AntiParkinsonians is often called Dopamine Replacement Therapy (DRT). Persons with Parkinson's and Parkinsonism illnesses do not naturally produce sufficient amounts of Dopamine. The goal of DRT is to increase their Dopamine levels in order to relieve Parkinson's symptoms and thereby improve general functioning. Research has shown that APs are beneficial and necessary in some regards but increases to higher doses usually decrease general functioning and high doses of APs often disable general functioning. This is a pervasive Catch-22 for which no non-surgical solutions have been found before the findings of this study. A surgical solution was sought in 1997 via Deep Brain Stimulation (DBS) but it did not turn out as well as was hoped [1]. DBS has all of the procedural dangers inherent to brain surgery including but not limited to brain infection, stroke, inter-cranial bleeding, and exacerbation of seizures or new onset of seizures. DBS does not improve speech and does not improve cognition, the #1 factor in general functioning. DBS can worsen general functioning by worsening speech and cognition. DBS does not improve swallowing or freezing gait and does not inhibit illness progression. The majority of Parkinson's patients are elderly, often physically frail, and thereby highly susceptible to the dangers of brain surgery. DBS turned out to be more dangerous and less effective than DRT for the vast majority of patients.

In the long run, the dangers and harms of DRT and DBS and are no-win scenarios. They might relieve one set of symptoms but they make other symptoms worse and can create new symptoms. These are not problem-solutions. These are problems that have no solutions. Yet DRT and DBS are Neurology's core treatments for Parkinson's. On the other hand, previously overlooked Methylphenidate is a Dopamine agonist that stabilizes and controls the symptoms of Parkinson's without the dangers of DBS and without the adverse effects of APs such as illness-augmentation, excessive sedation, diminished cognition, black outs during activities, and black outs while driving.

This author hopes the information in this study will initiate a global movement among Physicians to switch their Parkinson's patients from diurnal APs to diurnal MPH. Millions upon millions of patients could predictably rise from disability and regain normal functioning for the rest of their lives. It happened to the world's first recipient of long-term MPH-treatment for Parkinson's symptoms. His MPH-treatment solved the Catch-22 of no-win Parkinson's treatments.

Methylphenidate was Alexander's sword that severed the Gordian Knot of debilitating APs.

Materials and Methods

The materials of this study were well over 400 pieces of scientific information that were gathered by the author. The methods of this study included an eight-year gathering of applicable information from available indirectly related studies. This article analyzed and compared Methylphenidate-treatment and AntiParkinsonian-treatment of Parkinson's symptoms. This author reviewed and analyzed over 400 published articles from clinical and neurobiochemistry studies, product monographs, and medication guidelines. This author also reviewed and analyzed Medical Records, communication *documents, and patient-reports from the world's first long-term MPH-treatment of Parkinson's symptoms. (The treatment recipient, Dr R, had progressive Parkinson's symptoms for 37 years starting in 1985. Symptoms were reported to his Physician in 2000. AntiParkinsonians started in 2005 and diurnal MPH was prescribed from 2014 through 2022.).*

Materials in this study were: (A) an eight-year MPH and AP neurobiochemistry analysis combined with (B) in- vivo data from 17 years of treatment and (C) related contents of over 400 published articles. Methods in this study were: unifying and analyzing this large array of information. The author thereby made several important scientific discoveries.

The discoveries in this study can g**r**eatly improve the medical care, health, and quality of life of over ten million Parkinson's-affected people worldwide including over one million in the United States [2]. The discoveries in this study can return normal functioning to millions upon millions of Parkinson's-disabled people (as it did for Dr R). Patients' return to normal functioning will improve the quality of life of their families. The average family household size worldwide is 4.9 people [3]. Given over 10 million Parkinson's patients with 4.9 family members, the discoveries in this study can improve the lives of more than 50 million people. The 50 million family members live in communities where each family member affects perhaps ten other members of his or her community, the discoveries in this study can improve the lives of 500 million people.

Adverse reactions to antiparkinsonians

AntiParkinsonians have been used to treat Parkinson's symptoms for decades. Their adverse effects are well known but no viable alternative was found before this study. The value of the remedy herein is best understood by noting the problems it resolves. The most widely prescribed AntiParkinsonians are Carbidopa-Levodopa ("Sinemet"), Pramipexole ("Mirapex"), and Ropinirole ("Requip"). Their product monographs list dozens of "potential" adverse effects. Examples are presented below in a context of long-term treatment.

Ropinirole ("Requip")

"Requip" is a brand name of Ropinirole, a Dopamine agonist. The manufacturer's product monograph [3] lists several potential adverse reactions that include nausea, dizziness, syncope, sweating, sedation, somnolence, and falling asleep in activities (e.g., watching television, as a passenger in a car, and driving a car) [4].

Dr R's first AntiParkinsonian medication was 1 mg of Requip at bedtime. The primary effects quickly diminished so the dose was increased to 2 mgs despite nausea from 1 mg. The increase to 2 mgs improved the primary effects but caused occasional vomiting. Requip was replaced by bedtime Sinemet after five years because nausea and vomiting became too frequent and were intolerable.

Carbidopa-Levodopa ("Sinemet", "Carb-Levo")

"Sinemet" is a brand name of Carbidopa-Levodopa, a combination of the Dopamine precursor Levodopa and a decarboxylase inhibitor Carbidopa. When doses of Carb-Levo became high and frequent Dr R experienced eight categories of adverse reactions that are listed in the product monograph [4] (a) Syncope, sudden falling asleep without warning that is dangerous while driving ("There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living"), somnolence, fatigue, dizziness, and faintness. (b) Shortness of breath (Dyspnea), cough, odd breathing patterns, and hoarseness. (c) Involuntary movements, increased tremor, and muscle twitching. (d) Hypotension and hypertension. (e) Increased urinary frequency and urinary incontinence. (f) Nausea. (g) Weight gain. (h) Memory impairment and decreased mental acuity [5].

Dr R's Carb-Levo started with one 10/100 mg tab at 1:00 pm to control dangerous leg spasms while driving. Doses slowly increased to 1-2 25/100 mg extended-release tabs in the morning, 1-3 10/100 mg tabs four times during the day, two 25/100 mg extended release tabs at bedtime, and 1-3 10/100 mg tabs up to every three hours through the night. Four years after Carb-Levo started Dr R's Neurologist noted a likelihood of augmentation. He added Mirapex because it was widely believed to minimize augmentation from Carb-Levo.

Pramipexole ("Mirapex")

"Mirapex" is a brand name of Pramipexole, a Dopamine agonist. Potential adverse reactions listed in the Mirapex product monograph [5] include: "falling asleep in activities of daily living (including driving), somnolence, syncope, hypotension, vomiting, and weight increase." Narcolepsy (i.e., "falling asleep in activities, somnolence, and syncope") is a major symptomatic problem of Parkinson's illnesses. Warnings about Narcoleptic adverse reactions are listed in the product monographs of Mirapex, Requip, and Sinemet. Medication-induced Narcolepsy was a major concern in the Mirapex monograph. Six paragraphs repeatedly warned of Narcolepsy reactions as follows.

"falling asleep during activities of daily living; sudden onset of sleep without warning; most common adverse reactions: somnolence, somnolence, somnolence; falling asleep while engaging in activities of daily living including the operation of motor vehicles sometimes resulting in accidents; somnolence that had no warning signs (sleep-attack) such as excessive drowsiness and… were alert immediately prior to the event; some of these events had been reported as late as one year after the initiation of treatment; somnolence is a common occurrence… at 0.5 mg three times per day; somnolence; falling asleep while engaging in activities of daily living; somnolence; drowsiness; sleepiness; drowsiness; sleepiness; drowsiness or sleepiness during specific activities; drowsiness; somnolence; daytime sleepiness; falling asleep during activities that require active participation; advise patients not to driveor participate in other potentially dangerous activities that might result in harm if patients become somnolent; there is insufficient evidence to establish that dose reduction will eliminate episodes of falling asleep while engaging in activities of daily living; falling asleep during activities of daily living; and somnolence" [6].

"Sudden onset/no warning" appears three times. "Sleepiness" appears four times. "Drowsiness" appears four times. "Falling asleep" appears seven times. "Somnolence" appears ten times. These warning phrases appear 28 times across six paragraphs in the Mirapex monograph. The Requip and Sinemet monographs present the same types of Narcolepsy warnings.

