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Research Article

Methylphenidate Superior Efficacy Dosing Schedule: Three Hour Schedule for Immediate Release Tablets and Six Hour Schedule for Extended-Release Capsules

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Abstract

Background: Methylphenidate Hydrochloride is used mostly for treating Attention Deficit and Hyperactivity Disorder and Narcolepsy. It is available in Immediate Release tablets, liquids, extended-release doses, and transdermal patches. Clinicians instruct patients to take Immediate Release tablets four hours apart or eight to nine hours after an extended-release dose. Four-hour dosing has been used for decades while many patients complain of a "roller coaster" of symptoms stopping and returning several times each day. Four-hour dosing is inaccurate because Immediate Release tablets are effective for two to three hours.

Methods: The "roller coaster" was addressed with information from a 2014 to 2022 research program and from analyzing over 400 Dopamine deficiency articles.

Results: The four-hour Immediate Release schedule and the eight-to-nine-hour extended-release schedule are inaccurate for research and treatment. Four-hour dosing causes two hours of non-efficacy during transitions between doses. The eight-to-nine-hour schedule causes three to four hours of non-efficacy during transitions. Three-hour and six-hour schedules sustain efficacy across and between sequential doses.

Conclusion: Under four-hour dosing, soon after hour-three a patient's plasma concentration drops below and stays below the efficacy threshold for an hour and forty-five minutes. The loss of efficacy occurs during every transition from one dose to the next. Under four-hour dosing, patients who take four sequential doses experience 205 minutes of loss of efficacy every two hours three times every day, totaling 615 minutes per day. To the best knowledge of this author, he is the first person to find three-hour dosing stops the roller coaster. Efficacy occurs during transitions because dose-onset adds plasma concentration at the same rate that termination loses plasma concentration. Sequential doses taken at hour-3 combine into a level that stays above the efficacy threshold. When sequential doses are taken sometime after hour-3, the termination-dose drops below the efficacy-threshold and the sequential onset-dose does not create enough plasma concentration to bring a terminating plasma concentration to a higher level. Proper timing is critical for patients to receive high quality benefits of Methylphenidate. Three-hour dosing matches the biochemistry of Methylphenidate and enables high quality benefits.

Keywords: Dopamine; Methylphenidate; ADHD; Narcolepsy; Parkinson's; Efficacy Onset; Efficacy Decline; Efficacy Termination; Methylphenidate Serum Concentration; Methylphenidate Plasma Concentration

Abbreviations

ADD: Attention Deficit Disorder; ADHD: Attention Deficit and Hyperactivity Disorder; AP: AntiParkinsonian; DA: Dopamine Agonist; DPC: Decrease of Plasma Concentration DSC: Decrease of Serum Concentration; ER: Extended Release; IR: Immediate Release; IPC: Increase of Plasma Concentration; ISC: Increase of Serum Concentration; Mg: Milligrams; MPH: Methylphenidate. Qd: Once Per Day; BID: Two Times Per Day; TID: Three Times Per Day; QID: Four Times Per Day; X5qd: Five Times Per Day

Introduction

Methylphenidate (MPH) is available in Immediate Release (IR) tablets, liquids, Extended Release (ER) tablets and capsules, and epidermal patches. This article discusses the differences between the traditional four-hour MPH-IR administration schedule versus a newly discovered three-hour MPH-IR administration schedule and the differences between the traditional eight-to-nine-hour ER administration schedule versus a newly discovered six-hour ER administration schedule [1,2]. The differences do not alter side effects because proper uses of MPH rarely have noticeable side effects and if they occur, they are almost always minor. MPH is so safe that it is routinely prescribed to millions of children as young as 6 years [3].

For the past 67 years after the FDA approved MPH clinicians have instructed patients to take doses of MPH-IR four hours apart and to take an IR dose eight-to-nine-hours after an ER dose [4]. Clinicians and researchers have used the four-hour IR schedule since 1955. The effects of MPH are extended to longer periods of time by prescribing two or more sequential IR doses and/or an ER capsule or tablet. Manufacturers' product monographs say an IR dose lasts for three to four hours and an ER dose lasts for eight to nine hours [5]. Many patients report that sequential IR doses cause a "roller coaster" of efficacy that starts and stops then starts and stops again. Many patients report that ER efficacy is more consistent. Plasma concentration graphs confirm the "roller coaster" and the more consistent ER efficacy.

The "roller coaster effect" occurs for three reasons: (1) Product monographs say MPH-IR lasts for three to four hours. (2) Clinicians instruct patients to take a sequential IR dose when the previous dose wears off at hour-four (3) but the monographs say "three- to four-hours" not just "four hours". The four-hour IR dosing schedule is a 67-year tradition that is not accurate for clinical and research applications and is not accurate or best for patients due to the roller coaster effect. Many clinicians address the "roller coaster effect" by prescribing ER pills. However, ER pills do not solve the problem because ER pills take 1.5 to two hours to become effective and patients are told to take an IR tablet eight to nine hours after an ER pill but ER pills start losing efficacy at six hours.

Frequency instructions are given according to product monographs. Monographs are written by manufacturers' marketing experts. It is common practice for monographs to present a duration time without differentiating efficacy termination from termination of chemical structure. MPH monographs say "three-to-four-hour" duration without differentiating events that occur at hour-3 from events that occur at hour-4. The co-mingling of events gives an impression that the longer "four hours" is the duration and the shorter "three hours" is nebulous. The difference between events at hour-3 and hour-4 is not found in the written text. It is found by analyzing the plasma concentration graphs. Marketing experts capitalize on clinicians' non-analytic use of product monographs. Corporate marketing experts write misleading monographs because seemingly four-hour pills sell better than three-hour pills.

