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Methylphenidate and dexamethylphenidate formulations in children with attention-deficit/hyperactivity disorder

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Abstract:

Purpose: To review the current literature on the various extended-release methylphenidate stimulant preparations regarding safety and efficacy in children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

Summary: The literature reviewed establishes the efficacy of the different long-acting methylphenidate stimulant formulations in treating children and adolescents with ADHD. Comparing and contrasting the different extended-release preparations allows for clinicians to help tailor ADHD treatments to individual patients. The extended release methylphenidate products provide the same efficacy as the immediate release formulations, but add the convenience of less frequent dosing. There are a few options for patients with difficulty swallowing tablets or capsules, including the Daytrana[®] transdermal patch and the liquid Quillivant XR[®]. Focalin XR[®], Metadate CD[®], and Ritalin LA[®] can all be opened and sprinkled on applesauce.

Conclusions: Extended-release methylphenidate is effective in treating the symptoms of ADHD in children and adolescents. The different available dosage forms gives the clinician the opportunity to individualize treatment based on patient needs.

* Data Sources: The literature included was retrieved from PubMed/MEDLINE using the terms methylphenidate, stimulant, extended-release, children, and attention/hyperactivity disorder. Reference citations from publications identified were also reviewed.

Study Selection and Data Extraction: Double-blind clinical trials found using the search strategy above were included in this review. Open-label studies were included if no double-blind trials were published for that methylphenidate preparation.

Introduction

Attention-deficit hyperactivity disorder (ADHD) affects approximately 5% of school aged children worldwide. The disease typically presents in early childhood and can significantly impair academic achievement and development.¹ Children with ADHD may present with symptoms including hyperactivity, impulsivity, and inattention which are all more pronounced than expected for a child's developmental age.² These symptoms can persist all the way into adolescence and adulthood, impairing the child's development in all stages. The etiology of ADHD is still not known, but evidence has shown that it consists of neurologic components and the child's environmental factors.³

ADHD can be treated with medications, behavioral therapy, or a combination of the two. Stimulants including methylphenidate and amphetamine are considered first line drug treatment.⁴ There are many approved formulations of methylphenidate available on the market, therefore prescribers need to make clinical decisions as to which formulation is appropriate to initiate therapy or change therapy if needed. Prescribers, such as physicians and nurse practitioners, have the ability to tailor pharmacological therapy to meet the needs of each individual patient. The objective of this paper is to review and compare the current methylphenidate preparations available for children to provide clinicians with the opportunity to individualize their patients' therapy. By summarizing the information and data from current literature on the topic in this article, prescribers have access to the data needed to optimize ADHD therapy.

Methods

Working in a community pharmacy setting, I have interacted with patients and caregivers to ensure that their methylphenidate prescriptions are filled appropriately and safely. This

process often includes counseling the parent on the medication, communicating with the prescriber, and managing the logistics of providing the medication for the patient. There are many factors that affect the prescription when being filled at the pharmacy including patient-specific factors, insurance billing and cost, and availability of the drug product. All of these factors have the potential to inhibit the ability for the patient to receive the medication: child is experiencing adverse effects from medication, medication is too expensive or is not covered by insurance plan, product is not currently available on the market, and other problems that may arise. As the pharmacist, it is our responsibility to contact the prescriber in these circumstances and discuss alternatives appropriate for the patient.

Since there are many available formulations to choose from, I wanted to create a document to utilize during these situations that would enable the prescriber to choose an agent to treat the symptoms experienced by the patient. In order to accomplish this I performed a literature search via PubMed/MEDLINE using the terms methylphenidate, stimulant, extended-release, children, and attention/hyperactivity disorder. In addition, reference citations from publications found were reviewed. Double-blind clinical trials found using the search strategy above were included in this review. Open-label studies were included if no double-blind trials were published for that methylphenidate preparation. I chose to limit my search to methylphenidate because it has become the more commonly prescribed initial medication for children with ADHD.⁵

Results

The data I obtained from the search is presented below and was constructed into an article that was published in the American Journal of Health-System Pharmacy (Am J Health-

Syst Pharm. 2014; 71:1163-70). Included in the article is Table 1, which provides summary data on currently available methylphenidate and dexamethylphenidate products.

