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Case Report

Long-term Methylphenidate Monotherapy for Parkinson's: Biochemistry Analysis and 17 Year Case Study

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Abstract

Background: Information in this study can improve the health and quality of life of over ten million people with Parkinson's. This paper presents long-term treatment of Parkinson's with Methylphenidate that was found safe and effective to use instead of traditional anti-Parkinsonians such as Carbidopa-Levodopa and Pramipexole that cause augmentation (neural damage), excessive sedation, sudden passing out and slowed cognition. Methylphenidate strengthens and protects neural tissues and sustains normal alertness and cognition.

Methods: This article analyzes the neurobiochemistry of Methylphenidate-therapy vs. AntiParkinsonian-therapy based on this author's review of over 400 published studies and guidelines. This article also presents a Case Study involving a case-subject who has a very severe Parkinson's disorder with a well-documented nine years of AntiParkinsonian-therapy followed by eight years of Methylphenidate-therapy. The case-subject is a 66 year-old male with a PhD who is a published Neurobiochemistry Researcher. At age-55 he was medically 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 known remedy. Thus he conceived and designed the world's first long-term Methylphenidate treatment of Parkinson's and implemented it with the cooperation of a prescribing Physician.

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Results: Adjunctive 30 mg doses of diurnal Methylphenidate overcame adverse effects of AntiParkinsonians. 20 mg doses of diurnal Methylphenidate monotherapy controlled Parkinson's illness better than AntiParkinsonians. A 3-hour dosing schedule resulted in smooth and uninterrupted efficacy between and across doses of Methylphenidate. Sequential doses every three hours extended efficacy duration to 16 hours. Continued high-dose AntiParkinsonians at bedtime gave good sleep.

Conclusion: This author recommends that clinicians use these findings to replace diurnal AntiParkinsonians with diurnal Methylphenidate in order to provide safer and more effective long-term treatment of Parkinson's illnesses.

Keywords

AntiParkinsonians; Augmentation; Carbidopa-Levodopa; Cognition; Dopamine; Methylphenidate; Narcolepsy; Parkinson's; Pramipexole, Somnolence

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 is a two-part study. One part is a Case Study of the world's first long-term treatment of Parkinson's with Methylphenidate (MPH). The other part presents the means by which Methylphenidate treats Parkinson's more effectively and safely than AntiParkinsonians (APs).

Treatment with AntiParkinsonians is often called Dopamine Replacement Therapy (DRT) because the goal is to increase patients' Dopamine levels in order to improve general functioning by relieving Parkinson's symptoms. Research has shown that AntiParkinsonians are beneficial and necessary in some regards but increased doses usually decrease general functioning and high doses often disable general functioning. This is a pervasive Catch-22 for which no solution was found before now. A previous solution was sought via Deep Brain Stimulation (DBS) but it did not turn out as well as was hoped. DBS has all of the procedural dangers inherent to brain surgery. This includes but is not limited to brain infection, stroke, inter-cranial bleeding and exacerbation or new onset of seizures. DBS does not improve speech and does not improve cognition, the #1 factor in general functioning. DBS can in fact worsen

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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 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 solution. 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 bad effects AntiParkinsonians such as illness-augmentation, excessive sedation, diminished cognition and black outs during activities and driving.

This author hopes the information in this study will initiate a global movement among Physicians to switch their Parkinson's patients from diurnal AntiParkinsonians to diurnal Methylphenidate. Millions upon millions of patients could predictably rise from disability and regain normal functioning for the rest of their lives. It happened to our case-subject. He solved the Catch-22 of no-win Parkinson's treatments. Methylphenidate is Alexander's sword that severed the Gordian Knot of APs.

Materials and Methods

This article has two components. One component presents a Case Study of a patient's well-documented 36-year history of Parkinsonism, primarily focusing on his 17 years of medications with nine years of AntiParkinsonian monotherapy followed by eight years of Methylphenidate therapy. The other component of this article is a neurobiochemistry analysis of Methylphenidate and AntiParkinsonians in treatment of Parkinson's. For this component the author reviewed and analyzed over 400 published articles including clinical research, biochemistry research, product monographs and medication guidelines. Data from the Case Study and the analytics component are frequently presented conjointly to formulate a unified and cohesive format that found many new scientific discoveries. The previously unpublished discoveries in this study are combined with a compendium of previously published information. This unified combination of scientific information can greatly improve medical care and quality of life for over ten million Parkinson's-affected people and their families including over one million affected people and their families in the United States.

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Case Study: Nine years of AntiParkinsonian therapy followed by eight years of Methylphenidate therapy

Adverse effects of nine years of increasing amounts of AntiParkinsonians contributed to total disability and adding daytime Methylphenidate stopped the adverse effects of AntiParkinsonians. The case-subject then discovered that Methylphenidate could replace daytime AntiParkinsonians and was more effective and safer than AntiParkinsonians for controlling severe symptoms of Parkinson's. This ended his daytime AntiParkinsonians and their adverse effects, controlled his illness symptoms and ended his total disability. He regained normal functioning within a week and controlled his Parkinson's symptoms with daytime Methylphenidate and bedtime AntiParkinsonians for eight years. His regimen remains ongoing after this study ended. To the best knowledge of this author this is the first study to present outpatient treatment, long-term outpatient treatment and long-term treatment of Parkinson's with Methylphenidate.

Case Presentation

The subject in this Case Study had a very severe and very rare Parkinson's illness with a population prevalence of 0.0000003% affecting three people among ten million. This was calculated by appending "constant very severe symptoms" and "constant very severe distress" factors into the prevalence equations of the International Restless Legs Syndrome Group 2012 Revised IRLSSG Diagnostic Criteria for RLS1 and the Restless Legs Syndrome Rating Scale Clinical Guideline, v1.2 Our case-subject was a Ph.D.-educated 66 year-old American Caucasian male with a progressively disabling 36-year Parkinson's illness. The first section of this Case Study presents the case-subject's illness-onset, progression and nine years of AntiParkinsonian treatment. Dose-amounts of AntiParkinsonians and their adverse effects increased for nine years. Severe adverse effects from high doses became disabling and together with his disabling illness caused total disability. The second section of this Case Study presents the case-subject's world's first discovery and use of long-term Methylphenidate for Parkinson's. The case-subject discovered that adjunctive Methylphenidate 30 mg counteracted and overcame the disabling effects of high dose anti-Parkinsonians. Adjunctive Methylphenidate returned him to normal functioning in two weeks. Soon after making that discovery he discovered that lower-dose Methylphenidate 20 mg monotherapy controlled his illness-symptoms better than anti-Parkinsonians. He extended the efficacy duration of Methylphenidate to 16 hours with five sequential doses taken every three hours.

Our case-subject was the first person to discover and use adjunctive Methylphenidate for counteracting the adverse effects of high dose anti-Parkinsonians. He was the first person to discover and use 16-hour Methylphenidate as the replacement of all daytime anti-Parkinsonians. He was the first to discover that daily 16-hour Methylphenidate monotherapy was significantly more effective and safer than daytime AntiParkinsonians. He was the first to discover that three-hour Methylphenidate dosing was significantly more effective and safer

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than traditional four-hour dosing. The case-subject was already a science journal published Neurobiochemistry researcher and author. For this research study and for his health he extensively researched and gained preeminent expertise in the biochemistry of long-term Parkinson's-Methylphenidate. He taught it to his private practice Neurologist in 2014. He taught it to three Primary Care Physicians in 2014, 2015 and early-2019. In mid-2019 he taught it to an Attending Physician of a preeminent University Hospital Neurosciences Center who then agreed to prescribe for our case-subject. Our case-subject's history of Parkinson's-Methylphenidate discoveries started with nine years of AntiParkinsonian treatment.

Case Study with nine years of Anti-Parkinsonian treatment

Mild leg spasms in bed started at age-30. The spasms gradually worsened and at age-35 he started having incidents of sudden passing out. At age-45 he reported the problems to his Physician who wrote that bedtime Benadryl for sleep might be causing his spasms and his passing out might be Vasovagal Syncope. The spasms worsened despite stopping Benadryl. At age 49 his Physician diagnosed Restless Leg Syndrome and prescribed a low-dose AntiParkinsonian, Ropinirole 1 mg, at bedtime. By age-54 he was on Carb-Levo 750 mg per day: 10/100 three times in the day and three times in the night and 25/250 at bedtime. It was noticeably less effective by age-55½ when his Physician wrote a referral to Neurology saying, "This is a chronic problem. The current episode started more than 1 year ago. Without appropriate dosage of meds, gets severe RLS-unable to function. Relieved by: sinemet. Worsening" meaning the patient was disabled by his illness, current Sinemet was becoming ineffective and adjustments by a Neurologist were needed to maintain the patient's diminishing ability to function.

Four weeks later the patient got in with a Neurologist who stayed with him from 2011 to 2019. The Neurologist added Pramipexole 0.25 mg three times in the day and 0.50 mg at bedtime. He changed bedtime Carb-Levo to ER-25/100. Night Carb-Levo increased to two 10/100s every three hours. Daytime Carb-Levo remained the same but with a suggestion to try taking less to see whether Pramipexole might be more helpful than Carb-Levo. It helped only when taken with Carb-Levo. AntiParkinsonians increased from 750 mg daily to 936 mg. They increased a year later to 1,621.25 mg.

The increases reflected the patient's worsening illness and were necessary to control his symptoms. Unfortunately they brought increasingly severe adverse effects. The major increases started in May 2011. In June 2013 the patient was ambulated to Emergency Care for sudden passing out. He told the doctor it was from Parkinson's illness and high-dose medications, but she diagnosed "Syncope" from his 2001 Medical Record. Six days later the Neurologist increased his APs again. The increase was 21% to 2,061.25 mg. The patient continued worsening and became totally disabled in June 2014. A longitudinal history of the patient's AP dose-amounts is listed in Fig. 1 below.

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An RLS etiology of very severe Parkinsonism is extremely rare with a population prevalence of 0.0000003%, or 3 in 10 million. There is no known treatment research on this small population. Cases might be too rare for researchers to locate subjects and too many cases are misdiagnosed and unrecognized for researchers to know this group of people exists. To the best knowledge of this author this is the only study to present treatment research involving this extremely rare disorder. The etiology and severity of this case are extremely rare but cross-analyses that compare this case to Parkinson's subjects in other studies show that this case's symptoms, neurological properties and neurobiochemical responses to treatment are the same as those of ten million other people with Parkinson's disorders worldwide. Therefore the findings of this study generalize markedly well to the larger population affected by Parkinson's. To the best knowledge of this author this is the first and only long-term outpatient study of Methylphenidate treatment for Parkinson's. To the best knowledge of this author this is the first and only comparative study of outpatient Methylphenidate for Parkinson's vs. outpatient AntiParkinsonians. To the best knowledge of this author this is the first and only comparative study of long-term Methylphenidate for Parkinson's vs. long-term AntiParkinsonians.