The 2021 Mirapex ER product monograph presented a placebo-controlled double-blind study with 33% of Pramipexole IR subjects reporting somnolence (Narcolepsy) at 33 weeks. This rate means that in one year 52% would have Pramipexole IR-induced Narcolepsy and in less than two years 100% would have Pramipexole IR-induced Narcolepsy. The study reported that Mirapex ER had an almost identical rate of 36% in 33 weeks. Somnolence (Narcolepsy) was the most frequently reported adverse reaction to Mirapex. The 2007 Mirapex IR monograph presented a placebo-controlled double-blind study with 22% of Mirapex subjects reporting somnolence compared to 9% of placebo subjects. The 22% was more than double the placebo 9%. This seemed consistent with the 2021 double rate above placebo. If the 22% rate in 2007 had a 22-week timeframe it would be consistent with the 2021 33% rate, but no timeframe was given in 2007. Because no timeframe was given, the listed 22% rate was significantly inconsistent with the listed 2021 rate of 33%-36%. This was a significant discrepancy between the two monographs.

Another discrepancy was that (A) the 2021 ER-monograph did not mention or allude to augmentation whereas (B) the 2007 IR-monograph spoke of an RLS study with 20% reporting augmentation at 12 weeks, and (C) the 2021 IR- monograph spoke of an RLS study with 12% reporting augmentation at 26 weeks. The Mirapex monographs misrepresented the rates of augmentation by not stating accumulations over longer periods of time: 12% every 26 weeks means 24% in 52 weeks (one year) and 100% in 4.25 years; 20% in three months means 40% in six months and 100% of subjects would have Mirapex-augmentation in 1.25 years.

These are high rates for a medication that supposedly prevents or minimizes augmentation. A separate 2015 review reported Levodopa-augmentation rates averaging 27.33%. Timeframes were poorly defined but the listed rate was almost the same as Mirapex-augmentation. Mirapex is generally used in Parkinson's treatment to prevent or minimize Carbidopa-Levodopa augmentation but research shows that Mirapex causes nearly the same rate of augmentation. Across-studies inconsistencies, internal contradictions, and deceptive wording show that the Mirapex product monographs are not scientifically valid. They contain deliberately dishonesties such as omissions of vital facts. The Sinemet and Requip product monographs have the same problems.

Methylphenidate treatment for Parkinson's symptoms

Early studies of Methylphenidate for Parkinson's

Methylphenidate is a highly effective Dopamine agonist that the FDA approved for ADHD and Narcolepsy in 1955, twenty years before approving Carbidopa-Levodopa, 42 years before approving Pramipexole, and 50 years before approving Ropinirole. The earliest study of MPH and PD that this author found was published in 1998 [7]. It did not investigate MPH as a potential treatment for PD but found that PD patients had less mood elevation and stimulant response from MPH than healthy subjects. A study from 2001 [8] found that MPH 10 mg increased the motor effects of adjunctive low-dose APs with minimal effect on cognition and affect. A 2001 co-author led a 2007 study [9] that found adjunctive MPH 20mg significantly reduced Carb-Levo resistant tremors. The two studies showed that 10 and 20 mgs ofMPH were safe for Parkinson's.

The above studies were not the norm in 2001 to 2017. There were significant stigma-related flaws in Neurology MPH-research such as deliberately intending to fail by using doses that were too low. Studies that failed were considered to be successful under the widespread Neurology stigma against MPH. Anti-MPH authors commented that their disproof of MPH was "consistent with previous studies". The clinical and research communities marginalized the 2001 study for contradicting the stigma. The 2007 study was deliberately and secretly sabotaged to make MPH fail.

One of its experiments was designed for below-efficacy doses of Carb-Levo but subjects were secretly given their normal doses.

Studies of Methylphenidate for Parkinson's-Narcolepsy

A 2017 study by Loddo., *et al*. reported that sleep disorders affect 64% of people with Parkinson's and 78% of those with "complicated" Parkinson's [10]. Sleep Disorders were the second most frequent complaint amoung people with Parkinson's. 21% (2.1 million) have Narcolepsy, also known as Excessive Daytime Sleepiness (EDS). Lotto., *et al*. found that Parkinson's-Narcolepsy is a Dopamine neurotransmitter deficiency that cannot be detected by Sleep Studies. Another 2017 study [11] and a 2013 study [12] said Sleep Study test-retest reliability was poor for Dopamine- deficiency Narcolepsy.

Parkinson's-Narcolepsy EDS is not a Sleep Disorder per se. It is a symptom of Dopamine deficiency. Loddo., *et al*. investigated the effects of MPH on Parkinson's-Narcolepsy for three months. Daily amounts of MPH were determined by body-weight at 1mg/kg per day. Daily amounts were divided into three equal doses, i.e., 60mg per day was given as 20 mg three times per day. Patients' routine doses of Carb-Levo were administered at bedtime. Diurnal MPH replaced daytime Carb-Levo. The study found that MPH relieved Narcolepsy "sleep attacks" and fatigue and improved motor symptoms, particularly gait, for patients with advanced PD. Loddo., *et al*. reviewed previous EDS studies that used Sodium Oxybate at night or Modafinil (a stimulant) in the day. Some studies showed Sodium Oxybate and Modafinil reduced EDS but others did not. Sodium Oxybate and Modafinil had no effect on motor symptoms.

Loddo., *et al*. concluded that only MPH consistently relieved EDS and consistently reduced motor symptoms.

Methylphenidate as a potential treatment for Parkinson's

A 2016 study included Methylphenidate on a list of treatment options for Parkinson's Freezing of Gait (FoG) along with Levodopa; Monoamine Oxidase B Inhibitors (Selegeline and Rasagiline); Amantadine; L-Threo-3,4- Dihydroxyphenylserine; Botulinum Toxin; Bilateral subthalmic nucleus (STN) Deep Brain Stimulation (DBS); and Repetitive transcranial magnetic stimulation (rTMS). The authors conducted literature reviews of FoG-treatment efficacy and adverse effects. Then they ranked the listed treatments by greater to lesser effectiveness. Levodopa was rated the most effective. Methylphenidate and the MO Inhibitors shared spot #2. They were deemed as possible future FoG treatments. The other three medications (Amantadine; L-Threo-3,4-Dihydroxyphenylserine; and Botulinum Toxin) were dropped from the list because they were not good enough. DBS and Rehab exercise were given small credit but not general credit [13].

The 2016 authors wrote about a 2009-2011 research project in France that studied MPH as a treatment for FoG [14]. 66 subjects with advanced PD in 13 Parkinson's treatment facilities were enrolled for 90 days. Subjects were under 80 years old and were taking optimized-APs including optimized-Carb-Levo. All subjects also were receiving subthalmic nucleus stimulation and had medication-resistant FoG. The double-blind study consisted of giving 32 subjects placebo capsules for 90 days and giving 33 subjects 1mg/kg MPH per day for 90 days. Efficacy-outcomes were measured at day-90. Subjects in the MPH group showed significant improvements of PD-FoG and gait hypokinesia. The French authors reported "significantly more adverse events in the MHP group" than in the placebo group. This author notes that the number of affected subjects was not stated and the "adverse events" were harmless, consisting of an increase of 3-6 heartbeats per minute and a 3-month 2.2-pound weight loss. The 2016 authors deemed the MPH "events" as negligible and did not put them in the ranked list of outcomes.

The authors wrote that Methylphenidate significantly occupied and thereby inhibited presynaptic Dopamine transporters in the striatum and prefrontal cortex and, to a lesser degree, occupied and inhibited Norepinephrine transporters in the striatum and prefrontal cortex. Transporter inhibition led to significant increases in synaptic Dopamine activity and also led to some increases in

norandrenergic synapse activity. In such manners, MPH improvements in FoG came from increased synaptic Dopamine activity and possibly from increased norandrenergic activity. Spectrum Analysis showed a decreased density of striatal Dopamine transporters whereto MPH limited the production of new transporters. Synaptic Dopamine was retained and increased through (1) high MPH occupation of each DAT transporter and (2) MPH-limited fewer DAT transporters. PD FoG was improved by increased synaptic Dopamine. In the 2016 article concurrent high DAT-occupancy and limited DAT-production led to MPH being rated as one of only three effective FoG treatments and also led to MPH being commended as a future treatment for Parkinson's [13].

