Future NEUROLOGY

Plain Language Summary of Publication

Serdexmethylphenidate/dexmethylphenidate capsules for children and adolescents with attention-deficit/hyperactivity disorder (ADHD): a plain language summary

Scott H. Kollins[1,2], Andrea Marraffino[3], Andrew J. Cutler[4,5], Charles Oh[6], Matthew N. Brams[7], Rene Braeckman[8] & Ann C. Childress[9]

[1]Duke University School of Medicine, Durham, NC, USA; [2]Akili Interactive, Inc., Boston, MA, USA; [3]Accel Research Sites Network, Maitland, FL, USA; [4]SUNY Upstate Medical University, Syracuse, NY, USA; [5]Neuroscience Education Institute, Lakewood Ranch, FL, USA; [6]Corium LLC, Boston, MA, USA; [7]Bayou City Research, Houston, TX, USA; [8]Zevra Therapeutics Inc, Celebration, FL, USA; [9]Center for Psychiatry and Behavioral Medicine, Las Vegas, NV, USA

First draft submitted: 18 October 2023; Accepted for publication: 26 February 2024; Published online: 20 March 2024

Summary

What is this summary about?

This is a plain language summary of 2 articles published in the *Journal of Child and Adolescent Psychopharmacology*. It describes a medication called serdexmethylphenidate/dexmethylphenidate, or SDX/d-MPH for short. SDX/d-MPH is marketed under the name Azstarys®. It is in capsule form taken by mouth once a day in the morning and meant for treating patients aged 6 years and older with attention-deficit/hyperactivity disorder, commonly referred to as ADHD. This summary focuses on studies that were done in children and adolescents aged 6 to 12 years with ADHD. The study results showed how SDX/d-MPH reduced the symptoms of ADHD, how fast the medication began to work and for how long it worked in the study patients, as well as the medication's safety during 1 year of treatment.

What are the key takeaways?

Two main studies were done in patients with ADHD.

How to say (double-click on the icon to play sound)…

- **Azstarys:** Az-star-is
- **Methylphenidate:** meth-ill-fen-ee-date
- **Serdexmethylphenidate:** sir-dex-meth-ill-fen-ee-date
- **Amphetamine:** am-fet-ah-meen

Placebo: an inactive substance that has no medication but looks exactly the same as the actual medication and is taken in exactly the same way as the study drug.

Side effect: an undesirable effect of a medication.

Insomnia: difficulty sleeping.

Tolerable: means that a patient can endure a medication even with the some of the side effects.

1

The first study was conducted in a laboratory classroom, which is a simulated school classroom setting with children and adolescents aged 6 to 12 years with ADHD. The patients received either SDX/d-MPH or a **placebo**. The results of this study showed that the effect of SDX/d-MPH on reducing ADHD symptoms started approximately 30 minutes after taking the SDX/d-MPH capsule and lasted for approximately 13 hours. The placebo did not have this effect. The most common **side effects** for those taking SDX/d-MPH were headache, abdominal (belly) pain, **insomnia** and upper respiratory tract infection.

2

The second study was also done in patients aged 6 to 12 years with ADHD. The purpose was to examine how safe and **tolerable** SDX/d-MPH was during 1 year of treatment. In this study, no placebo was given. The findings from the second study showed that SDX/d-MPH was safe and tolerable during the 1-year treatment period, with the most common side effects being decreased appetite, upper respiratory tract infection, sore throat and nose, decreased weight and irritability.
This study also showed that SDX/d-MPH was effective throughout the 1-year treatment period.

Taylor & Francis
Taylor & Francis Group

What were the main conclusions?
In the first study, children with ADHD treated with SDX/d-MPH showed noticeable improvements in ADHD symptoms as early as 30 minutes after the medication was given, and those improvements lasted up to 13 hours. SDX/d-MPH was also found to be as safe as other ADHD treatments containing methylphenidate (MPH).

Results of the second study showed that children with ADHD could be treated safely with SDX/d-MPH.

Where can I find the original articles on which this summary is based?