Background

The main pharmacological treatment choice for ADHD has been stimulant medications. Over the last 35 years, methylphenidate has replaced amphetamine as the primary stimulant prescribed to treat ADHD.⁵ The Food and Drug Administration (FDA) approved the use of methylphenidate for the treatment of ADHD in 1955. All formulations excluding the methylphenidate patch are approved for the use in children over the age of 6.⁶ The mechanism of action of methylphenidate is its proposed ability to increase dopamine concentrations within the synapse. Methylphenidate blocks the dopamine transporters therefore reducing uptake of the neurotransmitter.⁷ Through Positron Emission Tomography (PET) it was determined that therapeutic doses of methylphenidate block over 50% of the dopamine transporters with d-threo-methylphenidate as the isomer that blocks the transporters.⁸

The mechanism of methylphenidate differs from the amphetamines in selectivity due to its main actions through the dopaminergic pathway, and to a lesser extent through norepinephrine. Amphetamines in contrast increase the release of both dopamine and norepinephrine as well as increasing extracellular serotonin.⁹ Methylphenidate has consistently shown efficacy and safety in comparison to placebo in the management of inattention, impulsivity, and hyperactivity symptoms in children.¹⁰

The adverse effects of the various methylphenidate formulations are similar across the group of medications. The side effects are dose-dependent, mild in severity, and can diminish with a change in medication dose or timing.¹¹ The most common adverse effects reported by children receiving stimulants are loss of appetite, insomnia, headaches, and stomachaches. These

side effects may subside after the first two weeks of treatment, but adverse effects are the main reason stimulant treatment is discontinued.¹² Proper drug administration may abate some of these adverse effects. For example patients on extended-release methylphenidate preparations should eat large meals in the morning and evening, when methylphenidate levels are the lowest to prevent anorexia.¹³ Doses too late in the day should be avoided due to methylphenidate's stimulant effects that may prompt insomnia.

A major concern with methylphenidate is its short half-life of 2.5 hours in children, creating a difficult dosing schedule. The elimination half-life is reported to be within the range of 2 to 6 hours, but most studies report an average of 2 to 3 hours.¹³ Children with ADHD require pharmacotherapy in order to reduce symptoms, to help promote better learning abilities while at school as well as in after school programs and at home. Short acting drugs will not cover the full school day requiring a school official or nurse to administer a second dose. Providing the child with an extended release methylphenidate formulation can reduce the dose frequency and potentially reduce incidence of side effects.

Intermediate-release oral methylphenidate

In order to decrease the frequency of methylphenidate doses, reduce the incidence of side effects, and increase efficacy, sustained release formulations were developed. Sustained release formulations also reduce abuse potential liability and severity of adverse effects such as tachycardia.¹³ Ritalin SR[®], Methylin ER[®], and Metadate ER[®] are all AB rated by the FDA even though they employ different matrices.⁶ Ritalin SR[®] and Metadate ER[®] deliver methylphenidate to the patient via a wax matrix for an approximated duration of action of 8 hours.¹⁵ Average time to peak concentrations (Tmax) for these products is 4.7 hours (1.3-8.2).^{15,16} The methylphenidate in the intermediate release products is more slowly but as extensively absorbed

as the immediate release tablets.¹⁷ Drug release through a matrix layer occurs in 2 stages: the first stage is the formation of a water channel, then the second stage is the release of drug through the channel. The release rate is a function of the permeability coefficient and thickness of the matrix layer.¹⁸ Due to the matrix technology, these formulations should be swallowed whole, not crushed or chewed. Splitting the tablets would increase the total surface area, therefore increasing drug release too early. Crushing or chewing the tablets destroys the wax matrix, which also reduces the sustained release properties. Taking the dose of the sustained release products with food results in a greater C_{max} and AUC, so it is recommended to take each dose 30 to 45 minutes before a meal.^{15,16}

Methylin ER[®] uses a dual acting hydrophilic polymer release technology, which controls the release of methylphenidate by diffusion and erosion. This technology allows drug to diffuse out of the hydrophilic gel, leading to tablet disintegration. This product should also be swallowed whole, 30 to 45 minutes before a meal, with water or another liquid. Methylin ER[®] can have effects that last up to 8 hours.¹⁷

Since these intermediate agents last up to 8 hours, they can be dosed once daily, but most patients will still require twice daily dosing to provide symptom control throughout the school day and after school at home.¹⁴ The sustained release plasma profile demonstrates that it takes almost 5 hours for peak concentrations so, patients may not experience full symptom control until mid-afternoon. For school aged children, this formulation may prove less useful if they are still experiencing ADHD symptoms in the beginning of their school day.