High volume sales are necessary in the 1.48-trillion-dollar pharmaceutics industry. Drug corporations often manipulate the FDA in the same manner. After approval of a medication the FDA publishes the same product monograph that the manufacturer uses. This disseminates marketing experts' misleading product information. FDA approval officially marks the information as trustworthy, authoritative, and valid. A drug corporation publicizes the information and clinicians receive and learn or store it. Clinicians don't analyze it. They are not trained in analysis and they believe FDA already analyzed it. Researchers extrapolate from the information but don't critically analyze it. Researchers don't want to contradict the drug corporation that developed the medication because the corporations fund the researchers. This process perpetuated the MPH roller coaster effect for 67 years. It is a reason for the lack of research into MPH four-hour and 8-to-9-hour schedules.

To the best knowledge of this author, he was the first to discover that the four-hour and 8-to-9-hour MPH dosing schedules and research constructs are inaccurate and not valid or reliable. To the best knowledge of this author, he was the first to design, conduct, and publish research using the 3-hour and the 6-hour MPH dosing schedules and research-constructs.

The four-hour and 8-to-9-hour dosing schedules and research-constructs were used as false á-priori premises in every piece of MPH research for more than 67 years. Therefore, other than some studies by this author, more than 67 years of MPH research produced inaccurate results and conclusions. Such research often provided useful and beneficial information but it was

inaccurate and non-valid. This author analyzed more than 400 published articles for an eight-year MPH-for-Parkinson's research project. He also analyzed an adult's 17-year medical treatment for a very severe Parkinson's illness. The treatment was nine years of Antiparkinsonian therapy followed by eight years of diurnal Methylphenidate therapy. The patient, Dr R, is a now-67-year-old American male. He is PhD-educated published Neurobiochemistry Researcher. At age-55, Dr R's Physician documented that he was disabled and in need of "appropriate medication" to function. This led a Neurologist to prescribe stronger and more frequent Antiparkinsonians. Signs and symptoms of a different form of disability set in and grew progressively worse during the next three years. Dr R read extensive medical literature on this type of disability and found it agreed with Physicians who told him that if this type of disability hit there would be no way out. At age-58, the different form of disability struck him down. This disability was permanent and total. No medications could improve it and no one recovered from it.

Dr R didn't give up. When disability struck, it made him black out in his office and he woke with the idea of using Ritalin to fight his disability. He was the world's first person to have that idea. From that idea he designed the world's first treatment of Parkinson's with long-term Methylphenidate. He started implementing the design four days later with the cooperation of a prescribing Physician. He used the 4-hour dosing schedule and was hit by the roller coaster effect so he tried 3-hour dosing. The roller coaster effect disappeared and efficacy became consistently stable. Ongoing use of the 3-hour schedule proved safe and successful. Dr R told some of his Adult ADHD/ADD patients about the successful 3-hour schedule and they asked to try it. They reported efficacy was steady, reliable, and safe through each day. Their "roller coaster" stopped. Since 2015 Dr R recommended the 3-hour schedule (6-hours for ER) to his ADHD/ADD patients and he includes it in consultations with prescribers. Among more than 400 analyzed articles this author found no research on long-term MPH for Parkinson's or about the 4-hour MPH schedule. He found no published evidence supporting the 4-hour schedule. The evidence supported a 3-hour dosing schedule that was unspoken and untried other than by Dr R.

Methylphenidate IR Works Best When Taken Every Three Hours

Some published research and guidelines say the onset of MPH-IR is sometimes a bit noticeable at 20 to 30 minutes after intake, partial efficacy is clearly noticeable at 45 minutes, and full-efficacy comes at 60 minutes [3,4]. MPH-IR plasma level increases to Cmax at hour-2 then gradually decreases by hour-3 to the same level as at hour-1. The plasma level continues to gradually decrease during dose-termination from hour-3 to hour-4. The time-length of dose-onset is one hour and the time-length of dose-termination is one hour [5]. The rates of dose-onset and dose-termination are virtually the same (Fig. 1).