The original article for the first study is called, 'A randomized, controlled laboratory classroom study of serdexmethylphenidate and d-methylphenidate capsules in children with attention-deficit/hyperactivity disorder.'
You can read the original article, published in the *Journal of Child and Adolescent Psychopharmacology*, for free at:
https://doi.org/10.1089/cap.2021.0077

The original article for the second study is called, 'Safety and tolerability of serdexmethylphenidate/dexmethylphenidate capsules in children with attention-deficit/hyperactivity disorder: a 12-month, open-label safety study.'
You can read the original article, published in the *Journal of Child and Adolescent Psychopharmacology*, for free at:
https://doi.org/10.1089/cap.2022.0076

Who is this article for?

The authors of the original article developed this summary to help patients, parents and caregivers, health care professionals, policy makers and insurance providers to understand the results of this study.

The purpose of this plain language summary is to help you to understand the findings from recent research on SDX/d-MPH (Azstarys®) approved to treat ADHD that is discussed in this summary.

Who sponsored the studies?

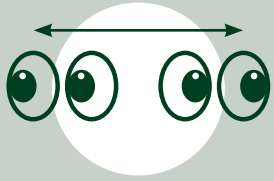
Sponsor: a company or organisation that oversees and pays for a clinical research study. The sponsor also collects and analyses the information that was generated during the study.

Clinical research was funded by Zevra Therapeutics Inc (previously KemPharm Inc). Funding for editorial and writing assistance in the form of proofreading, copyediting, and fact-checking was provided by Corium LLC (Boston, MA, USA).

What is ADHD?

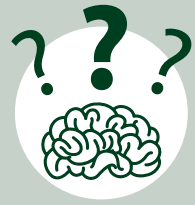
- ADHD is a chronic illness affecting 9.8% of children in the USA, with more than 90% of cases persisting into adolescent years
- ADHD is one of the most frequently diagnosed disorders in children and adolescents
- The USA has reported higher rates of ADHD diagnosis because of the various diagnostic tools used to diagnose it
- ADHD presents in 3 ways in patients based on the number of symptoms from each of 2 categories (inattentive and hyperactive/impulsive):
  - Predominantly inattentive: unable to keep focus
  - Predominantly hyperactive/impulsive: excessive movement/hasty action without thought
  - Combined: inattentive, hyperactive and impulsive
- ADHD symptoms include the following:

Difficulty focusing and inability to pay attention (inattention)



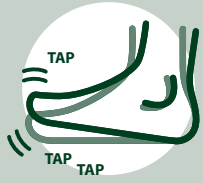
Being easily distracted (distractibility)

Forgetfulness



Disorganization

Being overly active (hyperactivity)



Acting without thinking (impulsivity)

Impatience

- These symptoms can affect a child or adolescent at home and school and can affect learning, behavior and social interactions that can lead to long-term problems like low self-esteem, relationship problems, educational difficulties and reduced quality of life
- For an ADHD diagnosis, besides having the required number of symptoms, those symptoms should have lasted for more than 6 months, occurred on more than 2 occasions (for example, occurred at home and a couple of times at school) and have negatively affected social and academic activities
- The exact cause of ADHD is not fully understood

10.2217/fnl-2023-0026

How is ADHD treated?

- For children and adolescents with ADHD, the first therapy that should be tried is training the parent in behavior management and/or behavioral classroom interventions. If these are not effective, the risk of starting a medication must be weighed against the harm of waiting to start to use the medication
- Children (aged 6 to 12 years) with ADHD should be treated with an ADHD medication approved by the US Food and Drug Administration (FDA), such as a medicine called a psychostimulant, in addition to parent training in behavior management and/or behavioral classroom interventions
- Adolescents (aged 12 to 18 years) with ADHD should also be treated with an FDA-approved ADHD medication but with the patient's agreement. Also, educational interventions and one-on-one therapy should be used
- ADHD medication doses should be slowly increased over time to ensure the best intended results (efficacy) with acceptable safety and tolerability
- Regular monitoring and follow-up visits with a health care provider, such as a doctor, nurse practitioner or physician associate, are required to address any issues
- If symptoms do not improve, it is recommended to re-evaluate the diagnosis and/or educate to improve on ways to stay on the medication or reconsider the treatment plan
- Comorbid" refers to a disease or health condition that appears along with another disease. Comorbid psychiatric and medical conditions must be considered in the evaluation and treatment of ADHD. If comorbid conditions are diagnosed, these conditions can be treated, or a referral to an appropriate subspecialist should be considered
- A potential problem with many ADHD treatments, including extended-release (medications that work over a long length of time) ADHD medications, is that they do not cover the important times of the day, such as the period of time when a child wakes up and prepares for school, is in school and then comes home from school to do homework

6:00 AM

Parents of children and adolescents with ADHD find that **early morning routine and evening homework periods** were the times of the day when uncontrolled ADHD symptoms cause the most problems. So, having a single-dose treatment that quickly starts to control symptoms in the morning and continues to control symptoms throughout the waking day is an unmet need in the treatment of children and adolescents with ADHD.