Adverse Reactions to AntiParkinsonians

Our case-subject had several adverse reactions that were listed in AntiParkinsonian product monographs and are summarized below regarding Ropinirole ("Requip"), Carbidopa-Levodopa ("Sinemet") and Pramipexole ("Mirapex") [3-5].

Ropinirole ("Requip")

Our case-subject's first AntiParkinsonian medication was 1 mg of Ropinirole at bedtime. It controlled his RLS leg spasms but also induced nausea. The primary effects soon diminished and it was increased to 2 mgs. This improved effectiveness but added occasional vomiting to the nausea. Ropinirole was discontinued after five years when vomiting became too frequent. The Physician then included Ropinirole to the subject's list of allergies.

"Requip" is a brand name of Ropinirole, a Dopamine agonist. The manufacturer's product monograph 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) [3]. The subject didn't notice side effects other than nausea and vomiting. The other side effects of bedtime Requip were incorporated into his sleep and wore off by morning. Requip was replaced by bedtime Carb-Levo when nausea and frequent vomiting from Requip became intolerable.

Carbidopa-Levodopa (“Sinemet”)

Eighteen months after Requip began at bedtime, a daytime tab of Carb-Levo 10/100 mg was added at 1pm to control leg spasms that were dangerous while driving home from work. Carb-Levo increased over the next six years to 1-2 extended release 25/100 tabs in the morning, 1-3 10/100 tabs x4 during the daytime, 2 extended release 25/100 tabs at bedtime and 1-3 10/100 tabs as needed up to every three hours through the night. Four years after Carb-Levo started the subject’s Neurologist noted that he saw a likelihood of augmentation.

“Sinemet” is a brand name of Carbidopa-Levodopa, a combination of Dopamine precursor Levodopa and decarboxylase inhibitor Carbidopa. The case-subject experienced eight categories of adverse reactions that are listed in the manufacturer’s product monograph⁴: (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.

Pramipexole (“Mirapex”)

“Mirapex” is a brand name of Pramipexole, a Dopamine agonist. Our case-subject experienced six adverse reactions that were listed in the Mirapex product monograph: falling asleep in activities of daily living (including driving), somnolence, syncope, hypotension, vomiting and weight increase [5]. Narcolepsy from his Parkinson’s illness and from AntiParkinsonians was a major problem for our case-subject. Warnings about Narcoleptic side effects were listed in the product monographs of Requip, Sinemet and Mirapex. Each monograph used synonyms and descriptors like those in the Mirapex monograph.

Six paragraphs in the Mirapex monograph warned of Narcolepsy 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 drive or 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. “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 of one monograph. Each of the three AP monographs presents 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 means that 52% in one year and 100% in less than two years would have Pramipexole-induced Narcolepsy. The study reported 36% in 33 weeks with Mirapex ER. Somnolence (Narcolepsy) was the most frequently reported adverse reaction. The 2007 Mirapex monograph presented a placebo-controlled double-blind study with 22% of Mirapex IR subjects reporting somnolence compared to 9% of placebo subjects. A time frame was not given. The IR-22% was more than double the placebo-9%. This was consistent with the double rate above placebo in the 2021 product monograph. However the 22% who reported somnolence was inconsistent with the 33% who reported it. No timeframe was stated for the 22%. If it had a 22-week timeframe it would have been consistent with the 33% but no timeframe was given. This was a defacto inconsistency between the 2021 ER monograph and 2007 IR monograph. Another defacto inconsistency was that the 2021 ER monograph did not mention or allude to augmentation. The 2007 IR monograph spoke of an RLS study with 20% of Mirapex subjects reporting augmentation at three months. The 2021 IR monograph spoke of an RLS study with 12% of Mirapex subjects reporting augmentation at 26 weeks.

20% reporting augmentation in three months (12 weeks) and 12% reporting augmentation in 26 weeks (6.5 months) were high rates for a medication that supposedly minimizes augmentation. The monographs dishonestly minimalized and misrepresented the incidence rates by not acknowledging an accumulating number of incidents across longer periods of time. At 12% every 26 weeks, 24% of subjects would have augmentation in one year and 100% would have augmentation in 4.25 years. At 20% every three months, 40% of subjects would have augmentation in six months and 100% would have augmentation in 1.25 years. These studies in two monographs showed that Mirapex/Pramipexole caused augmentation rather than preventing or minimizing augmentation. Pramipexole is used to treat Parkinson’s and to prevent or minimize Carbidopa-Levodopa augmentation but the Mirapex IR monographs show that it causes augmentation. These are two examples of inconsistencies and internal contradictions that show the monographs are not scientifically valid.

Case Study with eight years of Methylphenidate treatment

Increasing impairments from our case-subject’s Parkinson’s illness and nine years of AntiParkinsonians gradually progressed into total disability. Narcolepsy happened exclusively at home for 32 years before he began occasionally blacking out at his workplace. Blackouts at his at workplace increased into six months of daily occurrences. During that time Narcolepsy started trying to knock him out while driving. Narcolepsy-attacks while driving increased into

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four months of daily occurrences that progressively worsened into a need to yell and scream at himself while driving to keep from passing out.

On a Friday evening in June 2014 he blacked out at his office and had to constantly yell and scream at himself while driving home to keep from passing out. This evening, however, was worse than the ones that went before. The prolonged Narcolepsy-attack while driving home was more severe. It made him drift left and right and he almost crashed three times. The Narcolepsy-attack pushed and pushed harder and harder to make him pass out. He fought and fought against it and barely got home alive. In a brief moment of relief he said, “Thank God I’m home”. Then he blacked out while entering his driveway. A vibration of the steering wheel awakened him just in time to slam on the breaks and not drive into his house. His ability to fight driving-Narcolepsy failed. He could no longer drive and he passed out at his office every day. He was totally disabled but before he went home that Friday evening he thought of something that might make things better.

He called his Physician’s office on Monday and set an emergency visit for Tuesday. He told the doctor about his situation and his disability. He said this was an emergency and he needed to see if Ritalin could stop his disability. The doctor agreed to his experiment and prescribed Methylphenidate.

Our case-subject started with one 5 mg tab. It was ineffective but caused no problems so he took a second tab an hour later and a third tab another hour later. They were ineffective. Our case-subject knew Methylphenidate starts losing effect at 3-hours. Dose-1 would have no efficacy by hour-4 so taking another tab at hour-4 would be pointless. He ended his first trial after three 5 mg doses. The trial showed that 5 to 15 mgs was ineffective but safe. On the following day he started another trial using 10 mgs and another 10 mgs an hour later. 20 mgs made driving safer and slightly improved his concentration. 20 mg was minimally effective but seemed hopeful so he stayed with it for a week. It was minimally effective but insufficient. He found 25 mgs was not noticeably different. He tried 30 mgs and it worked as he hoped so he stayed with it for a week. It reliably stopped AntiParkinsonian side effects, cleared his cognition and gave no bad effects. It was the remedy he hoped to find.

30 mgs was effective so he never tried higher amounts, but other dose changes came about.

Before starting his Methylphenidate experiment he took AntiParkinsonians on a timed schedule for years. During those years, when he accidentally missed a dose of AntiParkinsonians his illness-symptoms surfaced and reminded him to take his medications. When 30 mgs of Methylphenidate was active, a missed dose of AntiParkinsonians did not bring illness-symptoms. Then he deliberately did not take AntiParkinsonians while Methylphenidate was active. His illness-symptoms did not surface. He told his Physician that 30 mgs controlled his illness without AntiParkinsonians. It seemed to be the optimal amount but he wanted longer duration than 3-hour doses. If he had long enough duration he might be able to stop taking daytime AntiParkinsonians. His MD said 30 mg Ritalin LA contained 30 mg b.i.d. with 6-8-hour duration. Our case-subject wanted longer duration than 6-8 hours so the doctor added Ritalin IR 10 mg to be taken when the LA wore off.

Our case-subject took Ritalin LA 30 mg and the add-on 10 mgs as prescribed but found he needed daytime AntiParkinsonians with it. It turned out that Ritalin LA 30 mg was made of 15 mg b.i.d., not 30 mg b.i.d. His doctor was prescribing 50% of the optimal dose. Our case-subject compensated by taking Ritalin LA with half of a 10 mg tab and he took the other half-tab 3 hours later. This made two consecutive 20 mg doses that lasted for 6 hours. He soon found that if he didn't take AntiParkinsonians with it, 20 mgs of Ritalin controlled his illness as effectively as 30 mgs. During trials with Ritalin LA 30 mg capsules and Ritalin IR 10 mg tablets our case-subject found that 20 mgs (not 30) was the optimal dose-amount but six hours was not an optimal duration. Methylphenidate IR tablets start gradually losing efficacy at 3-hours after oral intake. Our case-subject extended duration by a process of sequential dose building that he called the 5 mg Incremental Dose-Builder Model. He placed a minimal dose-amount (i.e., Ritalin IR 5 mgs) at 3 hours after intake of a regimen's last sequential dose. He monitored the added amount for a month or longer. When safety was assured another minimal amount was placed with the previously added amount at the 3-hour mark such that a new sequential dose of 5 mgs was increased to 10 mgs. Our case-subject monitored the new 10 mg amount for a month or longer. When safety was assured another minimal amount was placed with the previously added amounts at the 3-hour mark such that a new sequential dose of 10 mgs was increased to 15 mgs. The newly added amount was monitored for a month or longer. When safety was assured another minimal amount was placed with the previously added amounts at the 3-hour mark such that a new sequential dose of 15 mgs was increased to 20 mgs.

He stopped increasing each new sequential dose at 20 mgs because he previously established that 20 mgs is the optimal amount. To extend duration longer again by adding another sequential dose, he started the dose-building process again in 5 mg increments until a new sequential dose reached 20 mgs. Each 5 mg increment was added a month or longer after a previously added 5 mg increment. Our case-subject designed the 5 mg Incremental Dose-Builder Model during the three days after having the idea that Ritalin might resolve and end his state of total disability. Those were the three days before he started his initial emergency Ritalin experiment. He implemented the 5 mg Incremental Dose-Builder Model from Day-1 of the experiment in 2014 until July 2020. Our case-subject relied on optimal 20 mg doses since October of 2014. On August 19, 2020 he had enough confidence in the safety of 20 mg doses to add a third daily dose of 20 mg without building it in 5 mg increments.

Our Case-subject reached 16-hour duration in 2020 with a 25-mg dose upon waking, 3 hours later a 6-hour ER-40 mg capsule, 6 hours later a 20-mg tab and 3-hours later another 20-mg tab. His learning how to sustain of all-day steady efficacy began with noticing that IR efficacy declined for 45 minutes from hour-3 until hour-3:45. A dose taken at hour-3 increased in efficacy for 45-minutes until hour-3:45. The second dose stopped plasma concentration and efficacy from declining between hour-3 and hour-3:45. This regimen of Methylphenidate gave 16 hours of normal functioning. It strengthened and protected neural tissues. It slowed AntiParkinsonian-augmentation and Parkinson's progression. It reduced AntiParkinsonians by 88.28%. AntiParkinsonians decreased from 2,061.25 mgs across 24 hours to 470.5 mgs at

bedtime. There were no more daytime AntiParkinsonians and no more daytime AntiParkinsonian adverse effects other than morning grogginess from bedtime pills. The grogginess ended within an hour after a morning dose of methylphenidate.