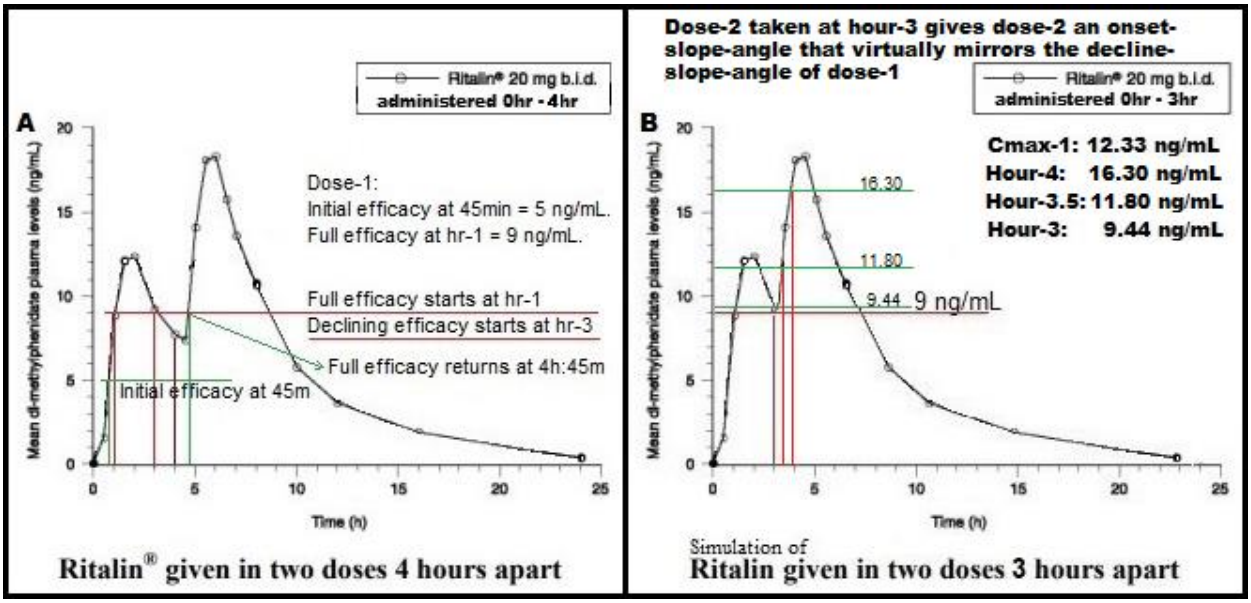

Figure 1: A: Plasma concentration 4-hour MPH dosing schedule; B: Simulated 3-hour MPH dosing schedule. In 1A the MPH plasma concentration of dose-1 on a 4-hour schedule is below 9 ng/mL-efficacy from hour-3 to hour 4:45 and the decline slope-angle differs significantly from the onset slope-angle of dose-2. In 1B the plasma concentration is continuously above 9 mg/mL-efficacy on a 3-hour schedule and the decline curve of dose-1 has virtually the same slope-angle as the onset of dose-2. The

rates are functionally the same for dose-1 decline and dose-2 onset and efficacy is maintained during the transition between doses. (Modified graphs from the Ritalin LA 2021 product monograph [5]).

When IR dose-2 is taken at hour-4: (1) there is an hour of no efficacy from the previous dose starting at hour-3 and (2) there is an additional 45- to 60-minutes of no efficacy starting when dose-2 is taken at hour-4. A 4-hour schedule causes a loss of efficacy for one-hour and 45- to 60-minutes during each transition from one dose to the next. When MPH-IR is taken on a 4-hour schedule x3 per day the loss occurs twice totaling 3.5 to 4 hours. When MPH-IR is taken on a 4-hour schedule x4 per day the loss occurs three times totaling 5.25 to 6 hours per day. When MPH-IR is taken on a 4-hour schedule x5 per day there are four losses totaling 7 to 8 hours.

The text in product monographs says the duration of MPH-IR is 3 to 4 hours. Clinicians take that to mean four hours of efficacy but plasma concentration graphs show efficacy is less than three hours. Each dose takes 45 minutes to reach partial efficacy, 60 minutes to reach full efficacy, Cmax is at hour-2, and there is a decline back to the hour-1 level at hour-3. A few minutes after hour-3 plasma concentration drops below efficacy. It continues declining until hour-4. A dose has an hour of onset and an hour of termination whereby supposedly" four-hour" doses have two hours of efficacy. When efficacy fades away there are two hours before it returns from a next dose. The text in monographs implies that the duration is four hours but graphs show only two hours of efficacy. The 4-hour schedule produces two-hour efficacy and two-hour lapses of efficacy [5].

The Valid 3-Hour Construct for Research and Practice

The 3-hour dosing schedule for Methylphenidate was discovered during this author's research that discovered long-term MPH-for-Parkinson's [6]. The 3-hour schedule proved valuable for patients by providing continuous efficacy even during transitions between doses. The 3-hour schedule is valuable for researchers by enabling measurement of variables without fluctuations of MPH efficacy.

The 3-hour schedule is easy to understand and easy to use: (a) At dose-intake, the increasing serum concentration of MPH-IR has a one-hour efficacy-onset. (b) At hour-3, decreasing serum concentration has a one-hour efficacy-termination. (c) When a second dose is taken at hour-3 after a first dose, the one-hour onset of the second dose occurs simultaneously with the one-hour termination of the first dose. (d) The plasma level increase of dose-2 combines with the decrease of dose-1. (e) The combined increase and decrease create a steady plasma level and steady efficacy during transitions from one dose to the next.

If the second dose is taken after hour-three, its onset increase will lag behind the decrease of the first dose such that the combined levels will remain below the efficacy threshold. Full efficacy will not return until sixty minutes after intake of the second dose. Smooth efficacy through the day comes from taking doses every three hours. This easily prevents the roller coaster of symptoms. This applies to any medicinal use of Immediate Release Methylphenidate. Use of Extended-Release Methylphenidate changes the three-hour time to six hours [7].

Accuracy and Reliability of 3-Hour Scheduling

Accuracy of the 3-hour MPH schedule was initially tested during the above-mentioned MPH-for-Parkinson's research. The treatment subject took a 20 mg dose of MPH-IR at the 3-hour mark after a previous dose for two weeks, totaling 52 doses. Efficacy-fluctuations stopped and no side effects occurred during the trial. The 3-hour schedule demonstrated consistent 100% reliability in thousands of *in-vivo* test-retests during a subsequent eight years of MPH treatment [6].

This author's clinical patients who asked to try the 3-hour schedule tested it for Adult ADHD/ADD. Each patient reported that the efficacy fluctuations stopped. All patients reported that efficacy became smooth and beneficial through each day. Every patient reported there were no side effects. The patients' Therapist observed no side effects and observed that each patient progressed better and faster in Mental Health therapy. The Therapist monitored the patients for six months. He saw consistent benefits with no problems. The 3-hour schedule proved successful and superior. The Therapist recommended it from 2015 onward to all of his Adult ADHD/ADD patients. It benefited them significantly.

Research That Used The 4-Hour Schedule Produced Wrong Results

During 2022 two science journals published articles by this author about treating Parkinson's with diurnal Methylphenidate [6,7]. The articles presented the discovery of multiple inaccuracies in 4-hour research designs and clinical dosing. The articles reflected eight years of research about MPH-for-Parkinson's. The research methods included analyses of more than 400 published articles. None questioned or doubted the 4-hour MPH schedule. No empirical evidence validated the schedule or showed reliability. The schedules came from product monographs that didn't show proof that the schedules were accurate. This type of misinformation-by-omission was also the reason that the FDA approved of the "60 mg maximum daily amount" without any proof.