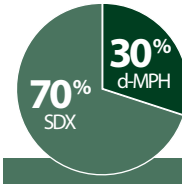
6:00 PM

- Of the various medications used to treat ADHD, medications classified as psychostimulants, which broadly make a person more alert and awake, have shown beneficial effects as the first choice for type of medication therapy
- There are 2 types of FDA-approved psychostimulants used to treat ADHD: **methylphenidate (or MPH)** and **amphetamine**. Although they are thought to work similarly, there can be differences in individual patients
- Extended-release psychostimulant medications are recommended to treat ADHD because of the longer length of time the medication is working, which means only a single dose is needed throughout the day, making the medication more tolerable and lessening the risk of abuse and misuse
- **Methylphenidate (MPH)** helps in reducing ADHD symptoms in children and adolescents, and after many years of it being available to patients, it has been found to be safe and effective for children aged 6 years and older and for adults when used under a health care provider's supervision
- MPH by itself is processed quickly in the body, resulting in only 3 to 4 hours of effectiveness, which often means a patient needs to take the medication 2 or 3 times a day to control symptoms. There are various extended-release MPH medications intended to increase the length of time that they work, which means a patient can take the medication once a day

What is SDX/d-MPH?

SDX/d-MPH, brand name Azstarys®, is an ADHD medication approved by the FDA for the treatment of patients aged 6 years and older with ADHD.

It is taken by mouth once daily either in a capsule form or it can be sprinkled on food and mixed in drinking liquids.



SDX/d-MPH contains 70% SDX, a prodrug of d-MPH, and 30% d-MPH.

A prodrug, in this case SDX, is an inactive prior form of the active drug, d-MPH.

Once SDX is taken by mouth, the inactive SDX mostly stays in the gut, where it is gradually converted to the active d-MPH by proteins in the gut.

d-MPH is then absorbed in the lower intestinal tract and is transported by blood vessels to the brain, where it does its work to reduce ADHD symptoms.

SDX/d-MPH begins working around 30 minutes after a person takes it and controls ADHD symptoms for about 13 hours.

The d-MPH is released into the body, is rapidly absorbed and begins working immediately.

SDX is an inactive form of the drug and is converted to active d-MPH in the gut. The conversion of SDX to d-MPH is gradual, which leads to slow, steady absorption, resulting in up to 13 hours of effectiveness.

The ways that SDX/d-MPH helps to reduce the symptoms of ADHD are not yet fully known, but d-MPH is known to change the levels of certain chemicals in the brain, thereby helping to reduce ADHD symptoms.

Why were the studies done?

To support FDA approval of the drug, 2 main studies were done in children and adolescents aged 6 to 12 years with ADHD. One study was done in a classroom environment to examine how quickly and for how long SDX/d-MPH worked and also if it was safe. The other study was done to examine the safety of SDX/d-MPH for 1 year. ADHD affects children, adolescents and adults. However, this study was focused on children and adolescent patients aged 6 to 12 years. There are many treatment options for children with ADHD. FDA-approved options include the use of medication for most patients, but counseling and behavioral therapy are also recommended for best outcomes.

Stimulants are usually used first, because they have been demonstrated to be effective.

Nonmedication treatments also have been shown to be effective, including trigeminal nerve stimulation, which is a non-invasive, mild electric stimulation to the forehead, and digital therapeutics (for example, an app on a patient's own smartphone, tablet, or computer) that can be used alongside medication if required. In 2021, the FDA approved SDX/d-MPH, marketed under the name Azstarys®. It is used for the treatment of ADHD in patients aged 6 years and older. SDX/d-MPH is a type of medication called a **psychostimulant**. SDX/d-MPH capsule should be taken by mouth once a day in the morning to help increase attention and decrease hyperactivity and impulsiveness in patients with ADHD.

Psychostimulant: any medication that increases the activity of the central nervous system and the body.

Who took part in the studies?