Our case-subject did not experience adverse effects from Methylphenidate other than morning-dose upset stomach that was easily curtailed by preventively taking each day's first dose with a tall glass of milk.

Our case-subject was the first person to break free from the Parkinson's/AntiParkinsonians Catch-22. At age-66, he plans to continue his current regimen into the future. Timelines of his AntiParkinsonian and his Methylphenidate therapies are presented in Fig. 1.

A History of anti-Parkinsonian Dopamine Replacement Therapy 10/31/2005 Age-49: daily-total DRT = <u>1mg</u> Ropinirole 1mg at bedtime 8/7/2006 Age-50: daily-total DRT = <u>2mg</u> Ropinirole 2mg at bedtime 4/30/2007 Age-51: daily-total DRT = <u>112mg</u> Ropinirole 2 mg at bedtime Carb-Levo 10/100 mg, 1 tab at 1:00 pm 10/4/2010 Age-54: daily-total DRT = <u>750mg</u> Carb-Levo 10/100 mg, 1 tab x2-3 diurnal per day Carb-Levo 25/100 mg, 1 tab at bedtime 5/25/2011 Age-55: daily-total DRT = <u>936mg</u> Carb-Levo 10/100 mg, 1 tab x2-3 diurnal per day Carb-Levo 10/100 mg, 1-2 tabs as needed every 3-4 hours through the night Carb-Levo 25/100 mg, 1 tab at bedtime Pramipexole .25 mg, 2 tabs at bedtime Pramipexole .25 mg, 1 tab in the morning and 1 tab in the afternoon 2/27/2012 Age-56: daily-total DRT = <u>1,621.25mg</u> Carb-Levo 10/100 mg, 1-3 tabs x4 diurnal per day Carb-Levo 25/100 1-2 tabs as needed Pramipexole .25 mg, 1 tab x3 diurnal per day Pramipexole .25 mg, 2 tabs at bedtime Carb-Levo ER 25/100 mg, 1-2 tabs at bedtime 6/28/2013 Age-57: daily-total DRT = <u>2,061.25mg</u> Carb-Levo 10/100, 1-3 tabs up to x4 diurnal per day as needed. Carb-Levo ER 25/100, 1-2 tabs in the morning Pramipexole .25 mg, 1 tab x3 diurnal per day Pramipexole .25 mg, 2 tabs at bedtime Carb-Levo ER 25/100, 2 tabs at bedtime	B Methylphenidate Replacing Diurnal anti-Parkinsonians 6/24/2014 Age-59.5: Methylphenidate began, adjunctive with APs 6/24/2014: Multiple 5 mg IR tabs for self-guided initial titration. 7/3/2014: 30 mg IR x1 qd 7/11/2014: 30 mg IR x2 qd 10/22/2014 Age 60: Methylphenidate replaced APs for 6 hours every day 10/22/2014: 30 mg Ritalin LA with 5 mg IR q 3hr b.i.d. 3/8/2017: 30 mg Metadate ER with 5 mg IR q 3hr b.i.d. 7/28/2017: 40 mg Metadate ER followed by 20 mg IR 10/24/2017: 40 mg ER, followed by 20 mg IR, followed by 5 mg IR 10/18/2018: 40 mg ER, followed by 20 mg IR, followed by 10 mg IR 4/15/2019 Age 64: Methylphenidate replaced APs for 12 hours every day 4/15/2019: 20 mg IR, followed by 40 mg ER, followed by 20 mg IR 8/19/2020 Age 65: Methylphenidate replaced all daytime APs. 8/19/2020: 25 mg IR, followed by 40 mg ER, followed by 20 mg IR, followed by 20 mg IR C anti-Parkinsonians Taken at Bedtime for Sleep APs were bedtime-only, reduced by 78% Age 65: daily-total DRT = <u>470.5mg</u> (22% of previous daily-total) Carb-Levo 10/100, 2 tabs at bedtime Carb-Levo ER 25/100, 2 tabs at bedtime Pramipexole .25 mg, 2 tabs at bedtime
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Figure 1: (A) 9-year history of 24-hour anti-Parkinsonians. (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.

When the FDA approved Methylphenidate in 1955 the manufacturer said 60 mg was the maximum daily amount. Healthcare providers were taught this for more than 65 years despite research that disproved it and despite higher amounts being approved in other countries around the world. Our case-subject's optimal daily amount of 105 mg has been deemed as excessive by many clinicians whose perspectives came from the outdated limit of 60 mg per day (Fig. 2).

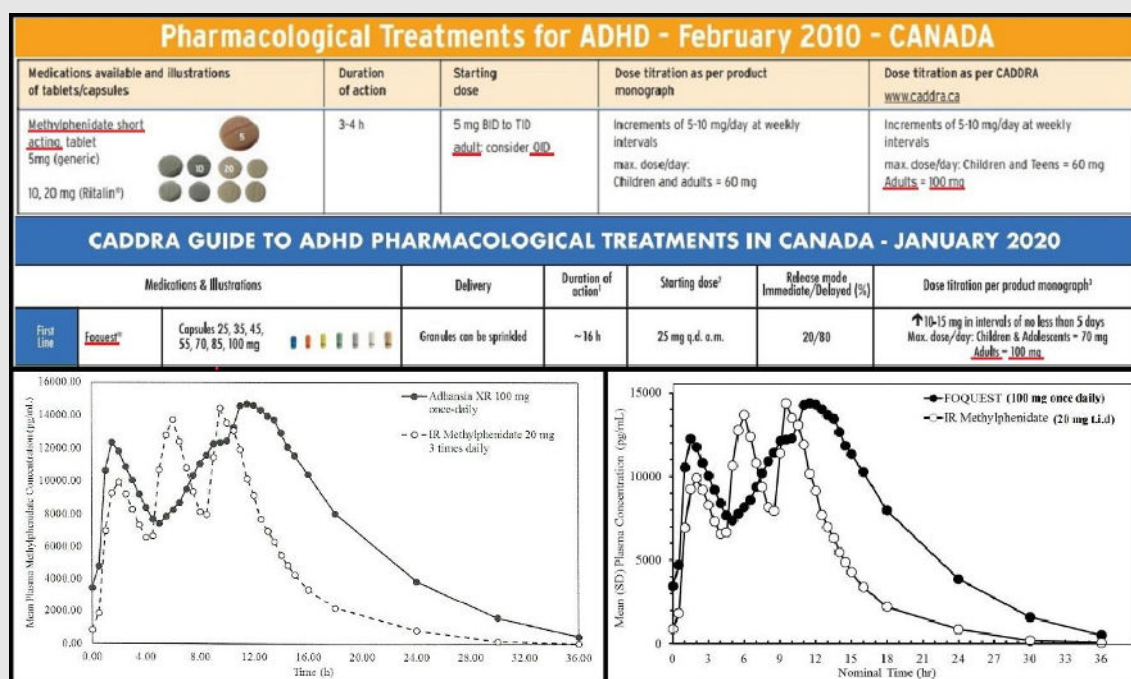


Figure 2: Canada approved MPH IR 100 mg per day in 20106 and approved 100 mg Foquest in 2019. The U.S. FDA approved Adhansia XR 85 mg (bottom left) based on 100 mg research by which Canada approved Foquest (bottom right) [7-9].

Our case-subject's optimal 105 mg per day was comparable with Canada's approval of IR 100 mg per day and 100 mg [6,7].

Foquest, The FDA approved Adhansia XR 85 mg based on the 100 mg research by which Canada approved 100 mg Foquest [9].

The Adhansia XR product monograph has data from the original 100 mg research as seen in the bottom-left plasma concentration graph above [8].

In 2014 our case-subject developed and enacted history's first long term Methylphenidate-for-Parkinson's outpatient treatment. He assembled and led a Treatment Team. His Neurologist prescribed AntiParkinsonians and approved Methylphenidate and a General Practitioner prescribed the Methylphenidate. At our case-subject's request five years and four GPs later, an

Attending Physician from a University Hospital Neuroscience Center replaced the Neurologist and General Practitioners.

Treatment Summary: Methylphenidate was Superior to Anti-Parkinsonians

Warnings about AntiParkinsonians in AntiParkinsonian product monographs were consistent with our case-subject's reports that long-term adverse effects from AntiParkinsonians negated their short-term benefits. AntiParkinsonians controlled his involuntary movements but significantly impaired his cognition and alertness and significantly worsened his longstanding Narcolepsy. His Physician wrote in 2011, six years into AntiParkinsonians that the case-subject was disabled and needed appropriate medications. "The case-subject's Neurologist addressed this by prescribing higher doses of Carb-Levo and by adding Pramipexole. The patient's daily total went from 750 mgs to 936 mgs. The Neurologist wrote that he added Pramipexole because the patient was undergoing augmentation from Carb-Levo. He told the patient to see whether it would work as well as Carb-Levo in hope to decrease Carb-Levo doses and slow down augmentation. The effort to restrict augmentation failed.

At his second Neurology visit five months after the first, our case-subject's medications increased to 1,621.25 mg. He accepted such things gracefully because he trusted that his Neurologist was treating his disorder in the best possible way. He was correct. His Neurologist was doing everything that could be done in the field of Clinical Neurology.

The treatments did not work as well as expected and no one knew why not. The question of 'why the treatments didn't work as expected' turned out to be secondary and essentially moot for this study. The pertinent important question is "Why didn't anyone know why not?" A short-version of the answer will suffice. The people who own and control Pramipexole/Mirapex have hidden a corporate secret for decades: Pramipexole/Mirapex does not minimize, prevent, or protect against augmentation. The public image and marketing strategy say it does, but in truth it does not.

Our case-subject's Neurologist prescribed Pramipexole in order to restrict Carb-Levo augmentation. He did not know why his prescription did not provide the expected restriction. He increased the doses on two occasions because each prescription did not restrict augmentation. He did not know why it did not provide the expected restriction of augmentation. The Mirapex manufacturer didn't tell providers why Pramipexole didn't work as well as expected. Our case-subject was ambulated to Emergency Care for Narcolepsy in 2013. Then his Neurologist increased his AntiParkinsonians again. Our case-subject's illness worsened further and was compounded by the greater adverse effects of the higher-doses of AntiParkinsonians.

In 2011 he was documented as disabled and in need of appropriate medications. In 2014 he was totally disabled because of his AntiParkinsonian medications. Providers had no solutions

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for his disability. On his own volition he requested and received Methylphenidate from his Primary Care Physician and added diurnal Methylphenidate to his AntiParkinsonians. He overcame disability, regained normal functioning and permanently stopped daytime AntiParkinsonians. Methylphenidate 20 mg every three hours was the “appropriate medication” he needed. It sustained his normal functioning for eight years. Our case-subject was the world’s first person to conceive, develop and implement long-term outpatient Methylphenidate treatment for Parkinson’s.