The FDA was impressed by Methylphenidate in 1955. It was unique and seemed highly beneficial. There was no significant precedent for comparative analysis so the FDA approved the manufacturer's proposals. The manufacturer wanted to begin product sales right away so their research was hasty and minimal, yielding inaccurate findings. For example, the manufacturer did no research above 60 mgs per day so the FDA approved 60 mgs as the maximum daily amount. Another example was that the FDA approved MPH as a 4-hour medication because: (1) The manufacturer presented MPH research under the 4-hour schedule and under no other schedules. (2) It was difficult to interpret the manufacturer's graph of plasma concentrations (Fig. 2) so the FDA approved what was written in the monograph text [4].

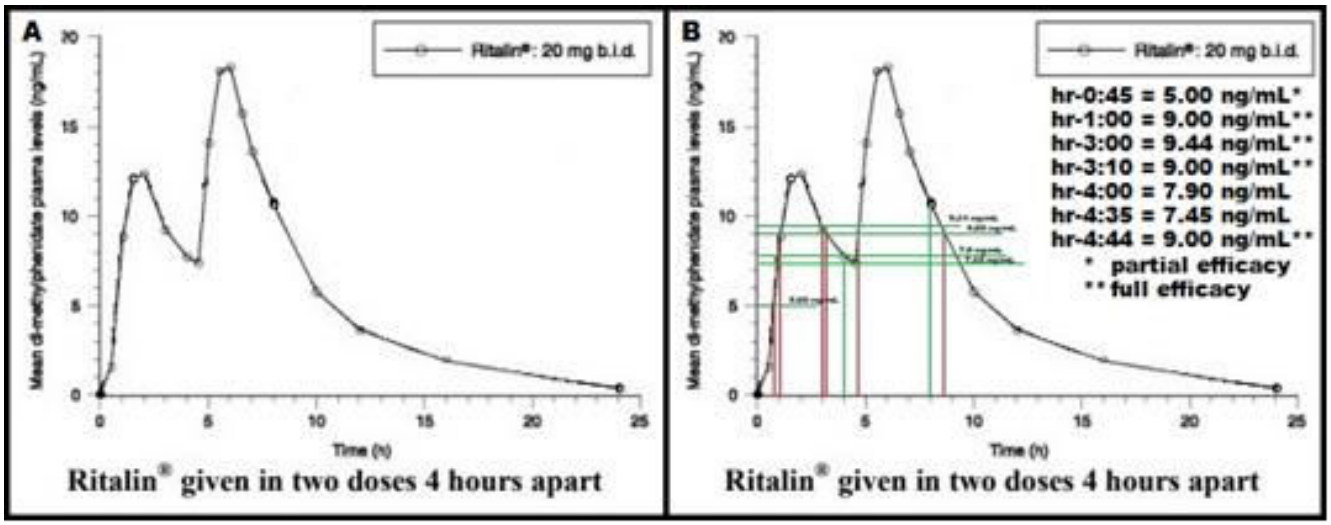

Figure 2: A: IR graph in the 2021 Ritalin LA product monograph; B: Graph with descriptive data. In 2A: The manufacturer's authors printed this minimal-information graph in the product monograph. Vague concepts and poorly defined parameters make it impossibly difficult to interpret the plasma concentrations. Readers must rely on the authors to interpret the truth for them. This leaves readers susceptible to potentially misleading statements by the authors, such as MPH-IR lasts for four hours. Fig. 2B: Accurate data inside a graph can show the accurate meaning of the plasma concentrations. For example: If the authors of Fig. 2A wrote that MPH-IR lasts for 4 hours, Readers can't know whether that's true based the absence of data in Fig. 2A. It only says the plasma curve starts at hour-0 and extends beyond hour-4. If the authors of Fig.2B wrote that MPH-IR last for 4 hours, the data inside Figure 2B says the term "lasts" is misleading. The plasma curve starts at hour-0 and extends beyond hour-4 but efficacy begins at hour-1 and ends at hour-3. MPH-IR "lasts" for two hours, not four hours.

Minimal information in graph A of Fig. 2 is presented above the way the manufacturer presented it in the product monograph. Vague concepts and poorly defined or undefined parameters make the curve difficult or impossible to interpret so Readers must rely on monograph authors to interpret the curve, leaving Readers susceptible to believing the authors' potentially misleading interpretations. For example, the monograph authors wrote that MPH-IR "lasts" for three to four hours. Conversely graph B in Figure 2 includes data and lines of demarcation by which Readers can interpret the curve and gauge the veracity of the authors' interpretations. Graph B shows MPH-IR 20 mg b.i.d. on a 4-hour schedule. It shows plasma concentrations at hour-0:45 = 5 ng/mL (partial efficacy), hour-1 = 9 ng/mL (full efficacy), hour-3 = 9.44 ng/mL (full efficacy), hour-3:10 = 9.00 ng/mL (full efficacy), and hour-4:44 = 9.00 ng/mL (full efficacy). Full efficacy begins at hour-1 and ends soon after hour-3. There is an hour and 44 minutes

below full efficacy going from minutes after hour-3 until dose-2 reaches full-efficacy at hour-4:44.