Methylphenidate inhibitions of Dopamine mobility retain more naturally produced Dopamine in the brain. The brain inherently differentiates the binding of natural Dopamine to dorsal receptors versus the binding of less natural Dopamine to the more Dopamine-sensitive ventral receptors. Dorsal receptors control Parkinson's motor symptoms and ventral receptors control non-motor symptoms such as cognition, wakefulness, stress, and stress-related breathing.The brain does not differentiate the dorsal vs. ventral absorption of Carb-Levo induced Dopamine (CL-DA). Amounts of CL-DA that dorsal receptors absorb are equally absorbed by ventral receptors. Dose-amounts that are needed for dorsal symptoms are too high for ventral functions. Ventral non-motor deterioration worsens with every dose increase. On the other hand MPH facilitates natural Dopamine that is differentially absorbed by dorsal vs. ventral receptors. MPH has immediate and short-term advantages over APs by stabilizing dorsal receptors without overloading ventral receptors. MPH has long-term advantages over APs by slowing the progression of Parkinson's through strengthening neural tissues.

It seems appropriate to end this section with a quote of positive findings from a previous study

- ***"Results:*** *An improvement was observed in the number of steps and time in the SWS Test, the number of freezing episodes, the Tinetti Scale score and the UPDRS part III score in the absence of L-dopa after3 months of taking MPD. The L-dopa-induced improvement in these various scores was also stronger after the 3-month course of MPD than before. The Epworth Sleepiness Scale score fell dramatically in all patients. No significant induction of adverse effects was found.*
- ***"Interpretation:*** *Chronic, high doses of MPD improved gait and motor symptoms in the absence of L-dopa and increased the intensity of response of these symptoms to L-dopa in a population with advanced PD."* [15]

Dorsal and ventral receptors

- Parkinson's causes more depletion of Dopamine in the dorsal striatum than in the ventral striatum.
- The amount of APs needed to (i) control dorsal striatum motor symptoms applies (ii) an excessive amountof Dopamine to the ventral striatum.
- The excess impairs ventral striatum cognition and worsens Narcolepsy [16,17].

There is a vexing conundrum in AP Dopamine Replacement Therapy

- Stabilizing dorsal striatum motor symptoms with APs overdoses the more sensitive ventral striatum.
- Reducing AP medications to not overdose the ventral striatum provides too little Dopamine to stabilize dorsal striatum motor symptoms.

Ventral receptors that become overwhelmed during AP treatment do not become overwhelmed during Methylphenidate treatment. The primary mechanism of MPH is a reduction of Dopamine Transporter (DAT) and Norepinephrine Transporter (NET) activity. The 2019 Ritalin product monograph states, "Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron…" [18]. The 2015 Ritalin package insert states, "As an inhibitor of dopamine reuptake, Ritalin may be associated with pharmacodynamic interactions when co- administered with direct and indirect dopamine agonists (including Dopa…)" [19]. MPH effects on DAT, NET, and APs. When MPH is administered in sufficient amounts with APs it alters (increases) the neural interactions of APs. When MPH is administered in sufficient amounts without APs it retains a supply of naturally produced Dopamine that does not expose dorsal and ventral receptors to Dopamine added by Carb-Levo. MPH vs. AP interactions with dorsal vs. ventral sensitivity are key factors in MPH not inducing the disabling adverse effects of APs.

Another significant biochemical difference between MPH and APs is that APs cause augmentation that damages and destroys

neural tissues especially in Dopamine systems whereas MPH strengthens and protects neural tissues and Dopamine systems [19]. Parkinson's illnesses are progressive and inherently worsen across time. AP-augmentation accelerates their inherent worsening. Conversely MPH slows the progression by strengthening neural tissues that Parkinson's illnesses affect. MPH does this by retaining pools of naturally produced Dopamine (DA) in places where it contacts and stimulates brain receptors or in nearby places where it can easily be drawn into receptor- stimulating/activating contact. The retained natural Dopamine is largely pooled where it surrounds, bathes, and stimulates Dopamine receptors. Receptor activity from the Dopamine-stimulation maintains a steady blood-flow in the receptors. Blood flows through the surrounding neural tissue on its way to the stimulated receptors. The blood brings nutrients to the Dopamine system and surrounding tissues. This is one of the ways that MPH strengthens Dopamine systems and neural tissues.

MPH also protects Dopamine systems and neural tissues. Retaining pools of natural Dopamine is one of the protective mechanisms. When a brain-location lacks Dopamine it transmits messages telling the person's hormone systems to produce and transport more Dopamine. But people who have Parkinson's illnesses cannot produce as- needed Dopamine. Insufficient Dopamine triggers increased production of Thyroid hormones. Increased amounts of Thyroid hormones are transported to low-Dopamine locations. Among healthy people the flow of increased Thyroid is blocked at locations that have a healthy amount of Dopamine. The healthy amounts of Dopamine trigger the body to stop producing and transporting extra Thyroid hormones. In locations where the extra Thyroid hormones arrived and were blocked, the extra Thyroid becomes overcrowded. Thyroid hormone cells have internal programs that tell the cells to die (apoptosis) in overcrowded situations in order to make room for newly produced extra Thyroid. Then the rapidly increasing dead Thyroid cells are taken away by Dopamine-based transporter cells.

People who have Parkinson's illnesses don't have enough Dopamine to tell the body to stop producing and stop transporting extra Thyroid hormones. Thus the extra Thyroid hormones become more and more overcrowded and die in large numbers. People who have Parkinson's illnesses don't have enough Dopamine to make Dopamine-based transporter cells to take away the dead Thyroid cells. Large volumes of dead Thyroid cells have nowhere to go so they become larger volumes of dead Thyroid cells. The dead cells decompose into acidic remains that absorb into surrounding neural tissues. The acid weakens and erodes the neural tissues that absorb it. Conversely, MPH retains pools of natural Dopamine that protect neural tissues from these destructive events. MPH retains pools of natural Dopamine by occupying DAT transporter cells that would otherwise transport DA away from the brain.

By inhibiting Dopamine Transporters (DAT), MPH increases Dopamine concentrations in the brain. This manifests as prolonged and/or intensified postsynaptic DA signals. In other words significant amounts of DA are unable to exit the brain so pools form mostly in the same in locations as many DA receptors. Pools of DA stay bound to activated receptors. The authors of a 2008 study [20] wrote: "At therapeutic doses of 0.3-0.6 mg/kg, orally administered MPD may actually bind to and occupy more than half of the DAT in the human brain." For a 150-pound person 0.3-0.6 mg/kg is 20-40 mgs. For a 120-pound person it is 16-32 mgs. For a 190-pound person 0.3-0.6 mg/kg is 26-52 mgs.

Key points in the 2008 article included

- Abnormal cytoplasmic DA accumulation contributes to the development of Parkinson's disease. a) MPH- induced increases in vesicular DA sequestration attenuate the disease's progression. b) Researchers found MPH improves motor functions in Parkinson's patients. c) The VMAT-2 is a vesicular membrane-spanning protein that functions to transport the cytoplasmic DA inside of neurons into vesicles for storage and subsequent release. d) This is caused by vesicle trafficking in the cytoplasmic vesicles and by kinetic upregulation of VMAT-2 in the membrane- associated vesicles.
- These MPD-induced increases in vesicular DA sequestration have several functional consequences. a) The increase in vesicular DA transport increases vesicular DA content with no change in whole striatal tissue DA content. b) By increasing vesicular DA transport velocities, MPH redistributes DA within the striatum from the cytoplasm and into the vesicles. c) As a consequence of increased vesicular DA sequestration and DA content, MPD also increases the speed and extent of stimulated DA release from striatal suspensions. d) The amount of vesicular DA content and the speed of neurotransmitter release influences receptor activation. e) MPH thus influences quantal synaptic transmission in the striatum by increasing the rate at which DA receptors are exposed to DA, and by the magnitude and/or duration of this effect.

MPH has the ability to provide neuroprotection against Methamphetamine-induced neurotoxicity and perhaps Parkinson's disease through possible mechanisms involving direct interactions with the DAT and additional mechanisms involving indirect effects upon the VMAT-2. These mechanisms attenuate or prevent the abnormal accumulation of cytoplasmic DA and the resulting formation of potentially neurotoxic DA-associated reactive species.

Methylphenidate dose amounts for treating Parkinson's

The manufacturer of Ritalin obtained FDA approval in 1955 for up to 60 mg per day [19]. Most healthcare providers in the US adhere to the 60 mg limit despite later research that disproved it, despite approval of higher amounts by Canada [21-23] (see figures 1A, 1B, and 1D) and other countries, and despite FDA approval of 85 mgs in 2019 [24] (see figure 1C).