Biochemistry of Methylphenidate Treatment for Parkinson’s

Early Studies of Methylphenidate Treatment for Parkinson’s

The FDA approved Methylphenidate (1955) twenty years before Carbidopa-Levodopa (1975), 42 years before Pramipexole (1997) and 50 years before Ropinirole (2005). Methylphenidate was shunned by Neurology for 46 years. The earliest study of Methylphenidate and PD that this author found was published in 1998 [10]. The study used 10, 15, 20, 25 and 30 mgs of Methylphenidate and found PD patients had less mood elevation and stimulant response from Methylphenidate than healthy subjects had. The study did not investigate Methylphenidate as a potential treatment for PD. A pilot study published in 2001 seems to be the first study of Methylphenidate treatment for PD [11]. The pilot study found 10 mg doses of adjunctive Methylphenidate increased the motor effects of efficacy-threshold low-dose Carb-Levo with minimal effect on cognition and affect. John Nutt, a co-author of the 2001 pilot study, led a study in 2007 that found 20 mg doses of adjunctive Methylphenidate significantly reduced Carb-Levo resistant tremors [12]. The 2001 and 2007 studies also showed that 10 mg and 20 mg doses of Methylphenidate were safe for Parkinson’s. The 2001 and 2007 findings were similar to those of our case-subject.

Our case-subject asserts that in order to be accurate it is necessary to acknowledge the dark side of Neurology research into Methylphenidate. The majority of research from 2001 to 2017 was designed to fail by using low-dose Methylphenidate because it would fail. Studies that disproved Methylphenidate were and are considered successful. Anti-Methylphenidate authors proudly comment that their disproof of Methylphenidate was “consistent with previous studies”. The Neurology Clinical and Research Communities marginalized the 2001 pilot study for contradicting the stigma against Methylphenidate. The 2007 follow up study was sabotaged in ways that made Methylphenidate fail. For example one of the experiments was designed for below-efficacy doses of Carb-Levo but it was given to subjects in their normal doses.

Clinical studies of Methylphenidate treatment for Parkinson’s Narcolepsy

Our case-subject noticed mild bedtime illness-symptoms around 1980 or 1985. Jerking-leg symptoms were reported to a physician for the first time in 2001. It was originally diagnosed as a reaction to taking Benadryl at bedtime. Narcolepsy was reported for the first time six

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months later. It was originally diagnosed as “probably Vasovagal Syncope”. The illness was diagnosed as Restless Leg Syndrome (RLS) in 2005. Medical treatment started with Ropinirole in 2005, initiating traditional Dopamine Replacement Therapy (DRT) that typically begins with a Dopamine agonist such as Ropinirole or Pramipexole. Carb-Levo is typically added later when the initial agonist is no longer sufficient. This controls motor symptoms but our case-subject also reported Narcolepsy. DRT typically worsens Narcolepsy and his Narcolepsy became worse.

Our case-subject’s Narcolepsy was originally diagnosed in 2001 as “probably Vasovagal Syncope” although the Physician found no heart irregularities and did not seek any cardiac tests. The Physician did not consider the possibility of a Dopamine-deficient Narcolepsy because it was four years prior to the diagnosis and Dopamine-treatment of RLS. Narcolepsy is typically categorized as a sleep disorder. Sleep disorders are fairly common with Parkinson’s. A 2017 study reported that sleep disorders affect 64% of people with Parkinson’s and 78% of those with complicated Parkinson’s [13]. The study said sleep disorders are the second most frequent complaint among people with Parkinson’s. It said 21% (2.1 million) are affected by Narcolepsy, also known as Excessive Daytime Sleepiness (EDS). The study said Sleep Studies cannot detect Parkinson’s Narcolepsy because it is a “neurotransmitter deficiency”. The deficient neurotransmitter was Dopamine. A 2013 study¹⁴ and another 2017 study said Sleep Study test-retest reliability was poor for this kind of Narcolepsy [15]. Although Narcolepsy is typically categorized as a Sleep Disorder, Parkinson’s Narcolepsy and ADHD Narcolepsy are Dopamine deficiency disorders, not Sleep Disorders per se. RLS is also categorized as a sleep disorder and has a 5-10% USA-prevalence [16]. Conversely, our case-subject’s illness progressed to a rare form of severe Parkinsonism with a prevalence of 0.0000003% or three people per 10 million.

The 2017 study investigated the effects of Methylphenidate on Parkinson’s Disease Narcolepsy for three months [13]. Doses per day were determined by body-weight at 1 mg/kg, approximately 60 mg that was administered as 20 mg three times per day. Each subject’s routine Carb-Levo was administered at bedtime. Methylphenidate started each morning and replaced daytime Carb-Levo. This relieved Narcolepsy “sleep attacks” and fatigue and improved motor symptoms, particularly gait, for patients with advanced PD. The authors reviewed previous EDS studies that used other “stimulants”, Modafinil and Sodium Oxybate. Some studies showed reduced EDS but others did not. The 2017 authors concluded that only Methylphenidate influenced motor symptoms and consistently reduced EDS. The 2017 study discussed our case-subject’s form of Dopamine-deficient Narcolepsy that he also observed in some of his ADD/ADHD patients. The 2017 findings matched what our case-subject found in 2014.

Methylphenidate strengthens neural tissue and AntiParkinsonians damage neural tissue

Biochemistry investigations of the relationship between Dopamine and Parkinson's found there is a greater amount of Dopamine depletion in the dorsal striatum than in the ventral striatum whereby amounts of Dopamine Replacement Therapy needed to control dorsal striatum motor symptoms apply excessive amounts of Dopamine Replacement to the ventral striatum causing a Dopamine overload that impairs cognition and worsens Narcoleptic sleep attacks (Narcolepsy) [17,18]. There is a vexing conundrum in traditional Dopamine Replacement Therapy that (1) stabilizing the dorsal striatum overdoses the more sensitive ventral striatum and (2) reducing Dopamine Replacement medications so to not overdose the ventral striatum provides too little Dopamine to stabilize the dorsal striatum. This is the primary reason why treating increasing motor symptoms with increasing amounts of AntiParkinsonians causes increasing levels of AntiParkinsonian adverse effects.

Lists of adverse effects of AntiParkinsonians that were previously provided in this study showed many results of the imbalance of dorsal versus ventral sensitivity to DRT. Methylphenidate has a different biochemical interaction with Dopamine receptors wherein ventral receptors do not become overwhelmed in order to achieve better functions in dorsal receptors. The difference of biochemical interactions of Methylphenidate compared to AntiParkinsonians has not been adequately delineated in previous studies. The differences of Methylphenidate vs. AntiParkinsonians in dorsal vs ventral sensitivity are key topics. The biochemical differences of Methylphenidate vs. AntiParkinsonians also go beyond that. Another difference is that Carb-Levo augmentation damages and destroys Dopamine systems neural tissues whereas a 2008 study showed Methylphenidate strengthens and protects Dopamine system neural tissues [19]. Augmentation from Carb-Levo accelerates the inherent progression of Parkinson's illnesses. Tissue strengthening from Methylphenidate slows the progression of Parkinson's illnesses. The 2008 study found Methylphenidate sustains the amount of Dopamine (DA) that is available for brain receptors to occupy significant percentages of transporter cells that DA would otherwise occupy while being transported away from the brain.

By analogy, Methylphenidate is like bus passengers who fill over 50% of the seats on the morning bus, preventing most of the people waiting at bus stops from getting in. Without riding the bus those people can't leave their neighborhoods. DA receptors in the brain are like neighborhood cafes where the stranded people go to buy food and drinks. They provide income that keeps the receptors-cafes active and open for business. By occupying a significant percent of Dopamine transporters, Methylphenidate prevents a significant percent of DA from being taken away from the brain.

The 2008 study stated that by inhibiting Dopamine Transporters, Methylphenidate increases Dopamine concentrations in the brain that manifests as prolonged and/or intensified postsynaptic DA signals. In other words significant amounts of DA were unable to exit the brain so pools formed that were mostly in the same locations as many DA receptors. The

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pools of DA bind to and activated those receptors. The 2008 authors often expressed conjectures and possibilities rather than findings and empirical observations. Some statements that might be important were written as “maybes”, such as: “At therapeutic doses of 0.3-0.6 mg/kg, orally administered Methylphenidate may actually bind to and occupy more than half of the DAT in the human brain.” For a 150-pound person this was 20-40 mgs. For 120-pounds it was 16-32 mgs. For a 190-pound person it was 26-52 mgs.

The syntax, math and almost everything were so vague as to seem essentially meaningless but in order to properly analyze the contents of the article it is important to bear in mind that the study was authored in 2008 at a time when biases against Methylphenidate were expected and Methylphenidate was vilified by the Neurology Research and Clinical Communities. This article was a bit unusual for 2008 in that it made several positive points about Methylphenidate without asserting overriding negative points. That approach could cause problems for researchers at that time such as difficulties with research sabotage that Nutt et al. encountered in 2007. The authors of the 2008 study avoided an appearance of praising Methylphenidate by presenting Methylphenidate in the context of Methamphetamine drug abuse and by giving Parkinson’s neural tissue strengthening a secondary position. By balancing an article analysis with that perspective, one can recognize that the authors were bold in addressing Methylphenidate in treatment doses up to 52 mgs. One can also see that the too-vague article was interspersed with apparent statements of fact that were drawn from the writings of other researchers but were written as vague “maybes” by the 2008-article authors. This author removed the unnecessary vagueness and paraphrased some of those statements as follows:

1. Abnormal cytoplasmic DA accumulation contributes to the development of Parkinson’s disease. a) Methylphenidate-induced increases in vesicular DA sequestration attenuate the disease’s progression. b) Researchers found Methylphenidate 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.
2. These Methylphenidate-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, Methylphenidate redistributes DA within the striatum from the cytoplasm and into the vesicles. c) As a consequence of increased vesicular DA sequestration and DA content, Methylphenidate 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) Methylphenidate 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.

Methylphenidate has the ability to provide neuroprotection against Methamphetamine-induced neurotoxicity and perhaps Parkinson’s disease through possible mechanisms involving direct

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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.

A 2016 study praised Methylphenidate as a potential future 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 (Selegiline and Rasagiline); Amantadine; L-Threo-3,4-Dihydroxyphenylserine; Botulinum Toxin; Bilateral subthalamic 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 [20].

The 2016 authors wrote about a 2009 to 2011 research project in France that studied Methylphenidate as a treatment for FoG [21]. 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-AntiParkinsonians including optimized-Carb-Levo. All subjects also were receiving subthalamic 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 1 mg/kg Methylphenidate per day for 90 days. Efficacy-outcomes were measured at day-90. Subjects in the Methylphenidate group showed significant improvements of PD-FoG and gait hypokinesia. The French authors reported "significantly more adverse events in the Methylphenidate 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 Methylphenidate "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 noradrenergic synapse activity. In such manners, Methylphenidate improvements in FoG came from increased synaptic Dopamine activity and possibly from increased noradrenergic activity. Spectrum Analysis showed a decreased density of striatal Dopamine transporters where to Methylphenidate limited the production of new transporters. Synaptic Dopamine was retained and increased through (1) high Methylphenidate occupation

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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 Methylphenidate being rated as one of only three effective FoG treatments and also led to Methylphenidate being commended as a future treatment for Parkinson's [20].