The monograph authors wrote that MPH-IR (Ritalin) "lasts" three to four hours, which implies four-hour duration. The product monograph contains Graph A from Figure 2 that provides no information to let Readers confirm, disconfirm, or otherwise interpret what the authors wrote. The absense of information in Graph A led to 67 years of clinicians, researchers, and the FDA erroneously treating MPH-IR as a four-hour medication. The data and lines of demarcation in Graph B show Readers that (1) the authors' use of the word "lasts" was misleading, (2) MPH was present at decreasing low levels in the blood for much longer than four hours, and (3) within the stated "four hours" two hours of efficacy from hour-1 to hour-3 were preceded by onset with no efficacy for an hour and followed by termination with no efficacy for an hour from hour-3 to hour-4.

This was a first-case example representing 67 years of research using the 4-hour schedule that produced wrong results. Researchers and clinicians in the USA continue adhering to the longstanding inaccuracies despite FDA approval of 70 and 85 mg 16-hour Adhansia XR in 2019. Canada approved 100 mg Foquest (Canadian Adhansia XR) (Fig. 3).

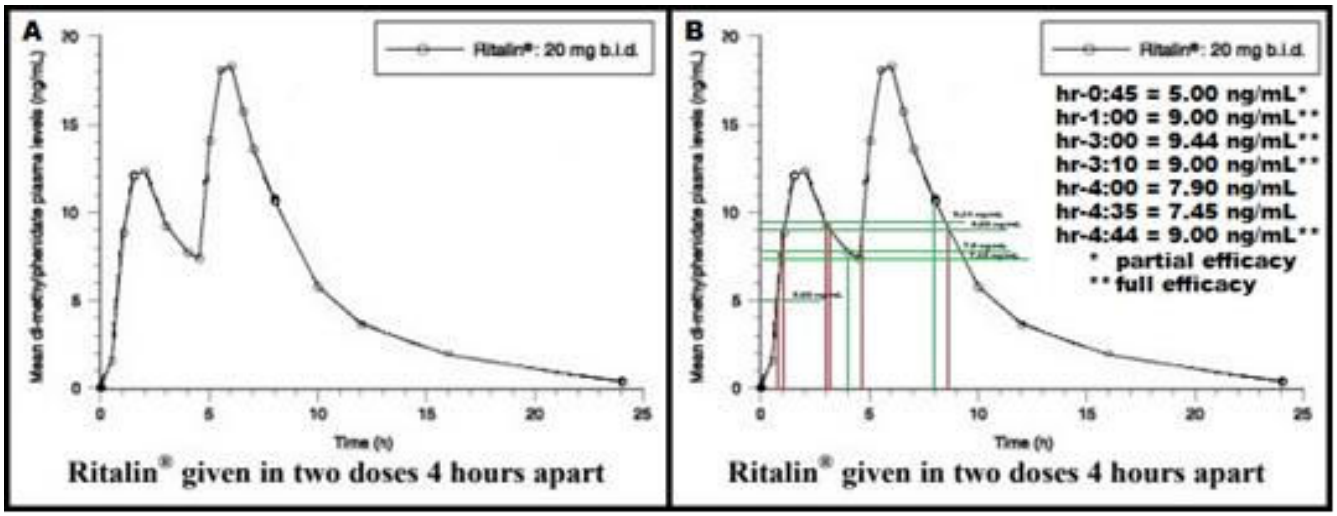

Figure 3: Canada approved MPH-IR 100 mg per day in 2010 (sections A and B) and Foquest 100 mg in March of 2019 (section D) [8-10]. The US FDA approved Adhansia XR 85 mg in July of 2019 (section C) based on the manufacturer's 100 mg research. The 2023 optimal amount of MPH for the MPH-for-Parkinson's subject is 105 mg per day. This is comparable to Canada-approved MPH-IR [11]. 100 mg per day (Fig. 1A,B) and Foquest 100 mg (Fig. 1D, The FDA approved Adhansia XR 85 mg (Fig. 1C) based on the 100 mg research by which Canada approved 100 mg Foquest. The Adhansia XR product monograph (Fig. 1C) [11] contains data from the manufacturer's 100 mg research [8-11].

Approval of Adhansia XR 70 mg and 85 mg shows the FDA approved and publicized inaccurate information about MPH for 67 years. Adhansia XR 85 mg has 30% more MPH than the previous 60 mg daily maximum. Foquest 100 mg has 44% more MPH than the 60 mg amount. The approval of higher daily amounts did not address the inaccurate 4-hour dosing schedule but it showed the manufacturer of Ritalin misled the FDA. The manufacturer has not admitted to this and has not changed the erroneous information in their product monographs. The manufacturer thereby perpetuates decades of incorrect practice that harms patients who need accurate high quality medical care.

From 2014 through 2022 this author conducted a research project that discovered and developed long-term Methylphenidate treatment for Parkinson's and for overcoming disability caused by Parkinson's and long-term high-dose Antiparkinsonians. Experiments found that 30 mg doses of adjunctive MPH overcame the adverse effects of AntiParkinsonians and 20 mg doses of MPH monotherapy-controlled Parkinson's symptoms better and safer than AntiParkinsonians. A four-hour dosing schedule in the research project gave erratic results due to the loss of efficacy 50% of the time. Analyses of plasma concentrations found the losses occurred during transitions from one dose to the next. This led to the 3-hour dosing schedule that gave uninterrupted efficacy during transitions. Experiments discovered MPH-IR every three hours was safer and more effective than every four

hours so the 3-hour schedule was adopted by the project henceforth. The research project also discovered that an IR tablet at six hours after an ER capsule was safer and more effective than at eight to nine hours, and an ER capsule three hours after an IR tablet was safer and more effective than at four hours [6,7].

Better safety and superior efficacy came from using IR tablets as three-hour medications and from using ER capsules as six-hour medications. This discovery led to development of 16-hour efficacy by using five sequential doses of MPH-IR every three hours. This was later modified to three sequential IR doses taken at hour-0, hour-9, and hour-12, with a 6-hour ER capsule taken at hour-3. It was also found that sequential doses gave a slight increase of plasma level from each dose (Fig. 4).