Figure 1: Canada approved MPH IR 100 mg per day in 2010 (Figures 1A and 1B) [21,22] and approved Foquest 100 mg in March of 2019 (Figure 1D) [23]. The U.S. FDA approved Adhansia XR 85 mg in July of 2019 (Figure 1C) [24] based on the manufacturer's 100 mg research by which Canada approved Foquest 100 mg.

Dr R's 2020 optimal 105 mg per day was comparable to Canada-approved MPH-IR 100 mg per day (Figures 1A and 1B) [21,22] and Foquest 100 mg (Figure 1D [23], The FDA approved Adhansia XR 85 mg (Figure 1C) based on the 100 mg research by which Canada approved 100 mg Foquest. The Adhansia XR product monograph [24] has data from the original 100 mg research.

Perhaps the greatest challenge for Parkinson's treatment is the dose-amounts of medications. AP treatment starts with low doses that often remain effective for years. Minimal side effects of initial low doses might not be noticed. As the illness progressively worsens, AP doses and their adverse effects increase. The absence of side effects from initial low doses deflects concern about future problems. Patients' and providers' enurement to those problems contributed to MPH not being seen as an option. In 2016 a shift toward awareness of MPH became noticeable as seen in the 2016 article above and in a 2017 Parkinson's Foundation guideline [25] that said MPH improves alertness.

A Mayo Clinic guideline published in 2000 boldly recommended up to 90 mg of Methylphenidate per day for adult ADHD and Narcolepsy, 50% more than the 60 mg limit put forth by the Ritalin manufacturer since 1955. Sixteen years later the above-mentioned 2016 study on treating PD FoG stated the amount of MPH for treating PD was the sameamount used for treating adult ADHD. Mayo said it is safe to break the 60 mg limit and the 2016 authors said MPH is safe for PD.

It is possible that the 2016 author of the FoG study was correct in saying the effective dose-amounts for FoG are the effective dose-amounts for ADHD. This opens the question of the effective dose-amounts for ADHD. The answer to that question is not as simple as it may seem. A 2017 study compiled a list of international guidelines for MPH dosing. Entries by Great Britain, England, and Wales said 100 mg per day. Sweden said 80 mg per day. Among the Guidelines from nine countries, only Spain and Malaysia listed the US-FDA's 60mg per day. Four Guidelines for adults said amounts depend solely on patient-reports of results. For example, four nations, including the United States, did not give specific limits. They said MPH should be individually titrated for optimal effectiveness [26]. Recommended limits of MPH sometimes differentiate between what is told to the public and what is suggested for consideration by healthcare professionals for therapeutic purposes [27]. Dr R entered his weight into the healthcare professionals dose calculator. The calculator stated a maximum of 60 mg per day for standard purposes, presumably ADHD, the same as the Ritalin product monograph. For healthcare professionals the calculator said 100 mg per day for "off-label" treatments, 40 mgs more than the Ritalin monograph. During 2020-2022 Dr R's MPH was 105 mgs per day, very close to the off-label amount listed in the healthcare professionals dose calculator.

A review of seven published Methylphenidate-dosage guidelines found there was no consistency across guidelines. The FDA approved Ritalin/MPH up to 60 mg per day because the manufacturer, Novartis, provided approval research up to 60 mg. The manufacturer wanted quick approval and didn't spend money on research above 60 mg. The 60 mg limit came about because the manufacturer didn't do research beyond 60 mg. Research by other parties showed MPH is safe at higher doses and at greater frequencies. A 2017 study focused on individualized optimization and therapeutic amounts of up to 80 mg per day. The study should have changed the manufacturer's 62-year upper limit, but it did not. The research team was made entirely of Novartis executives [26]. Regardless that this was a team of executives from the Ritalin manufacturer, this was the same article that was mentioned above that presented a list of international guidelines for MPH dosing. The team did not focus on upholding or justifying the Corporate statement of a 60 mg per day limit. The article was constructed around the concept of patient-centered professional flexibility. The authors said patients are the appropriate empirical guides in the process of optimization and ongoing treatment. Individualization and provider attentiveness to patient input were said to be the key factors for valid and successful MPH patient care.

Under that philosophy, a clinician who wishes to provide MPH for Parkinson's treatment does not need to identify and adhere to an "effective dose-amount for ADHD". As was shown above by the lack of consistency across published MPH dose-guidelines, there seems to be no universal "effective dose-amount for ADHD". Perhaps there is a universal effective dose. Perhaps there is not. Either way, attentive empirical patient-centered optimization is the only valid approach to MPH treatment of ADHD, Narcolepsy, or Parkinson's. The above review of published MPH dosing guidelines revealed some apparently wise and useful to incorporate into a patient-centered approach to titration and optimization. The review found widely varying suggestions regarding dose amounts, frequency schedules, extended-release capsules, and combining sequential extended release and immediate release doses. The review did not draw conclusions for specific amounts or frequencies because there was no consistency across the guidelines.

Research since 2016 suggests 20 mg doses as a generally effective amount for both adult ADHD and Parkinson's. It is important to bear in mind that a patient's individual response is the sole valid determinant of whether 20 mg is right, or too low, or too high, and how many sequential doses per day will best suit a patient's ability to function. The author of the above-mentioned study involving FoG and MPH wrote that he observed marginal but statistically significant improvements in at least one symptom of PD among inpatient subjects with advanced PD by using MPH 0.8 mg/kg to 1.0 mg/kg given in three equal doses on a 4-hour schedule. The daily maximum was 80 mg given as 26.6 mg doses. (Using our 143-pound Dr R as an example: 1.0 mg/kg t.i.d. was three 21.62 mg doses totaling 64.86 mg per day. 0.8 mg/kg t.i.d. was three 17.3 mg doses totaling 52 mg per day.) Study subjects were given weight- optimized MPH and their accustomed APs for 17-18 weeks. The study did not report the mg-doses. The study did not report the range, mean, and median mg-doses or the relationships between dose-amounts and outcome scores. The study gave too little information and reported the statistically significant results were "marginal". Despite statistically significant results, the information was insufficient for calculating effective dose-amounts.

Clinicians should consider prescribing the regimen that Dr R found to be best: (1) MPH IR 25 mg for the first dose of the day, (2)

followed at hour-3 by a 6-hour 40 mg cap of Metadate ER-CD, (3) followed six hours later by 20 mg IR, (4) followed three hours later by another 20 mg IR. This regimen gives uninterrupted normal functioning through the day and evening for 16 hours. The FDA approved Adhansia XR to provide 16-hour per day efficacy but Dr R's regimen provided smoother and more consistent efficacy than Adhansia XR. The use of APs at bedtime for sleep is necessary for Parkinson's. At bedtime Dr R took two tabs of Pramipexole .25 mg, two tabs of Carb-Levo 10/100, and twotabs of Carb-Levo ER 25/100. He found the combination of daytime MPH and bedtime APs worked well and worked much better than 24 hours of APs. Diurnal Methylphenidate can replace diurnal AntiParkinsonians very effectively and gives the extra benefit that Methylphenidate slows the progression of Parkinson's by strengthening and protecting neural tissues, especially Dopamine systems. Methylphenidate slows the progression of Parkinson's but does not stop it. Methylphenidate doses may need to increase a bit over time but in infrequent small amounts. Upon Dr R achieving his optimal MPH 105 mg regimen, he used the same regimen for two years. Whereas before MPH, his AP regimen increased eight times across eight years, notably going from 112 mg per day to 1,621.25 mg per day (see figure 2).

Figure 2: A) 9-year history of 24-hour AntiParkinsonians. (B) 8-year history of diurnal Methylphenidate. (C) Bedtime anti-Parkinsonians.

Methylphenidate therapy started with 5 mgs and optimized at 105 mg per day with 15-16-hour duration.

Methylphenidate IR works best when taken every three hours through the day

Published research and guidelines say the initial onset of MPH-IR is somewhat noticeable at 20-30 minutes after intake, clearly noticeable at 45 minutes, and functional full-efficacy is present at 60 minutes (hour-1) [28,29]. The plasma level of MPH-IR increases to C_{max} at hour-2 then gradually decreases by hour-3 to the same plasma level as hour-1 (the same level as 60-minute full-efficacy during initial-onset) [30]. The plasma level continues to gradually decrease from hour-3 to dose-termination at hour-4. The time of initial dose-onset is one hour from intake to full-efficacy. The time from loss of efficacy to dose-termination is one hour from hour-3 to hour-4. The one-hour rate of dose-onset is the same as the one-hour rate of dose-termination. Therefore when dose-2 is taken at hour-4 there is an hour of insufficient-to-no-efficacy starting at hour-3 before dose-2 is taken at hour-4. When dose-2 is taken at hour-4 there is also a dose-onset time of 45 minutes that starts at hour-4. A 4-hour dosing schedule leads to a one-hour and 45-minu-

tesloss of efficacy between doses. When MPH is taken three times per day, the efficacy fluctuation occurs twice per day. When MPH is taken four times, the lengthy fluctuation occurs three times. When MPH is taken every four hours five times per day, there are four one-hour and 45-minutes fluctuations totaling seven hours of insufficient-to-no efficacy per day.