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 Methylphenidate facilitates natural Dopamine that is differentially absorbed by dorsal vs. ventral receptors. Methylphenidate has immediate and short-term advantages over AntiParkinsonians by stabilizing dorsal receptors without overloading ventral receptors. Methylphenidate has long-term advantages over AntiParkinsonians by slowing the progression of Parkinson's through strengthening neural tissues.

Calculating Methylphenidate dose amounts for Parkinson's treatment

The primary mechanism of Methylphenidate 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" [22]. 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)" [23]. Methylphenidate effects on DAT, NET and AntiParkinsonians. When Methylphenidate is administered in sufficient amounts with AntiParkinsonians it alters (increases) the neural interactions of AntiParkinsonians. When Methylphenidate is administered in sufficient amounts without AntiParkinsonians it retains a supply of naturally produced Dopamine that does not expose dorsal and ventral receptors to Dopamine added by Carb-Levo.

Perhaps the greatest challenge for Parkinson's treatment is the dose-amounts of medications. AntiParkinsonian 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, AntiParkinsonian 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 Methylphenidate not being seen as an option. In 2016 a shift toward awareness of Methylphenidate became noticeable as seen in the 2016 article above and in a 2017 Parkinson's Foundation guideline that said Methylphenidate improves alertness [24].

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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 Methylphenidate for treating PD was the same amount used for treating adult ADHD. Mayo said it is safe to break the 60 mg limit and the 2016 authors said Methylphenidate 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 Methylphenidate 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 of Methylphenidate depend solely on patient-reports of results. For example, four nations, including the United States, did not give specific limits. They said Methylphenidate should be individually titrated for optimal effectiveness [25]. Recommended limits of Methylphenidate sometimes differentiate between what is told to the public and what is suggested for consideration by healthcare professionals for therapeutic purposes [26]. Our Case Study subject entered his weight into the healthcare professional's 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. Our case-subject's Methylphenidate for Parkinson's treatment was 105 mgs per day, very close to the off-label mgs of the healthcare professional's calculator.

A review of seven published Methylphenidate-dosage guidelines found there was no consistency across guidelines. It is common knowledge that the FDA approved Ritalin/Methylphenidate up to 60 mg per day. Few people are aware that the FDA specifically approved 60 mg because the manufacturer provided approval research only up to 60 mg. The manufacturer wanted quick FDA-approval so they could start making sales and profits. Therefore they didn't spend time or money doing research above 60 mg. The 60 mg limit didn't come from research or concerns for safety. It came about because the manufacturer was too cheap to do research beyond 60 mg. Subsequent research showed Methylphenidate 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 [27]. Regardless that this was a team of executives from the manufacturer of Ritalin this was the same article that was mentioned above that presented a list of international guidelines for Methylphenidate 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 Methylphenidate patient care.

Under that philosophy, a clinician who wishes to provide Methylphenidate 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 Methylphenidate 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 Methylphenidate treatment of ADHD, Narcolepsy, or Parkinson's. The above review of published Methylphenidate 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 of frequencies because there was no reliable consistency among recommendations 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 Methylphenidate 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 case-subject 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 Methylphenidate and their accustomed AntiParkinsonians 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 our case-subject found to be most best: (1) Methylphenidate 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 for 16 hours through the day and evening. The FDA approved Adhansia XR to provide 16-hour efficacy but our case-subject's regimen provides smoother and more consistent efficacy than Adhansia XR. The use of AntiParkinsonians at bedtime for sleep is necessary for Parkinson's patients. At bedtime our case-subject used two tabs of Pramipexole 0.25 mg, two tabs of Carb-Levo 10/100 and two tabs of Carb-Levo ER 25/100. Our case-subject found the combination of daytime Methylphenidate and bedtime APs worked well and worked much better than 24

hours of taking only APs. This means that diurnal Methylphenidate can replace diurnal AntiParkinsonians very effectively and with 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 our case-subject achieving his optimal Methylphenidate regimen, he used the same regimen for two years. Whereas before Methylphenidate, his AntiParkinsonian regimen increased every year eight times, notably going from 112 mg per day to 1,621.25 mg per day (Fig. 1).

Methylphenidate needs to be taken every three hours

Published research and guidelines say the initial effects of Methylphenidate IR are clearly noticeable in 45 minutes after intake and functional full efficacy is present at 60 minutes. The Ritalin LA product monograph²⁷ shows the serum concentration of IR 20 mg is 5 ng/mL at 45 minutes and 9 ng/mL at 60-minutes (Fig. 5). Thereby, according to the manufacturer's Ritalin LA monograph, 5 ng/mL is at the low-end of an efficacy threshold range and 9 ng/mL is the efficacy threshold.

Research studies state their doses and frequencies of Methylphenidate but the 4-hour schedule is so universally accepted that the time between doses is not always specified. Guidelines follow Methylphenidate product monographs in stating Methylphenidate is "usually taken 2 to 3 times per day" but the time between doses is not specified. This author came across only one guideline, an NHS UK website with two pages that gave a time: "Leave at least 4 hours between doses." No explanation of the time was provided [28,29].

Our Case Study subject followed a 4-hour dosing schedule when he started his experiments with Methylphenidate Parkinson's therapy. He was familiar with the 4-hour schedule from working with ADD/ADHD patients at his clinic. His patients sometimes expressed concern about fluctuations of efficacy. Everyone, including patients and practitioners, was taught that the fluctuations were normal. During his Parkinson's experiments our case-subject saw that the fluctuations impacted him more severely than his ADD/ADHD patients. His patients' ADD/ADHD surfaced during fluctuations but (1) they were accustomed to ADD/ADHD and (2) they could largely control it during fluctuations by using skills they learned in therapy with our case-subject.

The traditional 4-hour guidelines were intended for traditional uses of Methylphenidate. The traditional guidelines did not work for our case-subject who was doing something that no one had done before. The "normal" fluctuations impacted him much more severely than his patients. Fluctuations brought severe and uncontrollable Parkinson's symptoms that he was determined to defeat. He was doing experimental research that entailed analytic empirical methodology rather than adherence to established guidelines. Analytic empiricism began with a realization that his patients' fluctuations were "normal" only within an *a priori* 4-hour

schedule. By empirical observation he found Methylphenidate began losing effect at hour-3 then gradually diminished and terminated between hour-3.5 and hour-4. He observed that his illness symptoms surfaced around 20 minutes after post-intake hour-3. His symptoms were severe by hour-3.5. By hour-4 they oftentimes could not be stopped for several hours.

A previous section of this study mentioned that our case-subject discovered the optimal amount of Methylphenidate for treating Parkinson's symptoms. During the process of making that discovery he observed that each dose of Methylphenidate takes about 45 minutes to reach noticeable efficacy. He also observed that the efficacy of a dose started fading at hour-3 and took about 45 minutes to reach termination. Hypothetically if a new dose were taken when the old dose started to fade, the gradual increase from one and the gradual loss from the other would occur at the same time. The new dose and the previous dose would combine and add together into a plasma concentration that would not go up or down. The unchanging plasma concentration would produce unchanging efficacy. Our case-subject experimented with taking each new dose at the 3-hour mark and found the efficacy-fluctuations stopped. By discovering the therapeutic dose amount and by conceiving and proving the unprecedented 3-hour-Methylphenidate schedule, our case-subject's Methylphenidate-for-Parkinson's experiments became an all-around success.

Research consistently shows Methylphenidate plasma concentration reaches C_{max} at hour-2. Methylphenidate literature consistently says initial efficacy becomes noticeable at 20 to 30 or up to 45 minutes and functional full efficacy occurs at 60 minutes [29,30]. Our case-subject agreed with the literature. He observed that significant initial efficacy became noticeable at about 45-minutes and full efficacy seemed to be present at about 60 minutes. Those are the times that Methylphenidate reaches a threshold of therapeutic efficacy. Figure 5E below shows plasma concentrations of 5 ng/mL at 45-minutes and 9 ng/mL at 60 minutes. According to the data in Fig. 5, those plasma concentrations are the threshold range of efficacy (5 to 9 ng/mL) and 9 ng/mL is the efficacy-threshold.

Our case-subject discovered several things about Methylphenidate that no one is known to have noticed or reported before. To the best knowledge of this author this is the first study to present those discoveries. One thing our subject discovered was the mirror image slopes of dose-onset and dose-termination. He found a meaningfulness hidden in the mirror images when he overlaid a 1-hour slope of onset onto a 1-hour slope of termination. He discovered that the 1-hour slopes intersected at the 30-minute point. This led to a discovery that the 1-hour onset of a Methylphenidate dose could safely occur during the 1-hour termination of a preceding Methylphenidate dose. This confirmed and validated our case-subject's hypotheses and observations of 3-hour dosing that were described above. Three-hour Methylphenidate dosing is analogous to a leaky water bucket. A water bucket that has a hole leaks water at a steady rate. The amount of water in the bucket remains constant if water is poured into the bucket at the same rate that it leaks out.

Immediate Release Methylphenidate gradually loses efficacy across an hour starting at hour-3 until hour-4. A tablet of Methylphenidate IR reaches full efficacy across an hour after intake.

Townsend RW | Volume 2; Issue 3 (2022) | JNOR-2(3)-006 | Case Report

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A new dose is absorbed at the same rate that a previous dose dissipates. In the leaky-bucket analogy water (Methylphenidate from a new dose) pours into the bucket (the bloodstream) at the same pace that it leaks out (the pace that a previous dose dissipates). By ingesting doses at three hours intervals, plasma concentration remains constant during transitions between doses. Smooth transitions between doses require a 3-hour schedule. Methylphenidate levels diminished significantly during transitions between doses in each of dozens of reviewed 4-hour studies that are exemplified in Fig. 3,9.

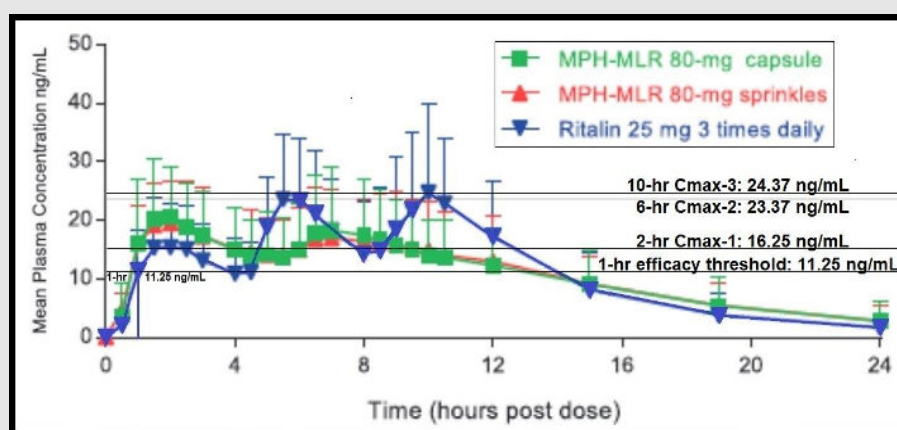


Figure 3: Plasma concentrations from 25 mg t.i.d. on a 4-hour schedule [30].