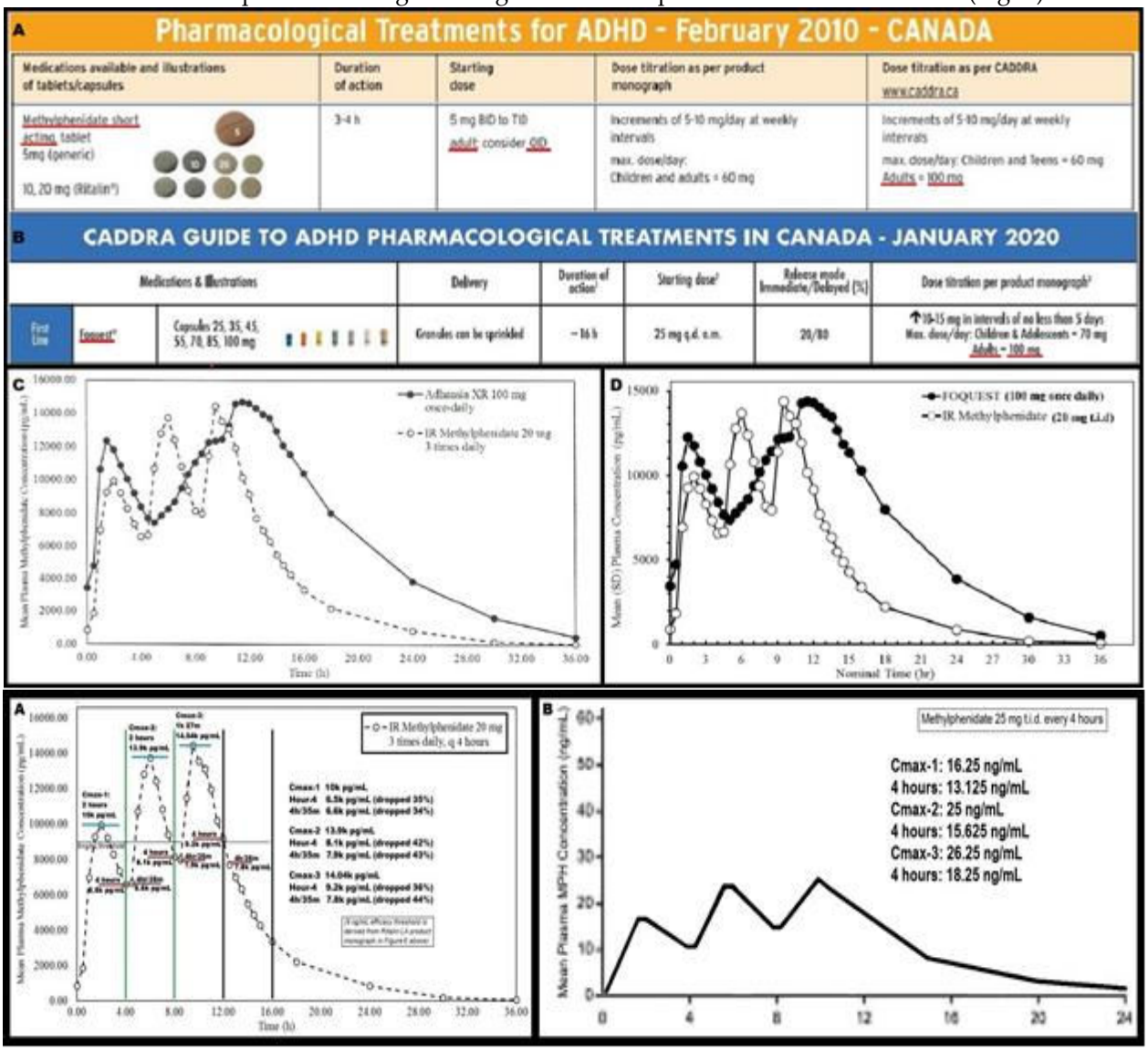

Figure 4: 4A: Increased plasma concentration in 20 mg t.i.d; 4B: Increased plasma concentration in 25 mg t.i.d. Graph A of Fig. 4 shows the plasma concentration increase from each sequential dose of MPH-IR 20 mg t.i.d. Graph B shows the plasma concentration increase from each sequential dose of MPH-IR 25 mg t.i.d. The largest increase is from dose-1 to dose-2. Dr R found it best to use 25 mgs for dose-1 and 20 mgs for subsequent doses.

The use of MPH-IR 25 mg rather than 20 mg upon waking overcame morning grogginess and improved morning efficacy. Contrary to product monographs that say ER capsules have an eight-to-nine-hour duration, the capsules contain two doses that are released three hours apart [5]. A 40 mg capsule has two 20 mg doses and the second dose is released three hours after the first (Fig. 5) [12]. The 6-hour ER schedule is simply a longer version of the 3-hour schedule.

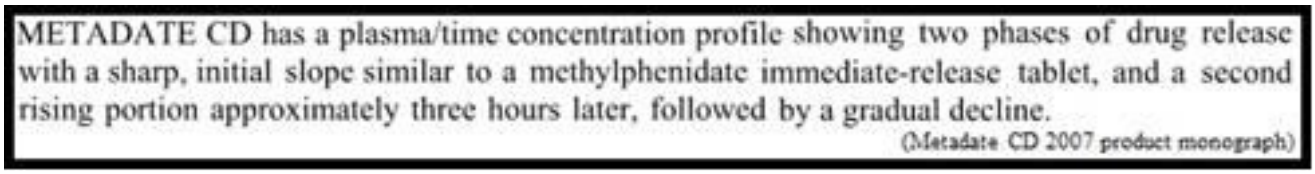

Figure 5: Excerpt from the Metadate CD 2007 product monograph. The 6-hour MPH-ER schedule is a version of the 3-hour schedule. ER capsules contain two 3-hour doses. The second is released three hours after intake.