Long-acting oral methylphenidate

Concerta

Methylphenidate is also available in an extended-release tablet Concerta[®]. Concerta[®] employs OROS[™] (osmotic controlled released oral delivery system) technology to deliver methylphenidate at a controlled rate.¹⁹ Each tablet is created to allow a once daily oral administration that has a 12 hour duration of effect. The Concerta[®] tablets are comprised of an osmotically active trilayer core that is surrounded by a semipermeable membrane with an immediate release coating. The trilayer core contains a push layer of osmotically active components and two drug layers containing drug and excipients. When the tablet is taken orally, the drug overcoat dissolves within one hour in an aqueous such as the gastrointestinal tract providing an immediate release of methylphenidate. The tablet has a precision-laser drilled orifice on the drug layer end. After the overcoat dissolves, water is able to permeate through the membrane into the tablet core and as the osmotically active polymer push layer expands, methylphenidate is released through the tablet's drilled orifice. The semipermeable membrane of Concerta[®] is what controls the rate at which water enters the tablet, therefore it is also controlling drug release from the tablet. Drug release rate increases with time over a period of 6 to 7 hours due to the concentration gradient of drug incorporated into the drug layers within the trilayer core. The rigid coating remains intact and is eliminated in the stool as a tablet shell.¹⁹

Children six to twelve years of age should not exceed 2mg/kg/day or 54mg of Concerta[®], according to the package insert. Adolescents and adults can be titrated up to the 72mg tablet if needed for symptom control. The plasma profile of Concerta[®] is similar to the profile of immediate release methylphenidate dose three times a day.¹⁹ A study compared the effects of Concerta[®] to immediate-release methylphenidate given 2 or 3 times a day and placebo; outcomes in the study were measured using the Swanson, Nolan and Pelham-Fourth Edition rating scale consisting of 18 ADHD symptoms. The study resulted in statistically significant superiority of

Concerta[®] to immediate release methylphenidate in remission rate of ADHD symptoms and severity of ADHD symptoms (-19.6 ± 13.9 vs -14.3 ± 11.6 , $p=0.01$).²⁰ This study also used a Parent Stress Index as an outcome which revealed that parents with children on Concerta[®] had a significantly greater decrease in parental stress than the parents in the IR methylphenidate group (14.0 ± 19.2 vs. 6.1 ± 14.8 , $p=0.008$).²⁰

There are no differences in the pharmacokinetics of Concerta[®] when administered after a high fat breakfast, so the dose can be taken with or without food. Concerta[®] tablets should not be crushed or chewed, but swallowed whole with liquids. Plasma concentrations of Concerta[®] reach an initial maximum at about 1 hour and then gradually increase over the next 5 to 9 hours. Concerta[®] minimizes the fluctuations between peak and trough concentrations associated with the immediate release tablets taken three times a day.¹⁹

Another study compared the efficacy of Concerta to three times daily immediate release methylphenidate in children diagnosed with ADHD, 6 to 12 years old.²¹ Results were reported using a parent and teacher recorded Daily Report Card which incorporated specific goals based on areas requiring improvement for each patient. There was an overall effect of drug, both immediate release and Concerta[®], for all the criteria of the Daily Report Card compared to placebo ($p<0.01$). Concerta[®] and the three times dosing IR methylphenidate had similar efficacy in most measures, with Concerta[®] having superiority in two of the parent ratings ($p<0.05$) establishing Concerta[®]'s ability to provide symptom control throughout a 12 hour period. With one morning dose, the effects of Concerta provided coverage through school, afternoon, and evening behavior.²¹ When deciding between the once daily methylphenidate formulations, it is important to consider when throughout the day the patient needs the most symptom control.

Ritalin LA

Ritalin LA[®] capsules, different from the Ritalin SR[®] tablets, have a bi-modal release profile which provides an immediate release as well as an extended-release component.²² The bead filled capsules utilize so called SODAS[®] (spheroidal oral drug adsorption system) technology, which coats an inert sugar sphere that contains the active product ingredient with either an immediate or controlled release coating. This mixture allows the full dose to provide a pulsatile drug release profile. Ritalin LA[®] capsules are bead filled with the capsule containing a 50:50 mixture of immediate release beads and enteric coated delayed-release beads, thereby providing the bi-modal profile.²²

Ritalin LA[®] provides in a single dose, the same amount of methylphenidate immediate release dosages given twice daily respectively. The plasma profile of Ritalin LA[®] reveals the two distinct peaks, with the time to first peak being 1 to 3 hours and the second peak achieved around 6 hours (5-11). The Ritalin LA[®] capsules have less peak and trough fluctuations than the immediate release methylphenidate tablets and have higher interpeak minimum concentrations.²² The release mechanism allows for the same total dose of methylphenidate to be provided for a longer, constant duration.