Plasma levels of MPH-Ritalin 25 mg t.i.d. on a 4-hour schedule. The hour-1 efficacy threshold (11.25 ng/mL) was the same as in 25 mg t.i.d. Figure 4. Cmax levels were similar to Fig. 4 (Fig. 5). 4-hour Fig. 3 had greater drops of MPH levels during dose-transitions than Fig. 4 (Fig. 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 of 3-hour dosing 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 six research studies and product monographs that were typical examples of more than 410 reviewed publications. Simulations of 3-hour schedules show Methylphenidate blood levels and graph curves that were moved from hours 4 and 8 to hours 3 and 6.

This author could not find any studies that administered Methylphenidate every three hours. He found one study from 2002 that administered Methylphenidate three hours after a first dose; however a third dose was given four hours later [31]. The study combined 3 and 4 hour schedules. It used a 3 hour schedule followed by a 4-hour schedule. Six hours between the first dose and three hours after the second dose constituted a 3-hour b.i.d. schedule. It was the sole published empirical data from 3-hour scheduling. This study used the 2002 data to analyze the 3-hour schedules that are simulated in Fig. 4-6,8,9. Data from the combined 3- and 4-hour

schedule is presented in Fig. 4. Fig. 4 separates the 3-hour b.i.d. schedule from the ensuing 4-hour schedule. Fig.4 uses data from 4 to simulate a 3-hour t.i.d. schedule.

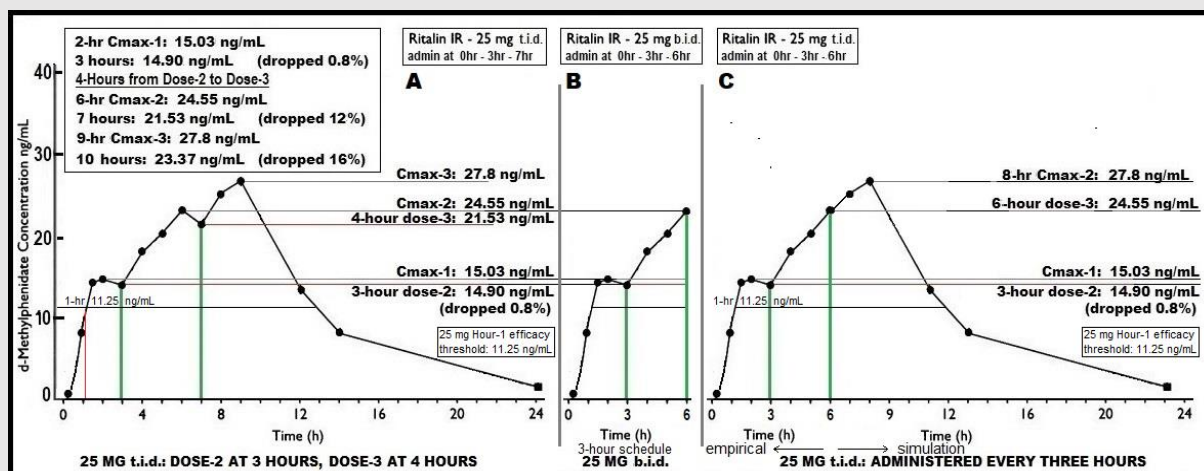


Figure 4: 4A is 25 mg t.i.d. with dose-2 at hour-3 and dose-3 at hour-7. 4B isolates the 3-hour schedule in hours-0 to -6. 4C simulates dose-3 at hour-6 [31].

Fig. 4A 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. Fig. 4B isolates hours-0 to -6 as a b.i.d. 3-hour dosing schedule. Fig. 4C uses data from 4A and 4B to simulate a t.i.d. 3-hour schedule by moving dose-3 from hour-7 to hour-6.

The 3-hour schedule in Fig. 4 had a 0.8% decrease of Methylphenidate 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 in Fig. 4 yielded no decrease between doses. The different Methylphenidate level-drops in 3- and 4-hour-dosing are further demonstrated in Fig. 5.

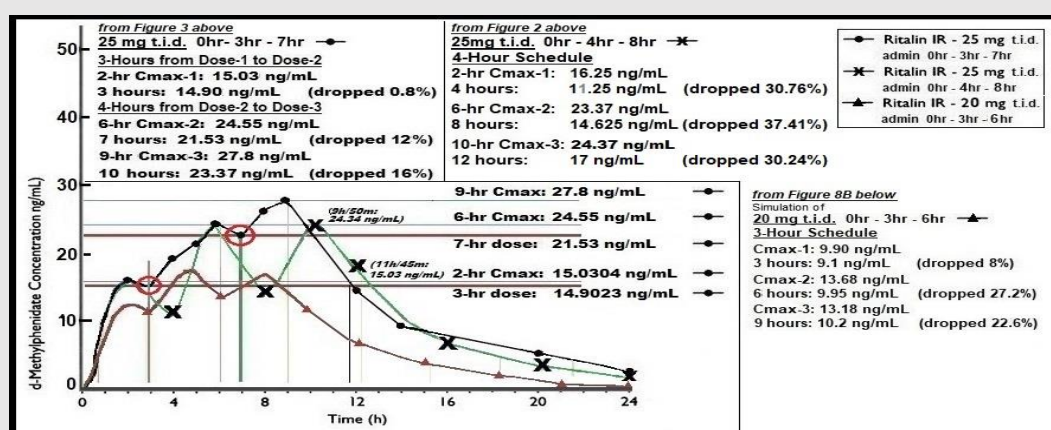


Figure 5: The 25 mg mixed schedule from Figure 4A is overlaid with a 25 mg 4-hour schedule from Figure 3 and a 20 mg simulated 3-hour schedule from Fig. 7.

The 0.8% and 12% plasma level drops in Fig. 4 are circled in red. They were significantly less than the 30.76% and 37.41% drops in the overlaid Fig. 2 25 mg t.i.d. 4-hour schedule [32]. The overlaid Fig. 8 20 mg 3-hour simulation reflected the lesser drop in the 3-hour schedule of Fig. 4 (8% - 0.8%) and had lesser drops than the overlaid Fig. 2 4-hour schedule (8% - 30.76%, 27.2% - 37.41%, 22.6% - 30.24%) and had lesser drops than the 4-hour schedules of Fig. 6 through 9 below.

The mixed-schedule of Fig. 4A is overlaid in Fig.5 with a 25 mg t.i.d. 4-hour schedule from Fig. 3 and a simulated 20 mg t.i.d. 3-hour schedule from Fig. 8 below [30]. Fig. 4 and 5 provide reference points for comparing 3-hour dosing to 4-hour dosing (Fig. 6 through 9). Plasma concentration in Fig. 4 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 Fig. 8B. The drops were similar to Fig. 6F and 8B in that all of the drops stayed above a 9 ng/mL efficacy threshold. Those drops were unlike the 4-hour schedule of Fig. 6C and 6E that show the Methylphenidate level dropped below full efficacy for an hour and 45-minutes.

The 12% drop after C_{max}-2 in Fig. 4 was considerably less than the 37.5% drop in the 4 hour schedule of Fig. 7 and Fig. 8A. Administering dose 2 at 3 hour in Fig. 4 kept Methylphenidate at a steadier level at hour 7, allowing the third dose at hour-7 to maintain a smoother dose-2 to -3 transition. That steadier-level effect translated to a zero drop after C_{max}-2 in the simulated 3-hour schedule in Fig. 4. 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 Methylphenidate 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-active Methylphenidate 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 occurred in Fig. 6-9.

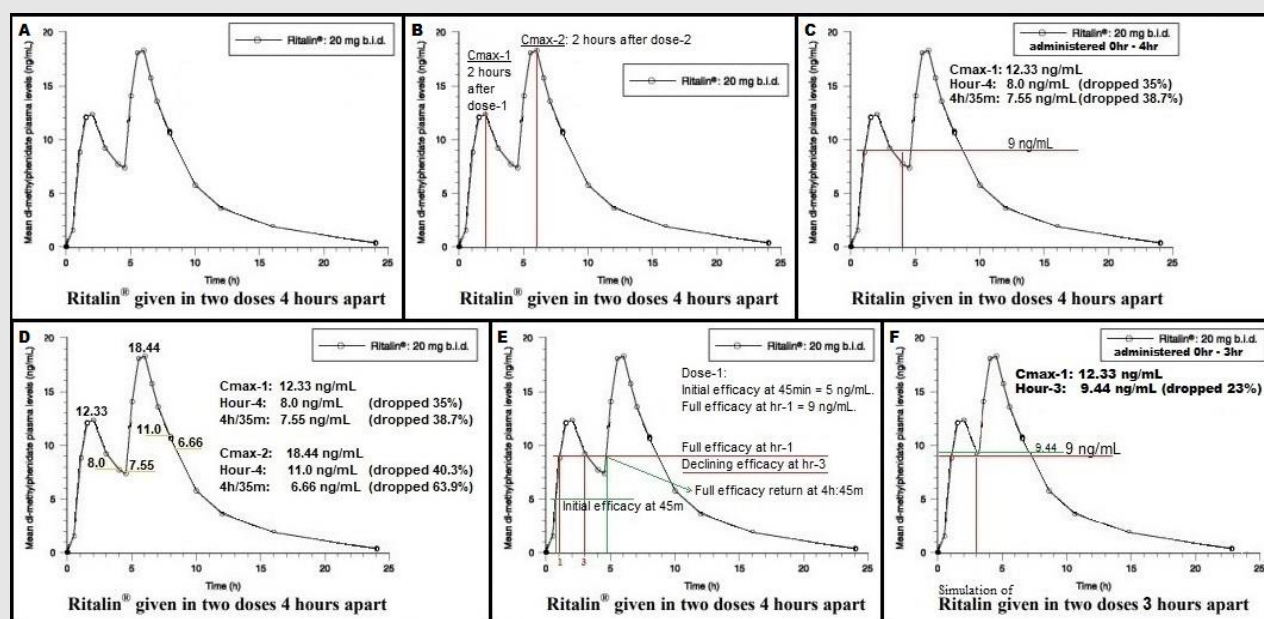


Figure 6: Plasma levels of an MPH 20 mg b.i.d. 4-hour schedule are shown in Fig. 6A through 6E. A 3-hour schedule is simulated in 6F [27].

Fig. 6A-E depict a MPH 20 mg b.i.d. plasma level with a 4-hour schedule. Fig. 6F simulates a 3-hour schedule by moving dose-2 to hour-3 from hour-4. Fig. 6 is adapted from the Ritalin LA product monograph [28].