Hypothetically

(A) If a new dose of MPH-IR is taken at hour-3 when the prior dose started to fade, the hour- long gradual increase from the new dose and the hour-long gradual decrease of the previous dose will occur simultaneously. (B) The gradual increase of serum concentration from a new dose and the simultaneous gradual decrease of the serum concentration of the previous dose will combine into an hour-long unchanging plasma concentration. (C) The resulting hour-long unchanging plasma concentrations will provide unchanging efficacy during hour-long transitions from one dose to the next. This hypothesis was tested by Dr R's taking each new dose at the 3- hour mark for two weeks. The efficacy-fluctuations consistently stopped across all 52 doses. The hypothesis of a 3- hour-schedule was empirically proved true. It was subsequently validated by eight years of in-vivo test-retest 100% reliability.

A graph in the 2021 Ritalin LA product monograph [30] (Figure 3) shows an MPH-IR 20 mg plasma level of 5 ng/mL at 45 minutes after intake and 9 ng/mL at 60-minutes after intake. Thus, 5 ng/mL is the low-end of an efficacy- onset range and 9 ng/mL is the plasma level threshold of full-efficacy. Figure 3A shows a 4-hour dosing schedule. At hour-3 the plasma level decreases to the efficacy-threshold then continues decreasing below the threshold until 35 minutes after hour-4. The level returns to the efficacy-threshold 45 minutes after dose-2. Figure 3B simulates a 3-hour dosing schedule that keeps the plasma level above the efficacy-threshold.

Figure 3: A) MPH-IR 4-hour dosing with dose-2 at hour-4. B) Simulated 3-hour dosing with dose-2 at hour-3.

An MPH-IR graph from the 2021 Ritalin LA product monograph: Figure 3A shows MPH-IR 20 mg b.i.d. with 4-hour dosing. At hour-3 the plasma levelfrom dose-1 stays below the efficacy threshold for an hour and 45 minutes, including 45 minutes after dose-2 at hour-4. The simulated 3-hour dosing in figure 3B shows the plasma level stays above the efficacy threshold with dose-2 at hour-3. (Graphs adapted from the 2021 Ritalin LA product monograph) [30].

This author found only one medication guideline that specified a time between doses, "at least 4 hours betweendoses", but no reason was given for the four hours [28,29]. The perfunctory 4-hour MPH dosing schedule is so thoroughly ingrained that product monographs, medication guidelines, and some research studies do not state a time between doses. This was seen in dozens published items that this author reviewed. Examples are shown in figure 3 through 10 to assist in demonstrating this study's global-scale discoveries that accurate/valid MPH-research findings and uninterrupted treatment-efficacy with smooth transitions between doses require 3-hour MPH dosing.

Figure 4: Plasma concentrations from 25 mg t.i.d. on a 4-hour schedule [31].

Plasma levels of MPH-Ritalin 25 mg t.i.d. on a 4-hour schedule: The hour-1 efficacy-threshold in figure 4 is the same as in figure 5A (11.25 ng/mL). Cmax levels in figure 4 are similar to figure 5 (Cmax-1: 15.05 ng/mL, Cmax-2: 24.55 ng/mL, Cmax-3: 27.9 ng/mL). The 4-hour schedule in figure 4 had greater drops of MPH levels during dose-transitions than in the mixed-schedule of figure 5.

To the best knowledge of this author this was the first study of 3-hour Methylphenidate dosing. Being as this was the first study there was a universal lack of published information on the topic. The absence of information necessitated construction of simulations derived from 4-hour schedules. The figures in this study were adapted from research studies and product monographs that were typical examples from more than 400 reviewed publications. Simulated graphs were constructed from 4-hour graphs by moving depictions of hour-4 to hour-3 by moving depictions of hour-8 to hour-6.

This author could not find any studies that administered MPH every three hours. He found only one study that administered MPH-dose-2 three hours after dose-1, however dose-3 was given four hours after dose-2 [32]. The study combined 3- and 4-hour schedules by following a 3-hour schedule with a 4-hour schedule. Nonetheless, the time from dose-1 to three hours after dose-2 was equivalent to hour-zero to hour-6 of a b.i.d. 3-hour-dosing schedule. This author isolated data from hour-zero to hour-6 to obtain the sole published empirical data from 3-hour scheduling.

This author used the isolated data to analyze his simulated 3-hour schedules in figures 5C, 6, 7F, 9B, 9C, and 10B. Figure 5A shows the original combined 3- and 4-hour schedule. Figure 5B shows the isolated b.i.d. 3-hour schedule. Figure 5C simulates a 3-hour t.i.d. schedule by using hours 0-6 in 5B and moving hour-7 in 5A to hour-6.

Figure 5: 5A is 25 mg t.i.d. with dose-2 at hour-3 and dose-3 at hour-7. 5B isolates the 3-hour schedule in hours-0 to -6. 5C simulates dose-3 at hour-6 [32].

Figure 5A shows plasma levels of MPH 25 mg t.i.d. with a mixed 3-hour and 4-hour dosing schedule. Dose-2 was given at hour-3 and dose-3 was given at hour-7 four hours after dose-2. Figure 5B isolates hours-0 to -6 as a b.i.d. 3-hour dosing schedule. Figure 5C uses data from 5A and 5B to simulate a t.i.d. 3-hour schedule by moving dose-3 from hour-7 to hour-6.

The 3-hour schedule in figure 5A had a 0.8% decrease of MPH during the transition from dose-1 to -2. The 4- hour schedule had a 12% decrease from dose-2 to -3, 15 times greater than under 3-hour scheduling. The simulated move of dose-3 to hour-6 in 5C yielded no decrease between doses. The different MPH level-drops in 3- and 4-hour- dosing are demonstrated further in figure 6.

Figure 6: The 25 mg mixed schedule from figure 5A is overlaid with a 25 mg t.i.d. 4-hour schedule from figure 4 and a simulated 20 mg t.i.d. 3-hour schedule from figure 9B.

0.8% and 12% plasma level drops in figure 5A (circled in red) were significantly less than the 30.76% and 37.41% drops in the overlay of a 25 mg t.i.d. 4-hour schedule in figure 4 [31]. The overlay of 25 mg t.i.d. in figure 5A simulates a 3-hour schedule and reflects the lesser drop in the 3-hour schedule of figure 9B (8% in figure 9B, 0.8% in figure 5A). Figures 5A and 9B show lesser drops than the overlay of 4-hour figure 4 (8% in figure 9B vs. 30.76% in figure 4, 27.2% in figure 9B vs. 37.41% in figure 4, 22.6% in figure 9B vs. 30.24% in figure 4). Figures 5A and 9B also show lesser drops than in the 4-hour schedules of figures 7, 8, and 9A below.

The mixed-schedule of figure 5A is overlaid in figure 6 with a 25 mg t.i.d. 4-hour schedule from figure 4 [31] and a simulated 20 mg t.i.d. 3-hour schedule from figure 9B [32]. Figures 6 and 9C provide reference points for comparing 3-hour dosing to 4-hour dosing (see figures 6 through 10 below). Plasma concentration in figure 5A dropped 0.8% an hour after C_{max}-1 and 12% an hour after C_{max}-2. The drops were similar to the 8% drop in overlaid figure 9B. The drops were similar to figures 7F and 9B in that the drops stayed above the 9 ng/mL efficacy threshold. The drops were unlike the 4-hour schedule in figures 7C and 7E that show the MPH level dropped below full efficacy for an hour and 45-minutes.