Development of the 16-hour regimen is a first-case example of the accuracy and reliability of the 3-hour schedule. This study and the Parkinson's research project used the 3-hour schedule as the independent variable whereas 67 years of previous MPH studies used the 4-hour schedule as the independent variable. Unfortunately, 4-hour MPH dosing is a non-valid premise. By using a non-valid independent variable, 67 years of research gave non-valid results. The results were often useful but they were false. "Double-blind" designs and findings of statistical significance were moot without a valid independent variable. In order for MPH to be a valid independent variable, it must be administered on the 3-hour schedule. The 4-hour variable became the norm by default because science journals published studies that used it. This author reviewed more than 400 articles for this study and found only one with a 3-hour schedule [13]. The study was not exemplary because dose-2 was given at hour-3 but dose-3 was given four hours later. The study included a 3-hour factor within a non-valid 4-hour independent variable.

The tenets of Formal Logic state that conclusions derived from false premises are false conclusions. The 4-hour MPH schedule is a non-valid false premise. The fallacy of the 4-hour premise caused more than six decades of false conclusions as evidenced by inconsistent findings across studies. The inconsistencies show that the findings were incorrect.

Methylphenidate Dose Amounts

The manufacturer of Ritalin persuaded the FDA to approve up to 60 mg per day in 1955. Most healthcare providers in the US still adhere to that limit despite research studies that disproved it, despite Canada and several other countries approving higher amounts and despite FDA approval of Adhansia XR 70 mgs and 85 mgs per day in 2019 [11,14]. A year-2000 Mayo Clinic guideline recommended up to 90 mgs per day for adults, 50% more than the 60 mg limit [15]. A 2017 research group compiled a list of international guidelines for MPH dosing. Great Britain, England, and Wales said the upper limit is 100 mg per day and Sweden said 80 mg. Among nine countries, only Spain and Malaysia listed the 60 mg limit. Four countries said adult daily amounts depend solely on patient reports of results. Four countries, including the United States, did not specify limits but said MPH should be individually titrated for optimal effectiveness [14].

Limit-statements sometimes differ between what is told to the public and what is suggested to healthcare professionals. Dr R entered his weight into a two-options dose calculator. The healthcare professionals' option recommended 100 mgs per day for "off-label purposes" and the patients' option recommended 60 mgs per day for "standard purposes". Dr R's two-year prescription for 105 mgs per day was very close to the professionals' calculator but 43% more than the patients' calculator [15]. A review found no consistency across seven MPH guidelines. The FDA originally approved up to 60 mg per day because the manufacturer did no research above 60 mgs. Research done later by other parties showed MPH is safe at higher amounts. The above-mentioned 2017 research team recommended individualized optimization and up to 80 mgs per day. The team espoused patient-centered professional flexibility and said patients are the appropriate guide for dose optimization and ongoing treatment, whereby individualization and attentiveness to patient input are the key factors for valid and successful patient care. All of the research team and authors were executives from the manufacturer of Ritalin but the limit in the product monograph did not change [14].

Some research says 20 mg per dose is typically effective for adults. However, patient-centered care is the best approach because there is no consistency across dosage recommendations. Patients who took MPH in the past might know the regimen they want. It is usually beneficial to provide the accustomed dose on a 3-hour schedule. For patients who are new to MPH it is best to start with 10 mgs two times per day for two weeks, then three times per day for two weeks, then 20 mgs three times per day for two weeks, then add a daily sequential dose every week until the desired daily duration is reached. From eight years of research Dr R found the best regimen is [6]:

1. MPH-IR 25 mg upon waking
2. MPH ER-CD 40 mg 3 hour later
3. MPH-IR 20 mg 6 hours later
4. MPH-IR 20 mg three hours later

This gives 16 hours of uninterrupted normal functioning with constant efficacy. The constant efficacy is superior to 16-hour Adhansia XR (Fig. 5).

Dr R was an independent researcher of Neurobiochemistry since 2001. He was unfettered from drug industry demands and financial pressure. In 2014 he discovered and fine-tuned high-quality aspects of Methylphenidate that no one else knew existed. His discovery of the 3-hour schedule greatly improved the quality, comfort, and safety of MPH treatment and ended the MPH roller coaster effect. Dr R's MPH-for-Parkinson's research showed that MPH has extra benefits of strengthening and protecting neural tissues and systems, especially Dopamine systems. He benefited the Medical and Research Communities by identifying misleading misinformation that manufacturers' marketing experts wrote in product monographs. Dr R's MPH discoveries brought treatment of ADHD/ADD, Narcolepsy, and Parkinson's to the highest possible level.

Adhansia XR also provides 16-hour duration. The manufacturer printed a 100 mg plasma concentration graph in the product monograph but the FDA-approved up to 85 mg, 15% less than in the 100 mg plasma concentration graph. This author modified the 100 mg graph to show the plasma concentration of an 85 mg capsule (Fig. 6).