The advantage of Ritalin LA[®] capsules is that the dose can be sprinkled on top of applesauce if the patient has difficulty swallowing the capsule whole.²² Per the package insert, if the patient chooses to sprinkle the dose over a spoonful of applesauce, the applesauce should not be warm and the mixture of drug and applesauce should be consumed immediately and entirely. The drug and applesauce mixture should not be stored for a future dose because it could disturb the release properties. If the applesauce and drug mixture is stored, the drug coating will potentially hydrate prematurely. The modified release properties of Ritalin LA[®] are pH

dependent, so coadministration of antacids or acid suppressants should be avoided as it could alter the release of methylphenidate.²²

Another advantage of Ritalin LA[®] capsules is that its absorption is independent of food intake. The morning dose can be taken with or without breakfast and still maintain the same first peak concentration and extent of absorption.²³ Ritalin LA[®] capsules have also been compared to Concerta[®] in a single-blind, placebo-controlled, crossover study.²⁴ In the study, Ritalin LA[®] reached its first peak quicker, with a Ritalin LA[®] 20mg capsule being statistically more efficacious with a greater mean change from predose Swanson, Kotkin, Atkins, M-Flynn, and Pelhma (SKAMP) scores 4 hours post-dose than a Concerta[®] 36mg tablet (34.1 vs. 24.6, p=0.043). Although not statistically significant, Concerta[®] provided greater late day symptom control 8 to 12 hours post dose than Ritalin LA[®] (33.8 vs. 20.9, p=0.208).²⁴ The differences in time to effect and duration of stimulant effect of the methylphenidate products should be considered when individualizing therapy.

Metadate CD

Methylphenidate CD (Metadate CD[®]), different from the product Metadate ER[®], is a bead filled capsule containing a mixture of 30% immediate release beads with 70% extended release beads (i.e. a 40mg Metadate CD[®] capsule is composed of 12mg bead and 28mg extended release beads).²⁵ A study compared methylphenidate CD capsules of 30:70 and 40:60 formulations to determine which had better symptom control throughout based on two different dosage strategies over the course of a child's school day. Both formulations showed a significant reduction in SKAMP-A scores compared to placebo, but only the 30:70 formulation was still superior over placebo 9 hours post dose.²⁶

The release rate of methylphenidate from the Metadate CD[®] capsules is fairly smooth much like Ritalin LA[®], with less peak and trough fluctuations than 2 methylphenidate immediate release tablets taken 4 hours apart.²⁵ The first peak concentration from the Metadate CD[®] capsules was observed approximately 1.5 hours after dose intake and the second peak was reached about 4.5 hours after dose administration. In a study comparing food effects on plasma concentration, a high fat meal delayed the first peak concentration by approximately 1 hour, so the dose should be taken in the morning before breakfast. According to the package insert, the contents of Metadate CD[®] capsules can be sprinkled over a tablespoon of applesauce and consumed right away without affecting bioavailability. The sprinkled dose should be taken immediately and entirely.²⁵

A multi-center, double blind cross over study compared the effects of Metadate CD[®] and comparable doses of Concerta[®] to placebo. Both Metadate CD[®] and Concerta[®] showed superior efficacy in the reductions of SKAMP scores compared to placebo ($p < 0.001$) but there were differences in effect throughout the time of day. Based on SKAMP measures, Metadate CD[®] 40mg had greater symptom control than Concerta[®] 18mg from dose administration to six hours post dose (14.17 vs. 17.00, $p < 0.001$). There was no significant difference between the two formulations at 7.5 hours and 12 hours post administration. A higher dose of Concerta[®] 54mg provides significant reductions in symptoms at 12 hours than high dose 60mg Metadate CD[®] (16.74 vs. 19.85, $p < 0.05$). For a child that requires more symptom control throughout an average length of a school day of around seven hours Metadate CD[®] would be more appropriate than Concerta[®]. Concerta[®] provides better late day symptom control than Metadate CD[®] and placebo.²⁷