- Both studies were done at multiple different clinics in the United States
- Study 1 was conducted between 2017 and 2018, and Study 2 was conducted between 2018 and 2019
- Children and adolescent boys and girls aged 6 to 12 years with ADHD were enrolled in the studies
- A total of 150 children and adolescents took part in Study 1
- A total of 238 children and adolescents took part in Study 2
- Participants were excluded if they had psychiatric conditions, for example, depression or bipolar disorder
- Participants in both studies were around 9 years of age, and approximately 60% were male, while the rest were female

How were the studies carried out?

The first was a randomized, placebo-controlled, double-anonymized and dose-optimized classroom study.

Randomized means that each patient receives either the study medication (SDX/d-MPH) or the placebo, chosen randomly by a computer program.

Placebo is an inactive substance that has no medication but looks exactly the same as the actual medication and is taken exactly the same way.

Placebo-controlled means that the efficacy of the active medication (in this case, SDX/d-MPH) is compared with that of the placebo in patients.

Taylor & Francis
Taylor & Francis Group

Double-anonymized means a type of study in which neither the patient in the study nor the people involved in giving the treatment (treatment team) knew which treatment the patients received until the study was over.

Dose-optimized or **dose optimization** means to find the dose of the medication that provides the best balance of efficacy and safety.

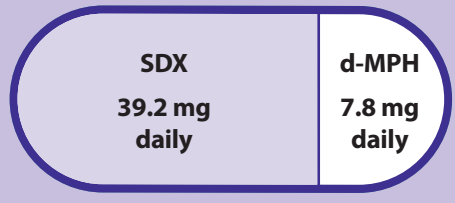
Classroom study means that the study setting simulated a school classroom setting to see how quickly and how long the treatment would work by observing the ADHD symptoms of inattention and hyperactivity/impulsivity as they were happening throughout a day.

Screening phase and dose-optimization phase

- Children and adolescents were screened to establish that they were eligible to participate

The dose of SDX/d-MPH capsules is shown with 2 values that represent how much in milligrams (mg) of each substance (SDX and d-MPH) is given. The first number is the amount of SDX, and the second number is the amount of d-MPH.

For example, 39.2 mg/7.8 mg means the patient received 39.2 mg of SDX and 7.8 mg of d-MPH daily.



- During a 3-week, open-label (meaning everyone including the doctors and patients could see they were getting the treatment), dose-optimization phase, children and adolescents started treatment with the middle dose of 39.2 mg/7.8 mg per day of SDX/d-MPH
- Each week, the dose of SDX/d-MPH was evaluated by a doctor for control of ADHD symptoms and for the tolerability and safety of the medication. Based on the results of that doctor's evaluation, the dose of SDX/d-MPH was decreased to 26.1 mg/5.2 mg, increased to 52.3 mg/10.4 mg or kept at the same a 39.2-mg/7.8-mg dose
- The symptoms and severity were evaluated weekly by the doctor by interviewing the patient and caregiver in the clinic using a standard rating scale called the ADHD-RS-5, which rates the 18 potential symptoms of ADHD from the Diagnostic and Statistical Manual, 5th Edition. Both the number of symptoms and severity of symptoms are measured. A decrease in the score indicates improvement. The dose was adjusted until the best efficacy with acceptable tolerability, or the "optimal dose," was reached. This is why this phase is called "dose optimization"

Treatment phase

Study 1

During the double-anonymized treatment phase, children and adolescents received their optimized dose of SDX/d-MPH or placebo for 7 days. Neither the treatment team giving the medication nor the patients receiving the medication or their caregivers knew if they were getting SDX/d-MPH or placebo. Placebo is given because sometimes patients say they feel better simply because they think they are getting a treatment. People giving the medication may act differently if they know whether they are giving a treatment or a placebo. For this reason, a placebo is used to compare with the active medication to reduce this risk of bias, without either the treatment team or patient knowing which is given.