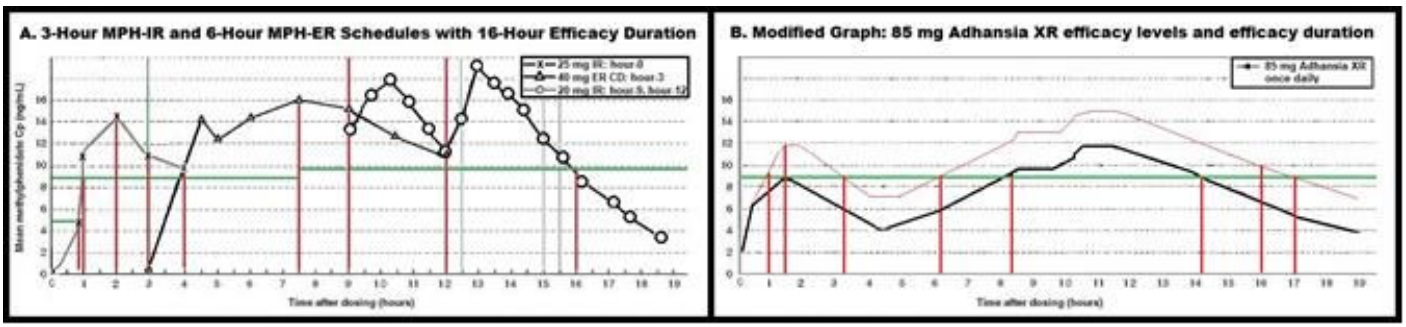

Figure 6: A: 3-hour IR and 6-hour ER regimen for 16-hour efficacy duration; B. Adhansia XR monograph modified to show plasma concentration of 85 mg. Fig. 6A: 3-hour IR and 6-hour ER schedules. Dose-1 is IR 25 mg. Partial efficacy is 5 ng/mL at 45 minutes. Full efficacy is 9 ng/mL at hour-1. Cmax is at hour-2. Dose-2 is a 40 mg ER CD taken at hour-3 with Cmax of 9.9 ng/mL at hour-7.5. Dose 3 is a 20 mg IR taken at hour-9. Dose-4 is a 20 mg IR taken at hour-12. Full-efficacy is continuous to hour-16. Fig. 6B: Depiction of FDA-approved Adhansia XR 85 mg plasma concentration. The plasma concentration for 100 mgs is shown by a red line for comparison. Plasma concentration from 100 mgs drops below the efficacy threshold for nearly three hours from hour-3:15 to hour-6. Plasma concentration from 85 mgs is above the efficacy threshold for only six hours, not 16 hours, from hour-8:15 to hour-14:15.

Plasma concentrations in Figure 6 show that the 16-hour duration in Fig. 6 is of significantly higher quality than 16-hour Adhansia XR in Fig. 6 [11]. Adhansia XR 85 mg is sub-therapeutic during 62.5% (10 hours) of the ostensive 16-hour duration. The FDA approved the 62.5% non-efficacy of 85 mgs and rejected the 18.75% non-efficacy of 100 mgs. The large percent of non-efficacy in Adhansia XR 85 mg leads to a logical deduction that FDA-approval protected the longstanding high marketplace status and financial profits of Ritalin and its subsidiary generics. The FDA-approval of Adhansia XR 85 mg also shows that the FDA approved and publicized inaccurate MPH information for 67 years. Adhansia XR 85 mg contains 30% more MPH than the previous daily maximum of 60 mg. Canada approved MPH-IR 100 mg in 2010 and Foquest (Canadian Adhansia XR) 100 mg in 2019. Canada's 100 mgs is 44% more than 60 mg. The approval of higher daily amounts shows that the FDA was misled or guided by non-evidentiary proposals from the manufacturer of Ritalin. This did not, however, address the inaccurate 4-hour dosing schedule. The manufacturer of Ritalin has not admitted to misleading the FDA and has not changed the misinformation in their monographs. Not changing the monographs perpetuates decades of inaccurate practices. It is unethical and harms patients who need accurate medical care.

Conclusion

Research found that adults do not abuse Methylphenidate prescribed for medical treatment [17]. Research also found that Methylphenidate protects and strengthens neural tissues and systems [18]. Clinical practice and research with Methylphenidate adhered to a premise of 4-hour scheduling for 67 years without questioning or investigating the accuracy and validity of the premise. In clinical practice the 4-hour schedule causes a "roller coaster effect" of efficacy that starts and stops in 2-hour increments, leaving only two hours of efficacy per MPH-IR tablet. This study discovered significant inaccuracies that make the 4-hour schedule non-valid and unreliable. This study showed that a 3-hour schedule is accurate, valid, and reliable. This study showed that a 3-hour schedule provides safe continuous efficacy. The author of this study was the first to present these findings. He was the first to show that the 4-hour premise caused 67 years of useful but non-valid research findings resulting from use of the 4-hour premise as an independent variable. The 4-hour schedule is a non-valid false premise and independent variable. The tenets of Formal Logic state that false premises yield false conclusions.

This study discussed an eight-year outpatient MPH research project that was the first to discover and adopt the accurate 3-hour schedule. It was used to develop a 16-hour regimen that is superior to 16-hour Adhansia XR (Fig. 5). This study used information from the 8-year research project and analyses of more than 400 published science articles. Literature analyses found that: (1) Methylphenidate strengthens and protects neural tissues, especially the Dopamine system. (2) Therapeutic-use adults do not abuse Methylphenidate. (3) Methylphenidate is non-addictive due to an hour-long dose-onset and an hour-long dose-termination that are unlike fast-acting substances of abuse and addiction such as Cocaine and Methamphetamine. (4) Properly used Methylphenidate is effective and quite safe. It is so effective and safe that it has been prescribed for decades for millions of children with ADHD/ADD as young as age six.

Based on information in this study the author recommends replacing four-hour Methylphenidate schedules with three-hour schedules. This will provide accurate and consistently effective treatment of Dopamine deficiency disorders such as childhood and adult ADHD/ADD, Narcolepsy, and Parkinson's illnesses.

Conflict of Interest

The author has no conflict of interest to declare.

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