Transdermal methylphenidate

Methylphenidate is also available as a transdermal patch (Daytrana[®]) that has FDA approval for children of the ages 6 to 12 years. The Daytrana[®] patch is commercially available as 12.5cm², 18.75cm², 25cm², and 37.5cm² sized patches with respective 10, 15, 20, and 30mg doses that represent the total amount of methylphenidate delivered over 9 hours.²⁸ Transdermal methylphenidate is not eliminated in the liver by first-pass metabolism, while oral methylphenidate is, therefore the dosage forms are not bioequivalent. When beginning the Daytrana[®] patch it is recommended to start at the 10mg dose, whether the patient is just starting methylphenidate or converting from another dosage form.²⁸ Transdermal delivery of methylphenidate provides a treatment option for children who have difficulty swallowing oral medications or if they would benefit from tailoring the duration of effect specifically for their daily needs.²⁹

The Daytrana[®] patch is a multipolymeric adhesive platform that is designed to release methylphenidate consistently upon application to intact skin. The methylphenidate is dispersed in an acrylic adhesive that is then dispersed into a silicone adhesive. The patch consists of three layers: a polyester/ethylene vinyl acetate laminate film backing that faces the outer surface, the adhesive layer containing methylphenidate, and a fluoropolymer-coated protective liner that must be removed before patch application.²⁹ The Daytrana[®] utilizes DOT Matrix technology where the active ingredient is solubilized in high concentrations in an acrylic adhesive. The drug acrylic adhesive is then mixed with a silicone adhesive allowing for concentrated drug cells in an uncompromised silicone adhesive. DOT Matrix technology allows for better adhesion to application site and more drug concentrated a through smaller area.

The advantage of the patch is that it can be removed at any time, therefore the duration of methylphenidate exposure can allow for individualized treatment schedules. Effect from the

methylphenidate patch was seen 2 hours post application and up to 3 hours after removal in clinical trials.^{30,31} This 3 hour post-removal duration of effect should be considered in determining when to remove the patch each day. Parents should apply the patch to children to insure proper application and adherence. The Daytrana[®] patch has a side effect profile that is similar to the other methylphenidate formulations. The patch may cause skin irritation at the site of application that would present with erythema and papules. Redness and papules will disappear within 24 to 36 hours of patch removal.³⁰ Disadvantages to the patch are that effects are not seen until 2 hours after application, meaning parents might have to apply patch to children while they are still sleeping in the morning.³¹

Proper education for patch wearers and parents is necessary in order to promote appropriate absorption and drug delivery. Children need to be informed not to remove the patch until instructed to do so to maintain proper drug delivery. While the patches can be worn while swimming or exercising, if the patch does fall off and will not adhere back on to skin, the patient may apply a new patch on. The total wear time between both patches should not exceed more than 9 hours per day. Daytrana[®] patches should be applied to the hip, beneath underwear, at rotating sites as described in the product insert.²⁸ Applying the patch to the hip minimizes skin absorption differences.³² The application site should be clean, dry, and be void of any cuts or previous irritation. Once the patch is applied, the patient should not apply any heat to the area (blow dryers, direct sunlight, electric blankets) because heat can increase the rate and amount of drug release from the transdermal delivery system. The patch should not be cut, and if the patch is cut or damaged it should no longer be used.²⁸

Methylphenidate extended-release oral liquid

Until recently there were no extended release methylphenidate products available as oral suspensions for children with difficulty swallowing tablets or capsules. Quillivant XR[®] is a new product available to treat ADHD, being the first methylphenidate powder that is reconstituted with water creating an extended release liquid formulation. This new product is intended to be prescribed as once daily oral administration. The powder is composed of cationic matrix polymers that can bind to the racemic *d-l*-methylphenidate mixture by ion exchange. The Quillivant XR[®] powder contains 20% immediate release and 80% extended release methylphenidate components.³³ The combination of multiple release profiles is possible due to the differences in the coating of the powder particles. A coating of varying thickness is applied to the intended extended release particles, creating an overall blend of coated and uncoated particles.³⁵