The 12% drop after C_{max}-2 in figure 5 was considerably less than the 37.5% drop in the 4-hour schedule of figure 9A. Administering dose-2 at 3-hour in figure 5 kept MPH at a steadier level at hour-7, allowing the third dose at hour-7 to maintain a smoother dose-2 to -3 transition. The effects of the steadier-level translated to a zero drop after C_{max}-2 in the simulated 3-hour schedule in figure 5C. Dose-2 at hour-3 allowed the blood level to drop only 0.8% because dose-2 was taken well before dose-1 terminated. The still-active MPH level from dose-1 combined with the gradual onset of dose-2 to create a steady state transition that fluctuated by only 0.8%. The same process occurred when simulated dose-3 was taken at hour-6, three hours after dose-2 and well before dose-2 terminated. The still-activeMPH from dose-2 was at a higher level during the onset of dose-3 to the effect that the blood level did not drop before the onset of dose-3 reached full efficacy. Administering dose-3 at hour-6 also precluded the level from being below full efficacy for up to an hour and 45 minutes as shown in figures 7C, 7E, 8, 9A, and 10 below.

Figure 7: Plasma levels of an MPH 20 mg b.i.d. 4-hour schedule are shown in figures 7A through 7E. A 3-hour schedule is simulated in 7F [30].

Figures 7A-E depict a MPH 20 mg b.i.d. plasma level with a 4-hour schedule. Figure 7F simulates a 3-hour schedule by moving dose-2 to hour-3 from hour-4. Figure 7 is adapted from the Ritalin LA product monograph [30].

Plasma level at hour-1 is labeled as full efficacy at 9 ng/mL in figures 7C and 7E. C_{max}-1 at hour-2 is 12.33 ng/mL in figures 7C and 7D. Plasma level declines below full efficacy a few minutes after hour-3 in figures 7C and 7D. At hour-4 the level drops to 8.0 ng/mL in figure 7D. Dose-2 is administered at hour-4 and the level continues declining for another 35 minutes to 7.55 ng/mL. After an hour and 45 minutes below full efficacy the level returns to full efficacy at 9 ng/mL in figure 7E. Dosing at hour-3 (as simulated in figure 7F) markedly reduces plasma level drops during the transition between doses. figure 7F shows a 23% decline that is 40% less than the 4-hour schedule decline of 38.7% in figures 7C and 7D.

There are marked inconsistencies regarding plasma levels and level-fluctuations across studies and across product monographs. For example there are significant differences between figure 7 (adapted from the Ritalin LA monograph [30]) and figure 8 (adapted from the Adhansia XR monograph [24]. C_{max}-1 is 12.33 in figure 7C vs 10 in figure 8 (a 18.9% difference). C_{max}-2 is 18.44 in figure 7D vs 13.9 in figure 8 (a 24.6% difference). The total difference of 43.5% is typical of the variance across studies and monographs.

Figure 8: MPH 20 mg t.i.d. plasma concentrations measured in pg/mL (1000 or 1k pg/mL = 1 ng/mL.13,900 or 13.9k pg/mL = 13.9 ng/mL) [24].

Plasma level of 20 mg t.i.d. on a 4-hour schedule. Figure 7 is adapted from the Adhansia XR product monograph [24].

The simulated 3-hour schedule in 9B differs markedly from the 4-hour schedule in 9A. The Cmaxs are the same under both schedules but under the simulated 3-hour schedule the plasma concentrations drop is considerably less between doses: 8% in 9B vs 28% in 9A and 27.2% in 9B vs 37.5% in 9A. The 3-hour schedule in 9B averages 30.3% less drop in plasma levels than the 4-hour schedule in 9A. Figure 9C overlays 9A with a transparency of 9B. The lesser drops of plasma levels in the 3-hour schedule are circled in red for easy comparison to the larger drops under 4-hour dosing. Figure 9 is adapted from a study by Katzman, Mattingly., *et al.* [33].

Figure 9: 9A is a 20 mg t.i.d. 4-hour dosing schedule. 9B simulates a 3-hour schedule by moving dose-2 to hour-3 and dose-3 to hour-6. 9C overlays 9B onto 9A with red circles highlighting the lesser drops of MPH plasma levels in 3hr 9B [33].

Published MPH studies and guidelines consistently used the 4-hour dosing schedule regardless of dose amounts. The most frequently used dose was 20 milligrams and some studies used 25 milligrams. Studies involving several inpatient subjects used a wide array of dose sizes. Authors who reported dose-amounts in milligrams per kilogram typically did not provide the weights of subjects and the actual milligram amounts could not be identified. Authors who reported doses in mg/kg did not say how they administered odd-sized amounts such as 21.772 mg or 27.216 mg. Figure 10 is an example of this quandary [12]. This author attached a list of various body weights and gave their mg/kg doses in milligrams beside the study's milligram per kilogram graph. The list of doses ranges from 21.772 mg to 30 mg. Figure 10B depicts a simulated 3-hour schedule derived from figure 10A. The drops of plasma levels in 10B during transitions between doses were less than in 10A

Figure 10A depicts plasma concentrations of 0.4 mg/kg t.i.d. on a 4-hour schedule. Figure 10B simulates a 3-hour schedule by moving dose-2 to 11 a.m. and by moving dose-3 to 2 p.m. Figure 10 is adapted from a study by Nutt., *et al*. [12].

The simulated 3-hour dosing in figure 10B totaled *26.1%* less drop during dose-transitions than in the 4-hour dosing of figure 10A. Transition-drops in figure 10B were 13.6% less from dose-1 to -2 and 12.5% less from dose-2 to -3. There was a 58.8% difference of time below "Good" efficacy. The 4-hour schedule had 287 minutes (over 4½ hours) below "Good" efficacy. The 3-hour schedule had 118 minutes (about 2 hours) below "Good" efficacy, less than half of the 4-hour schedule time. There was an 82% difference of time in "Low to Poor" efficacy and below "Poor" efficacy. The

Figure 10: 0.4 mg/kg t.i.d. with 4-hour (left) and 3-hour (right) schedules. A legend of dose-amounts from mgs per body weight is shown on the far left [12].

4- hour schedule had 151 minutes of "Low to Poor" efficacy. The 3-hour schedule had 27 minutes of "Low to Poor" efficacy,less than one-fifth of the 4-hour schedule time. The 4-hour schedule had 48 minutes below "Poor" efficacy. The 3-hour schedule had no "Poor" efficacy, 100% less than the 4-hour schedule time. Level drops with 4-hour dosing stayed below "Good" efficacy 2.45 times longer than with 3-hour dosing. Under the premise of an efficacy-threshold of 9-ng/mL (see figure 2) the 4-hour schedule in figure 10A had over 3½ hours below full efficacy. The 3-hour schedule had 49 minutes below full-efficacy, over 75% less time than the 4-hour schedule. In the 4-hour schedule, 40% of the expected 12-hour duration was spent below "Good" efficacy, giving 7.8 sporadically broken up hours of good efficacy. On the other hand, five sequential doses in a 3-hour schedule give 15-hours of consistently smooth efficacy.

Figure 5A showed a 0.8% level-drop under an empirical 3-hour schedule. 4-hour schedules (Figures 3A, 4, 6, 7A, 7B, 7C, 7D, 7E, 8, 9A, and 10A) averaged drops of 41%. The drops were 51-times greater (ranging from 30-times to 79.8-times greater) than the 3-hour schedule. 0.8% in figure 5A was a mere 0.14 ng/mL change from 15.03 to 14.9 ng/mL. This was uninterrupted efficacy whereas 4-hour dosing was a roller coaster of greatly fluctuating efficacy. The level drops in this study's simulated 3-hour schedules were consistently less than in the 4-hour schedules. The differences are validated by Dr R's empirical experiences and reliable observations. The differences are also validated by empirical 3-hour data from hours-0 to -6 in figure 5A.

The figures in this study simplify concepts that no one thought of before. Dr R developed the concepts into a foundation that applies to virtually any medical use of Methylphenidate. This foundation also facilitates accurate and consistent research results that never existed before and are not possible under the 67-year tradition of á priori 4-hour MPH dosing. The á priori 4-hour schedule is a false premise that has been used as a false independent variable in all MPH research since 1955.