Plasma level at hour-1 is labeled as full efficacy at 9 ng/mL in Fig. 6C and 6E. Cmax-1 at hour-2 is 12.33 ng/mL in Fig. 6C and 6D. Plasma level declines below full efficacy a few minutes after hour-3 in Fig. 6C and 6D. At hour-4 the level drops to 8.0 ng/mL in Fig. 6D. 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 Fig. 6E. Dosing at hour-3 (as simulated in Fig. 6F) markedly reduces plasma level drops during the transition between doses. Fig. 6F shows a 23% decline that is 40% less than the 4-hour schedule decline of 38.7% in Fig. 6C and 6D.

There are marked inconsistencies regarding plasma levels and level-fluctuations across studies and across product monographs. For example there are significant differences between Figure 6 (adapted from the Ritalin LA monograph) and Fig. 7 (adapted from the Adhansia XR monograph) [28,7]. Cmax-1 is 12.33 in Figure 6C vs 10 in Fig. 7 (18.9% difference). Cmax-2 is 18.44 in Fig. 6D vs 13.9 in Fig. 7 (a 24.6% difference). The total difference of 43.5% is typical of the variance across studies and monographs.

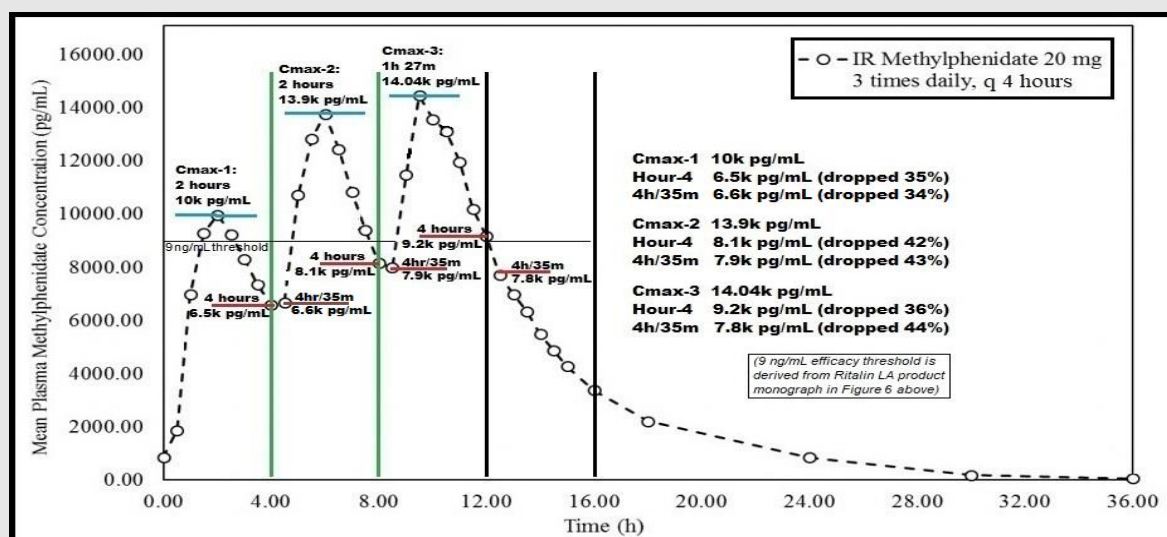


Figure 7: MPH 20 mg t.i.d. plasma concentrations measured in pg/mL (1000 or 1k pg/mL = 1 ng/mL. 13,900 or 13.9k pg/mL = 13.9 ng/mL) [9].

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

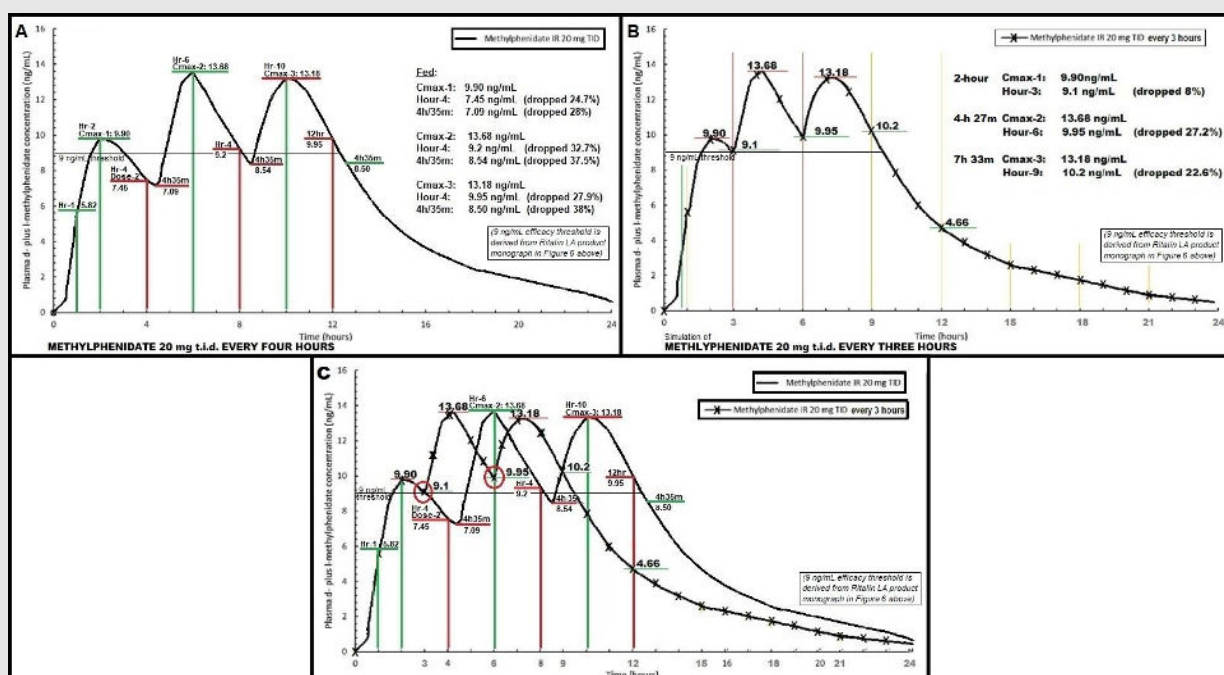


Figure 8: 8A is a 20 mg t.i.d. 4-hour dosing schedule. 8B simulates a 3-hour schedule by moving dose-2 to hour-3 and dose-3 to hour-6. 8C overlays 8B onto 8A with red circles highlighting the lesser drops of MPH plasma levels in 3hr 8B [31].

The simulated 3-hour schedule in 8B differs markedly from the 4-hour schedule in 8A. 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 8B vs 28% in 8A and 27.2% in 8B vs 37.5% in 8A. The 3-hour schedule in 8B averages 30.3% less drop in plasma levels than the 4-hour schedule in 8A. Fig. 8C overlays 8A with a transparency of 8B and the 3-hour schedule lesser drops of plasma levels are circled in red for easy comparison to the larger drops under 4-hour dosing. Figure 8 is adapted from a study by Katzman, Mattingly, et al. [29].

Published Methylphenidate 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. Fig. 9 is an example of this quandary. 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. Fig. 9B depicts a simulated 3-hour schedule derived from Fig. 9A. The drops of plasma levels in 9B during transitions between doses were less than in 9A.

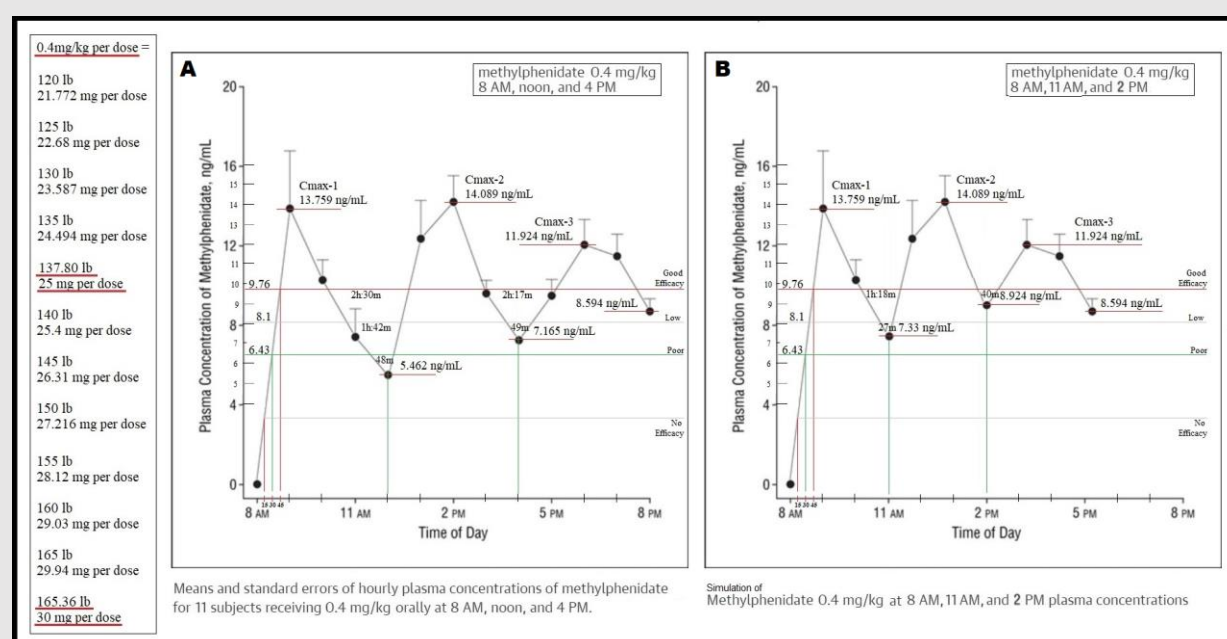


Figure 9: 0.4 mg/kg t.i.d. with 4-hour (left) and 3-hour (right) schedules. A legend of dose-amounts from mgs per body weight is shown on the far left [12].

Fig. 8A depicts plasma concentration of 0.4 mg/kg t.i.d. on a 4-hour schedule. Fig. 8B simulates a 3-hour schedule by moving dose-2 to 11am. By moving dose-3 to 2pm. Fig. 8 is adapted from a study by Nutt, et al. [12].

The simulated 3-hour dosing in Fig. 9 totalled 26.1% less drop during dose-transitions than in the 4-hour dosing of Fig. 9A. Transition-drops in Fig. 9 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 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 (Fig. 6) the 4-hour schedule in Fig. 9 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.

Fig. 4 showed a 0.8% level-drop under an empirical 3-hour schedule. 4-hour schedules (Fig. 6-9) averaged drops of 41%. They were 51-times greater (ranging from 30-times to 79.8-times greater) than the 3-hour schedule. 0.8% in Fig. 4 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 original 4-hour schedules. The differences are validated by our case-subject’s empirical experiences and reliable observations. They are also validated by empirical 3-hour data from hours-0 to -6 in Fig. 4.

The figures in this study simplify concepts that no one thought of before. Our case-subject 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 and are not possible under the 66-year tradition of *á priori* 4-hour MPH dosing. The *á priori* 4-hour schedule is a false premise, a false independent variable that has been used in all MPH research since the manufacturer’s original application-research for FDA approval in 1955.