The reconstituted liquid is available as a 25mg per 5mL oral suspension that does not require refrigeration.³³ Quillivant XR[®] is stable for up to 4 months after reconstitution when stored at room temperature (15-30°C). Prior to each dose, parents should shake Quillivant XR[®] suspension well for at least 10 seconds to ensure that a proper dose is administered.³³ In an open-label, single-dose study in children with ADHD ages 6 to 17 years, the average time to peak concentration was between 2 to 4 hours post dose.³⁵ A double-blind, placebo-controlled, laboratory classroom study evaluated the efficacy of Quillivant XR[®] in children ages 6 to 12 years. Quillivant XR[®] had significantly lower SKAMP scores from placebo at each time point tested to the last time tested at 12 hours post-dose ($p < 0.002$). The onset of action of Quillivant XR[®] was demonstrated at 45 minutes in the study, the first time point measured.³⁴ While Quillivant XR[®] has been shown efficacious for a duration of 12 hours in studies against placebo, future trials need to be conducted comparing it to other available extended-release

methylphenidate formulations.³⁴ Since Quillivant XR[®] is an oral suspension, it could become the preferred methylphenidate product in children with ADHD with difficulty swallowing.

Dexmethylphenidate

The methylphenidate compound exists as four isomer structures including the d-threo, l-threo, d-erythro, and l-erythro. The erythro isomers are not used in current methylphenidate stimulant products because the stimulant activity actually resides in the threo racemate.³⁶ The methylphenidate products discussed earlier are racemic mixtures of 50% d-threo and 50% l-threo isomers of methylphenidate. Preclinical studies have demonstrated that the d-threo isomer (*d*-MPH) is pharmacologically more active than the l-threo isomer.³⁷ One clinical study of children with ADHD found that *d*-MPH was just as effective as the *d,l*-MPH mixture 2 hours after administration, and no effect was seen for the l-threo isomer.³⁶ Since the d-threo isomer can be isolated and proven to be efficacious, the dose of dexmethylphenidate (*d*-MPH) can be half of the methylphenidate dose.³⁸

A randomized, double-blind, intent-to-treat study of children ages 6 to 17 years was conducted to demonstrate the efficacy of dexmethylphenidate compared to *d,l*-methylphenidate, with the dexmethylphenidate being administered at half the dose of methylphenidate.³⁹ Participants were initiated on either 2.5mg of dexmethylphenidate twice daily or 5mg of *d,l*-methylphenidate twice daily, and titrated up to a maximum of 10mg of dexmethylphenidate twice a day and 20mg of racemic methylphenidate twice a day. Outcomes were reported using the teacher-completed Swanson, Nolan, and Pelham Rating Scale (Teacher SNAP). Doses were administered by parents between 7:00 and 8:00am. Dexmethylphenidate provided significant decreases from baseline in the SNAP in the early afternoon assessment at 3:00pm (-0.7, $p < 0.0001$) and in the late evening assessment at 6:00pm (-0.6, $p = 0.0003$). While the racemic *d,l*-

methylphenidate provided early afternoon symptom control (-0.6,p=0.0073) it did not provide significant control at the late day assessment time. The d-threo methylphenidate group, racemic mixture group, and placebo all had comparable side effect reporting and frequency.³⁹ An extended release formulation of dexamethylphenidate was introduced, Focalin XR[®] to eliminate the midday dose of dexamethylphenidate immediate release, reduce side effects, and provide smoother plasma concentrations.⁴⁰

Extended-release dexamethylphenidate

Focalin XR[®] is another extended release formulation that utilizes the proprietary SODAS[®] technology to provide an immediate release and a second release of drug about 4 hours later. The initial rate of absorption of Focalin XR[®] is similar to that of its immediate release formulation with a time to first peak around 1.5 hours.⁴⁰ The second peak is reached about 4 hours later with a range of 4.5 to 7 hours after administration. Focalin XR[®] exhibits less peak and trough fluctuations than the immediate release tablets given in 2 doses 4 hours apart.⁴⁰ No racemization occurs with dexamethylphenidate extended release after administration and similar efficacy is achieved at half the dose of *d,l*-methylphenidate extended release.³⁹

The SODAS[®] extended release technology is pH dependent, so antacids should not be administered with Focalin XR as it may alter drug release. Focalin XR[®] may be taken with or without food, but absorption of the *d,l*-methylphenidate may be slowed down by the consumption of a high fat breakfast and it is expected to have the same effect on dexamethylphenidate.⁴⁰ The Focalin XR[®] capsules may be opened as stated in the package insert and sprinkled over a spoonful of applesauce and consumed right away if the child has a difficult time swallowing whole capsules.⁴⁰