Inconsistent findings within and across studies that used 4-hour dosing

Plasma concentrations from 20 mg doses on 4-hour schedules were reported above. There were marked differences across the 4-hour reports: C_{max}-1 was listed as 12.33, 10, and 9.9. C_{max}-2 was listed as 18.44, 13.9, and 13.68. C_{max}-3 was listed as 14.0 and 13.18. Treatment of Parkinson's with MPH proved to be beneficial in several studies but the proof failed to lead to clinical uses. The failure was largely due to an anti-MPH stigma that believed and feared MPH was an addictive drug of abuse. Authors of a 1996 study titled "Use of Stimulants in the Medically Ill" postulated that the fear dated to the "speed freaks" in the drug subculture of the 1960's [34]. The article pointed out the wrongfulness of the Medical Community's adherence to that fear: "Unfortunately, barriers (e.g., myths regarding addiction, abuse, and tolerance, and anorectic effects) to the prescription of psychostimulants by clinicians exist. Physicians distrust stimulants because of their checkered history; this distrust

has led patients to resist taking stimulants. Moreover, because they are classified as a scheduled drug with a potential for abuse, their use has been limited (by providers) to selected populations". A 2000 study by the Mayo Clinic took that point a step further and stated: "The abuse potential of methylphenidate is another issue that has received considerable attention… Numerous studies in adults have shown no indication that the use of oral methylphenidate in the medically ill population leads to problems of abuse" [35].

Unfortunately the anti-MPH stigma was so firmly and widely entrenched that virtually no one would speak out against it and stand their ground, including the Mayo authors. After disproving the stigma the Mayo authors wrote, "It is prudent, however, to always remember the possibility of abuse or diversion of the drug, keep careful records, and consider using non-stimulant medications…" Their words of "always remember", "abuse or diversion", and "drug" negated the anti-stigma scientific proof they cited vis á vis it was an oxymoron to write that there was no risk of abuse but there was "always" a risk of abuse. It was an illogical to tell providers that patients were not a risk so "keep careful records." Providers were told there was nothing to fear but "always remember" to be afraid. Providers were told that patients can be trusted but do not trust them. Mayo told providers that patients do not abuse MPH but "always remember" to treat patients like abusers. The ostensibly anti-stigma Mayo article told providers to emotionally abuse their patients. The 1996 research authors confronted the stigma and truthfully called it a "myth". The Mayo article also spoke out against the stigma but then encouraged and reinforced it with a message to be "prudent" and ignore the research.

Another way that many MPH-for-Parkinson's researchers reinforced the anti-MPH stigma was by using article- titles that carried misleading negative connotations. A 2007 study was titled "Improvement of gait by chronic, high doses of methylphenidate…" [15]. "Methylphenidate" was placed beside "chronic" and "high dose". "Chronic high dose" conveys an image of drug addiction. The authors might claim that "high dose" was a "technical term" but the study used commonplace 20 mg doses, not "high doses". The authors might claim that "chronic" was a technical term" but the study ended at 90 days which did not fit the common definition of "chronic". The study found positive benefits from MPH but the authors' title conveyed an inappropriate image of Methylphenidate addiction. Clinicians and the public don't see "technical terms". When they see a title that says "addiction" they are not going to read the article. The positive and powerful findings of the 2007 study were quoted earlier in this article. Under the misleading negative connotations of the title, the positive findings became lost into unread oblivion. The many examples of this phenomenon reinforced clinicians' and the public's stigma against "Controlled Substance" MPH. It drove clinicians and the public away from learning the superior benefits of MPH for treating Parkinson's.

Bear in mind that this "dangerously addictive Controlled Substance" has been safely prescribed to millions of 6-to-10 year-old children for over 50 years.

Due to false negative connotations in article titles and due to discrepancies across studies, the Neurology Community disregarded Methylphenidate research and remained prejudicially oblivious to the differences between Methylphenidate vs. amphetamines and cocaine. Amphetamines and cocaine are addictive because they take effect very quickly and wear off very quickly, causing a person to crave more. Methylphenidate is formulated to have a slow onset of 30 to 60 minutes and a slow termination of 30 to 60 minutes. This makes Methylphenidate non-addictive. Furthermore, published research consistently shows that ill adults do not abuse their prescribed Methylphenidate. The anti-MPH stigma is false.

Research shows that Methylphenidate is safe and effective and doesn't cause the serious difficulties of APs. However positive research findings failed to overcome clinicians' anti-Methylphenidate stigma. The failure was due to (a) authors who tainted positive results with misleading article-titles, (b) 4-hour schedule research findings that were inconsistent across studies even when findings were positive, and (c) practitioners' false fears that their ill patients would abuse Methylphenidate. Practitioners will not be convinced that MPH is safe until findings are consistent across studies.

Neurology research of Methylphenidate has used short-term (90 days or less) inpatient studies, usually co- administered MPH with other medications, and administered MPH on the wrong 4-hour schedule. The brief inpatient studies could not reliably predict the effects of long-term treatment. Participants were knowingly scrutinized by frequent observations whereby the studies were not valid facsimiles of natural real-life. These flaws in research-design were compounded by 4-hour scheduling that yields inaccurate results.

Historically every Methylphenidate study adhered to 4-hour dosing as an independent variable. By using the false independent variable, 67 years of Methylphenidate research gave sometimes useful but non-valid results. "Double-blind" designs and findings of statistical significance were moot without a valid independent variable. In order for Methylphenidate-use to be a valid independent variable, the doses must be administered every three hours. The á priori4-hour precedent was set by authors and journal Editors who were unaware that the 4-hour variable was not valid. Science journals published studies that used the 4-hour variable and it became the norm. This author reviewed more than 400 published articles for this study and found only one that approached dose-frequency empirically (see figure 5A). That study was not exemplary of 3-hour dosing because it used an hour-3 dose-2 followed by dose-3 four hours later. The research-design did not let go of the 4-hour false premise. Rules of formal Logic say that conclusions derived from false premises are false conclusions. The fallacy of the 4-hour schedule caused decades of false conclusions and inconsistencies across studies. The persistent inconsistencies demonstrate that the research results were incorrect. The necessity of identifying and defining the non-valid 4-hour inconsistencies inadvertently turned parts of this Parkinson's study into a meta-analysis exposé of nearly 70 years of flawed methodology.

Results and Discussion

Among several new discoveries in this study, two stand out among the most important. One was the discovery of the 3-hour dosing schedule for Methylphenidate. The other was the discovery that long-term diurnal Methylphenidate monotherapy was more effective and safe than AntiParkinsonian Dopamine Replacement Therapy.

The 3-hour MPH schedule is valuable for patients by providing them with continuous efficacy even during transitions between doses. The 3-hour schedule is also valuable for researchers by enabling them to measure dependent variables during non-fluctuating MPH efficacy. Flawed clinical treatments and flawed research cannot improve until clinicians and researchers stop using 4-hour dosing and switch to 3-hour dosing. The switch is absolutely necessary for accurate research findings and patient-centered clinical success. The second of two among the most important discoveries was the validation of the study's primary hypothesis that optimal dose-amounts and frequencies of Methylphenidate would overcome and counteract the difficult and eventually disabling adverse reactions induced by long-term and/or high-dose AntiParkinsonians. Long-term variable-dose experiments tested the hypothesis. Their findings validated the primary hypothesis and the three-hour control-times reflected the duration of MPH in the newly discovered three-hour dosing schedule.

Up to that point in the study, MPH was taken adjunctively with APs to counteract the adverse effects of APs. Then it came about that on some occasions the routine MPH 30 mg was taken but APs were inadvertently forgotten. It seemed that Parkinson's symptoms did not become active on those occasions. This led to a second primary hypothesis that optimal dose-amounts and frequencies of Methylphenidate diurnal monotherapy would temporarily overcome and counteract many or most symptoms of Parkinson's disorders. The additional hypothesis was validated by new experiments in this study. The new experiments demonstrated that optimal dose-amounts and frequencies of long-termdiurnal Methylphenidate monotherapy can replace diurnal AntiParkinsonians to provide safer and more effectivetreatment for Parkinson's symptoms.

The number of Parkinson's benefits from Methylphenidate is virtually endless as juxtaposed to the plethora of severe problems inherent to AntiParkinsonians. Methylphenidate is a highly effective Dopamine Agonist that is well known and widely used. Methylphenidate can quickly end the severe disability that is common with advanced Parkinson's disorders and with high-dose AntiParkinsonian medications.

Conclusions

The findings of this study are extremely valuable for over 10 million people who are affected by Parkinson's Disease and other Parkinson's disorders: (1) Methylphenidate was significantly more effective than anti-Parkinsonian Dopamine Replacement Therapy for controlling Dr R's very severe Parkinson's symptoms. (2) Methylphenidate was significantly safer than AntiParkinsonians because it did not cause the severe adverse effects of AntiParkinsonians such as Narcoleptic blackouts, diminished cognition, and augmentation. (3) Methylphenidate slows the progression of Parkinson's by strengthening and protecting neural tissues, especially the Dopamine system. (4) Research studies show therapeutic-use adults do not abuse Methylphenidate. (5) Methylphenidate is non-addictive. Its slow efficacy onset and termination are unlike fast-acting

substances such as Cocaine and Methamphetamine. (6) Methylphenidate is so safe that it has been prescribed for millions of children in the USA between ages 5 and 11.