Inconsistent findings in studies that used 4-hour dosing

Plasma concentrations from 20 mg doses on 4-hour schedules were reported in Fig. 6-8. There were marked differences across reports: Cmax-1 was 12.33, 10 and 9.9 in Fig. 6-8. Cmax-2 was 18.44, 13.9 and 13.68 in Fig. 6-8. Cmax-3 was 14.0 and 13.18 in Fig. 7,8. Treatment of Parkinson's with MPH proved to be beneficial in several studies but proof failed to lead to clinical uses. The failure was largely due to a 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.³³ 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" [34].

Unfortunately the anti-Methylphenidate 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, they 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 Methylphenidate 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 researchers reinforced the stigma was by giving their Parkinson's articles titles that carried negative connotations. For example a 2007 study was titled "Improvement of gait by chronic, high doses of methylphenidate" [35,36]. Placing "methylphenidate" beside "chronic" and "high dose" conveyed chronic high-dose abuse of Methylphenidate. The authors might claim "high dose" and "chronic" were technical terms but the study did not use "high doses". It used a common amount for adult ADHD (20 mgs three times per day). The study did not include "chronic" use. It ended after only 90 days.

Due to false negative connotations in article titles and 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 has a slow onset of 30 to 60 minutes and a slow termination of 30 to 60 minutes. This makes Methylphenidate non-addictive and research shows that adults do not abuse prescribed Methylphenidate.

Research demonstrated that Methylphenidate is safe and effective and it doesn't cause the serious difficulties of APs. However positive research findings failed to overcome clinicians' anti-Methylphenidate stigma. The failure was partly due to (a) authors who shared the stigma. They disguised and tainted positive results by giving studies titles such as the 2007 title above that conveyed the stigma. The failure to overcome clinicians' anti-Methylphenidate stigma was also partly due to (b) research findings that were inconsistent from one study to another even when the findings were positive. Inconsistent efficacy scores across studies came from a 4-hour Methylphenidate dosing schedule that is discussed below. The failure to overcome clinicians' anti-Methylphenidate stigma was also partly due to (c) practitioners' fears that their patients would abuse and become addicted to Methylphenidate. Such fears associate Methylphenidate with cocaine and street-amphetamines. Research proved there are no scientific foundations to those fears but practitioners will not be convinced until safety findings are consistent across studies. Safety findings were positive but outcome scores were not consistent across studies. Inconsistent safety scores across studies came from a 4-hour Methylphenidate dosing schedule that is discussed below.

Previous Neurology research of Methylphenidate used short-term (90 days or less) inpatient studies that co-administered Methylphenidate with other medications and/or with other treatments and administered Methylphenidate on a 4-hour schedule. The brief time frames could not reliably predict the effects of long-term treatment. Furthermore, the studies were conducted in facilities where participants were knowingly subjected to frequent observations. The studies were not valid facsimiles of real-life. Those flaws in research-designs compounded an underlying problem that 4-hour scheduling inherently gives inaccurate, inconsistent and non-valid results.

4-hour scheduling caused significant periods of low efficacy during transitions between doses. Dose-termination efficacy continuously diminished for 60 minutes starting at hour-3. When a next dose was ingested at hour-4, efficacy continued diminishing for another 35 minutes. Low efficacy continued for another 15 to 30 minutes during the 45 to 60 minute gradual onset of the second dose. This totalled up to 200 minutes of diminished efficacy during the termination of one dose until the next dose reached full efficacy. The efficacy-gap occurred again when there was a dose-3 and again when there was a dose 4 and again when there was a dose 5. The multiple fluctuations of efficacy happened every few hours of every day under a 4-hour dosing schedule.

Historically every Methylphenidate research-design used 4-hour dosing as an independent variable. The pattern adhered to a longstanding precedent of unknown origin that was inaccurately defined as “4-hour-Methylphenidate”. The manufacturer of Ritalin never said “administer every 4 hours”. The product monograph said, “Administer in divided doses 2 or 3 times daily”. Having no authoritative or empirical rationale, the *á priori* “4-hour” premise was a false assumption, not an empirical observation. It was not valid. The premise was a false *á priori* that was used as an independent variable across all Methylphenidate research for 67 years. By using the *á priori* false premise, all Methylphenidate research used a false independent variable. By using the false independent variable, 67 years of Methylphenidate research gave non-valid results. Authors' statements of statistical significance were meaningless. Statistical significance was moot without a valid independent variable. “Double-blind” designs also were meaningless and moot without a valid independent variable.

This was one of many reasons why Neurology research did not trigger clinical applications of Methylphenidate. For example, the above-mentioned 2007 study of Methylphenidate (1) reported beneficial results, (2) the double blind design was well constructed, (3) the doses were large enough to be effective, (4) the findings were “statistically significant” but the results were not valid because 4-hour dosing caused inaccurate test scores. In order for Methylphenidate-use to be a valid independent variable, the doses must be administered every three hours. 3-hour dosing maintains constant efficacy that does not start anew with each sequential dose (see Fig. 3A). Under 3-hour dosing, dependent variables are always measured during full efficacy. Under 4-hour dosing, dependent variables are often measured during long periods of diminished efficacy during transitions between doses (Fig. 9).

Neurology studies of Methylphenidate always adhered to the *á priori* 4-hour precedent that was set by previous authors and journal Editors who were unaware that the 4-hour independent variable was not valid. Science journals published research studies that used the non-valid independent variable and the non-valid variable became the standardized norm. In reviewing more than 410 items for this study, this author found only one article that partially approached dose-frequency empirically (Fig. 3). All other MPH studies adhered to the 4-hour schedule and incorporated the *á priori* false premise.

The rules of formal Logic say conclusions derived from false premises are false conclusions. The fallacy of the 4-hour schedule caused decades of inconsistent reports across studies and across product monographs. The persistent inconsistencies show that the results of the studies are incorrect. The inconsistencies are identified throughout this study. The inconsistencies were so persistent that this study inadvertently became a meta-analysis of nearly 70 years of flawed methodology and inaccurate findings.

Results

An important finding of this research study is the discovery of the 3-hour schedule for Methylphenidate. A clinical value of the 3-hour schedule is that it provides patients with

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continuous efficacy during transitions between doses. This also enables research to measure dependent variables during full efficacy rather than during diminished efficacy in transitions between doses in the 4-hour schedule. Flawed research and flawed clinical practice regarding Methylphenidate cannot improve until researchers and clinicians stop using the non-valid 4-hour schedule. The 3-hour schedule provides the primary means to accurate research findings and clinical success.

The primary finding of this research study is that diurnal Methylphenidate monotherapy for Parkinson's is more effective and safe than Dopamine Replacement Therapy with AntiParkinsonians such as Carbidopa-Levodopa, Pramipexole and Ropinirole. It is safer because it does not cause the adverse effects of excessive grogginess, sudden passing out, diminished cognition and augmentation. Methylphenidate sustains wakefulness, alertness and cognitive clarity. It also strengthens and protects neural tissues and neural systems, especially Dopamine systems. Methylphenidate facilitates normal functioning, a normal lifestyle and a healthy quality of life while it controls involuntary motor symptoms and non-motor symptoms whereas AntiParkinsonians control involuntary motor symptoms at the expense of many non-motor symptoms, normal functioning and a healthy quality of life. For example Parkinson's disorders are prone to cause narcoleptic blackouts while driving vehicles. Rather than remedy Narcoleptic blackouts while driving, AntiParkinsonians cause and increase narcoleptic blackouts while driving. Methylphenidate resolves narcoleptic blackouts by sustaining wakefulness and alertness. It makes driving safe.

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, well-known and widely used Dopamine Agonist. As it did for the case-subject in this study, Methylphenidate can quickly end the severe disability that is common with advanced Parkinson's disorders and high-dose AntiParkinsonian medications.

Conclusion

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 the case-subject'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.

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To the best knowledge of this author this is the first study to present (1) Long-term use and outpatient use of Methylphenidate for Parkinson's. (2) A 3-hour dosing schedule for Methylphenidate. (3) 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 (a) slows the progression of Parkinson's and (b) protects and strengthens Dopamine systems and other neural tissues. This study showed Methylphenidate does not cause the serious and disabling adverse effects of AntiParkinsonians. This study pointed out dozens of warnings in AntiParkinsonian 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 AntiParkinsonians stopped the adverse effects of AntiParkinsonians. This study showed that a lower 20 mg amount of diurnal Methylphenidate monotherapy controlled Parkinson's symptoms when AntiParkinsonians were not taken.

Acknowledgement of Our Case-Subject

Our case-subject had an extremely severe form of Parkinsonism with an extremely rare population prevalence of 3 in ten million. There were no remedies that could help him when he became disabled.

Upon becoming disabled he was the world's first person to accomplish eight major scientific achievements:

1. By his own wits and intellect and with no contributions or guidance from Physicians or Neurologists, he was the first person to discover and develop the benefits of Methylphenidate for long-term outpatient treatment of Parkinson's disorders
2. He was the first person to conceive and implement Methylphenidate to counteract the adverse effects of AntiParkinsonians
3. He was the first person to overcome total disability of Parkinson's illness and high dose AntiParkinsonians
4. He was the first person to discern that the adverse effects of high dose AntiParkinsonians were so powerful that 30 milligrams of Methylphenidate could do nothing other than fight against their neural destruction
5. He was the first person to discern that the fight against the adverse effects of AntiParkinsonians completely absorbed the chemical structure of 30 mg Methylphenidate
6. He was the first person to discern that when no AntiParkinsonians were taken, the fight against Parkinson's symptoms completely absorbed the chemical structure of 20-25 mg Methylphenidate
7. He was the first person to discern that a 3-hour Methylphenidate dosing schedule sustained constant efficacy with constant therapeutic plasma concentrations,
8. as opposed to fluctuating efficacy and plasma concentrations under a traditional 4-hour schedule

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This report ends with an excerpt from a letter by our case-subject to an Attending Physician of a University Hospital Neuroscience Center. The Attending Physician became our case-subject's Neurology Specialist.

“In severe and very-severe cases, WED destroys every aspect of one's core Humanity. It removes voluntary control from every form of physical and cognitive functioning. It does not diminish one's Quality of Life. It destroys one's Quality of Life. It wreaks havoc from deep inside every contorting, spastic and writhing muscle; and from inside every electrocuting, flame searing and razor-knife flesh-and-bone cutting nerve. The person is consciously aware during constant seizures punctuated by sudden narcoleptic blackouts. Respiration is irregular. Jumping between shallow, gasping and brief stopping. Respiratory chaos contributes to a-rhythmic and un-patterned heartbeats that send spastic electric signals conducted by already overloaded autonomic nerve-networks. The fact that this disrupts sleep is mere collateral damage. Proper medications bring comforting healthy sleep but good sleep matters not to the daytime. Proper wakeful-hours' medication is the sole salvation to be had. The necessary high amounts of Traditional Dopamine Replacement Therapy blocked involuntary movements and nerve pain but at the expense of wakefulness and clarity of mind. Conversely, the same amount of Methylphenidate that is commonly used for ADD synchronizes normalcy and inner peace”.

Conflict of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the manuscript.

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