A randomized, multicenter, double-blind, crossover study compared the effects of Focalin XR[®] to Concerta[®] tablets in children with ADHD aged 6 to 12 years. In the study, Focalin XR[®] had a faster onset of action than Concerta[®], with significantly greater mean change in SKAMP score 2 hours post dose (10.65 vs. 5.94, $p < 0.001$). Effects of Focalin XR[®] and Concerta[®] could be seen as early as 0.5 hours post dose in comparison to placebo, but Focalin XR[®] demonstrated stronger symptom ADHD control with a greater difference in SKAMP scores ($p = 0.044$).⁴¹ The study outcomes favored Focalin XR[®] at each time point from 1 to 6 hours post dose ($p < 0.05$). It wasn't till 10 hours post dose that Concerta[®] retained greater improvements in the study outcomes. During the last few hours of the laboratory classroom day, Concerta[®] provided better effects than Focalin XR[®] ($p < 0.05$ at 10 hours, $p < 0.001$ at 11 and 12 hours).⁴¹ This information could be useful in choosing the correct medication depending on when symptom control is needed the most throughout the patient's day.

Conclusion

The availability of the different extended-release formulations of methylphenidate can be used as options in treatment to satisfy individual needs. The methylphenidate products are all equally efficacious in treating ADHD symptoms. Clinicians can utilize the advantages and disadvantages of each product in order to individualize their patient's treatment.

Methylphenidate regimens can then provide patients with the ability to focus as suits them in their daily routine.

There are many other factors when deciding on appropriate therapy for a patient, aside from just the pharmacokinetics and pharmacodynamics of the medication. Until recently many of the extended-release formulations were accessible on the market as the brand name agent, with no generics available for a cheaper substitution. Another determinant is whether the desired

medication is on the patient's insurance formulary, the list of drugs that are preferred by their health care plan. These factors, like cost and market availability, need to be taken into consideration as they can be barriers to care that aren't seen until the patient reaches the pharmacy. Most of the tablet and capsule formulations are now available at a lower generic cost, but transdermal and oral suspension methylphenidate are still only available as the brand name agent. One way to expand the results of my research would be to incorporate some of this information along with the clinical information, therefore prescribers would be able to obtain all necessary information from one source.

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Table 1. Available Extended-Release Methylphenidate Preparations

Product	Delivery Mechanism	Time to peak (hours)	Dosing Frequency	Duration of action (hours)	Available Doses	Sprinkle/Divide	Ref.
Ritalin®	IR tablets	1-2	3 times daily	3-4	5, 10, 20mg	Split/crush	15
Ritalin SR®	tablet, contains a wax based matrix	□ 4-5	2 times daily	8	20mg	No, swallowed whole	15
Metadate ER®	tablet, contains a wax based matrix	□ 4-5	2 times daily	8	10, 20mg	No, swallowed whole	16
Methylin ER®	tablet, dissolution polymer that extends MPH release	□ 3-4	2 times daily	8	10, 20mg	No, swallowed whole	17
Concerta®	tablet, osmotic pressure delivers racemic MPH mixture at a controlled rate	1 st : 1-2 2 nd : 6-8	once daily	12	18, 27, 36, 54, 72mg	No, swallowed whole	19
Ritalin LA®	capsule, contains mixture of MPH filled beads to allow 50% IR and 50% enteric coated delayed release	1 st : 1-3 2 nd : 4-5	once daily	8-10	10, 20, 30, 40mg	Can be opened and sprinkled	22
Metadate CD®	capsule, beaded drug delivery system with 30% IR beads and 70% ER beads	1 st : 1.5 2 nd : 4.5	once daily	8	10, 20, 30, 40, 50, 60mg	Can be opened and sprinkled	25
Daytrana®	transdermal patch releases MPH continuously	10	once daily	Dependent on wear time	10, 15, 20, 30mg	Patch can't be cut or damaged	28
Quillivant XR®	suspension, reconstitute powder contains 20% IR component and 80% ER	2-4	once daily	12	5mg/5mL	--	33
Focalin®	IR tablets	1-1.5	2 times daily	3-4	2.5, 5, 10mg	Split/crush	40
Focalin XR®	capsule, contains mixture of dex-MPH filled beads to allow 50% IR and 50% enteric-coated delayed-release	1 st : 1.5 2 nd : 6.5	once daily	12	5, 10, 15, 20, 25, 30, 35, 40mg	Can be opened and sprinkled	40

IR = immediate release, MPH = methylphenidate, ER = extended release