To the best knowledge of this author this is the first study to present long-term and outpatient use of Methylphenidate for Parkinson's. To the best knowledge of this author this is the first study to present a 3-hour dosing schedule for Methylphenidate. To the best knowledge of this author this is the first study to present Methylphenidate as definitively safer and more effective than AntiParkinsonians for long-term treatment of Parkinson's. This study presented a biochemistry analysis of the mechanisms by which Methylphenidate slows the progression of Parkinson's. This study presented a biochemistry analysis of the mechanisms by which Methylphenidate protects and strengthens Dopamine systems and other neural tissues. This study showed that Methylphenidate does not cause the serious and disabling adverse effects of Anti-Parkinsonians. This study pointed out dozens of warnings in Anti-Parkinsonian product monographs regarding medication-induced Narcolepsy that Methylphenidate remedies and does not cause. This study showed that 30 mg amounts of Methylphenidate taken adjunctively with Anti Parkinsonians stopped the adverse effects of Anti Parkinsonians. This study showed that when Anti Parkinsonians were not taken, Methylphenidate 20 mg monotherapy-controlled Parkinson's symptoms.

This study described and explained the biochemistry of Methylphenidate treatment of Parkinson's. This study mentioned a regimen of MPH 20 mg every three hours five times per day plus APs at bedtime for sleep. Bedtime APs allow good sleep but cause heavy grogginess in the morning. Rather than taking MPH 20 mg upon waking, it is healthier to take 25 mgs. This slightly higher amount counteracts AP-induced morning grogginess. Counteracting grogginess as quickly as possible makes a person more alert and comfortable, enables productivity, and prevents grogginess from diminishing the efficacy of the other doses of the day. Taking 25 mgs upon waking uses the biochemistry by which 30 mgs defeated the adverse effects of APs during adjunctive therapy. When MPH doesn't have to fight against AP-induced adverse effects, lesser dose-amounts of MPH monotherapy can control the symptoms of Parkinson's illnesses and Parkinsonism.

This study described and explained the biochemistry of diurnal MPH as a superior replacement for diurnal APs.The superiority of MPH includes reducing APs by 78% to their bedtime-only dose (see figure 2). For people whose daily amount of APs dropped to 70.5 mgs at bedtime, the superiority of MPH includes 91,232 fewer milligrams of APs per year, or 91,232 fewer milligrams per year of medication-induced adverse effects and augmentation-induced neural- destruction. This information can greatly improve the health and lives of over 10 million Parkinson's-affected people worldwide. This can also significantly benefit their families (averaging 4.9 people per household) and communities (perhaps 10 people per family-member).

Replacing diurnal APs with biochemically superior MPH can significantly improve the lives of over 500 million people.

Consent to Publication

The author consents to publication of this study.

Ethics Approval

Not applicable. The author is the subject.

Consent

Not applicable. The author is the subject.

Authors' Contributions

Not applicable. There is one author.

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Bibliography

1. Parkinson's Foundation. "Surgical Treatment Options". *Parkinson's Foundation* (2022).

2. Parkinson's Foundation. "About Parkinson's Disease". *Parkinson Foundation* (2022).

3. Kramer Stephanie. "With Billions Confined to Their Homes Worldwide, Which Living Arrangements Are Most Common?" *Pew Research Center* (2020).

4. GSK group of companies. Requip/Ropinirole Product Monograph (2020).

5. Merck Sharp and Dohme Corp. Sinemet/Carbidopa-Levodopa Product Monograph (2020).

6. Boehringer Ingelheim International GmbH. Mirapex/Pramipexole product monograph (2021).

7. Persico AM., *et al.* "Parkinsonian patients report blunted subjective effects of methylphenidate"**.** *Experimental and Clinical Psychopharmacology* 6 (1998): 54-63.

8. Camicioli R., *et al.* "Methylphenidate Increases the Motor Effects of L-Dopa in Parkinson's Disease: A Pilot Study". *Clinical Neuropharmacology* 24.4 (2001) 208-213.

9. Nutt J., *et al.* "Effects of Methylphenidate on Response to Oral Levodopa, A Double-Blind Clinical Trial". *Archives of Neurology* 64.3 (2007): 319-323.

10. Loddo G., *et al.* "The Treatment of Sleep Disorders in Parkinson's Disease: From Research to Clinical Practice". *Frontiers in Neurology* (2017).

11. Lopez R., *et al.* "Test-Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence". *SLEEP* 40.12 (2007).

12. Trotti L., *et al.* "Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia". *Journal of Clinical Sleep Medicine* 9.8 (2013).

13. Zhang L., *et al.* "Freezing of Gait in Parkinsonism and its Potential Drug Treatment". *Current Neuropharmacology* 14.4 (2016): 302-306.

14. Moreau C., *et al.* "Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial". *Neurology* 11.7 (2012): 589-596.

15. Devos D., *et al.* "Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease". *Journal of Neurology, Neurosurgery, and Psychiatry* 78 (2007): 470-475.

16. Penn State Health Milton Hershey Medical Center. "Parkinson Disease". *Parkinsons* (2022).

17. MacDonald P., *et al.* "The effect of dopamine therapy on ventral and dorsal striatum- mediated cognition in Parkinson's disease: support from functional MRI". *Brain* 134.5 (2011): 1447.

18. Novartis Pharmaceuticals Corporation. "Ritalin/Methylphenidate product monograph 2019". *Novartis Pharmaceuticals Corporation* (2022).

19. Novartis Pharmaceuticals Corporation. "Ritalin/Methylphenidate product monograph 2015". *Novartis Pharmaceuticals Corporation* (2019).

20. Volz T. "Neuropharmacological Mechanisms Underlying the Neuroprotective Effects of Methylphenidate" *Current Neuropharmacology* 6.4 (2008): 379-385.

21. "CADDRA Guide to ADHD Pharmacological Treatments in Canada 2016". *CADDRA Version 2015* (2016).

22. "CADDRA. Canada ADHD Practice Guidelines 2019" *CADDRA Version* (2020).

23. Purdue Pharma. "Foquest product monograph March 2019". *Purdue Pharmaceuticals* (2019).

24. Purdue Pharmaceuticals LP. "Adhansia XR product monograph 2019". *Purdue Pharmaceuticals* (2019).

25. Houghton D., *et al.* "Parkinson's Disease Medications". Parkinson's Foundation website article (2018).

26. Huss M., *et al.* "Methylphenidate dose optimization for ADHD treatment: review of safety, efficacy, and clinical necessity". *Neuropsychiatric Disease and Treatment* 13 (2017): 1741-1751.

27. ADHD MedCalc. "ADHD Medication Calculator/Converter for Healthcare Professionals only". *MedCalc* (2017).

28. National Health Service United Kingdom (NHS UK). "Methylphenidate for adults". National Health Service United Kingdom website article (2021).

29. National Health Service United Kingdom (NHS UK). "Methylphenidate for children". National Health Service United Kingdom website article (2021).

30. Novartis Pharmaceuticals Corporation. "Ritalin LA product monograph 2021". *Novartis Pharmaceuticals Corporation* (2021).

31. Adjei Akwete., *et al.* "Single-dose pharmacokinetics of methylphenidate extended-release multiple layer beads administered as intact capsule or sprinkles versus methylphenidate immediate-release tablets (Ritalin®) in healthy adult volunteers". *Journal of Child and Adolescent Psychopharmacology* 24.10 (2014): 570-578.

32. Swanson J., *et al.* "Efficacy of a Pattern of Delivery of Methylphenidate for the Treatment of ADHD: Effects on Activity Level in the Classroom and on the Playground". *Journal of the American Academy of Child and Adolescent Psychiatry* 41.11 (2021): 1306-1314.

33. Katzman M., *et al.* "Randomized Controlled Crossover Trials of the Pharmacokinetics of PRC-063, a Novel Multilayer Extended-Release Formulation of Methylphenidate, in Healthy Adults". *Journal of Clinical Psychopharmacology* 40.6 (2020): 579-587.

34. Masand PS and Tesar GE. "Use of stimulants in the medically ill". *Psychiatric Clinics of North America* 19 (1996): 515-547.

35. Challman T and Lipsky J. "Methylphenidate: Its Pharmacology and Uses". *Mayo Clinic Proceedings* 75 (2000): 711-721.