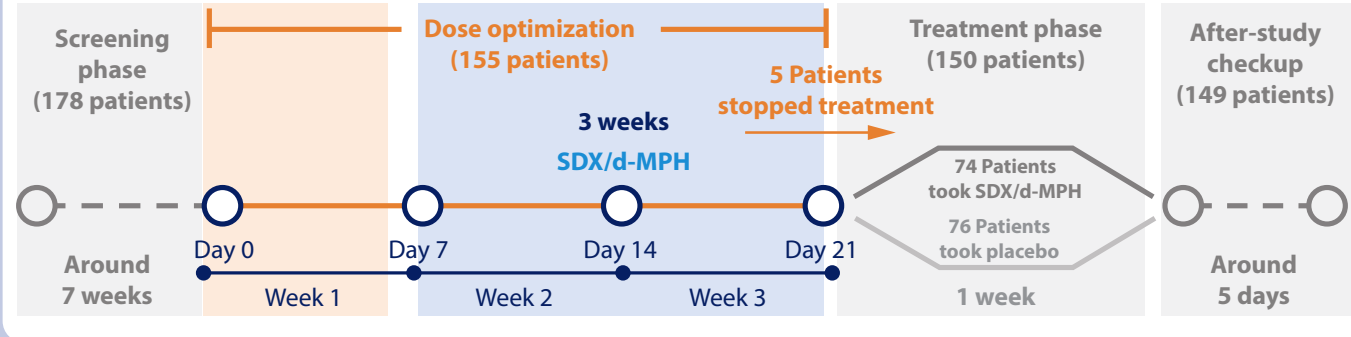
After a week of this double-anonymized treatment, how the medication was working was assessed in the simulated school classroom setting by 2 methods.

Attention and behavior of children and adolescents with ADHD in a classroom setting was measured. The examination tool used to assess this was the Swanson, Kotkin, Agler, M-Flynn, and Pelham scale (referred to as SKAMP), which has ratings ranging from normal to maximal impairment. The lower the score on this test, the more improvement for a child with ADHD.

A test known as the Permanent Product Measure of Performance (referred to as PERMP) was also used to determine if SDX/d-MPH worked as intended in children and adolescents with ADHD. The PERMP is a math test set to the individual child's math level and is used to measure attention, neatness and accuracy in children with ADHD. The higher the score, the greater the improvement for a child with ADHD.

The people who gave the test did not know the identities of the patients who took the test. Safety and tolerability of SDX/d-MPH were also assessed during this study.

Study 1



Taylor & Francis
Taylor & Francis Group

Study 2

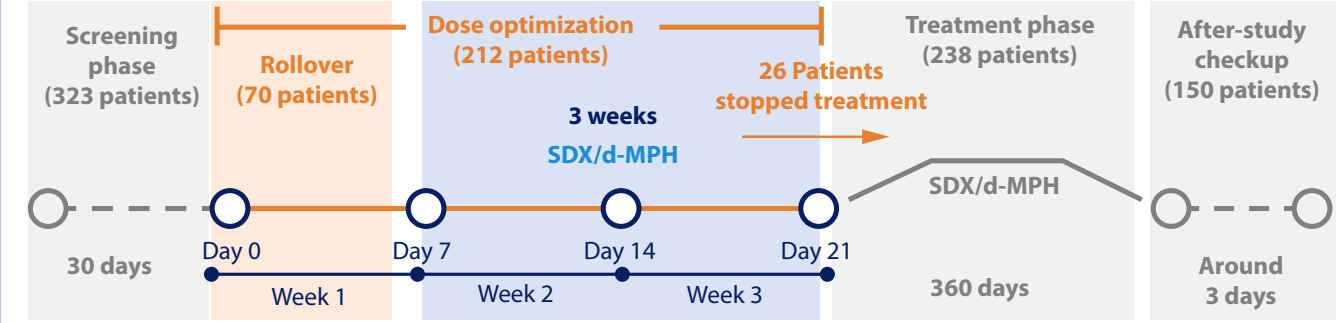
The 12-month study was an open-label study, meaning that there was no placebo and that all patients received SDX/d-MPH. The main purpose of this longer study was to look at the long-term safety and tolerability of SDX/d-MPH in children and adolescents aged 6 to 12 years with ADHD and to see if the treatment was still working during 12 months of use.

Children and adolescents aged 6 to 12 years with ADHD were enrolled in the 12-month study, including those who successfully completed the double-anonymized study mentioned previously (these patients were called "rollover" patients) and new patients who were not enrolled in a previous SDX/d-MPH study.

The study consisted of the following:

- An up to 30-day screening phase, where potential patients were screened to see if they were eligible for the study
- A dose-optimization phase for new patients only (rollover patients entered the treatment phase directly and were given their optimized dose from the previous classroom study)
- A 360-day treatment phase
- A follow-up phase

Study 2



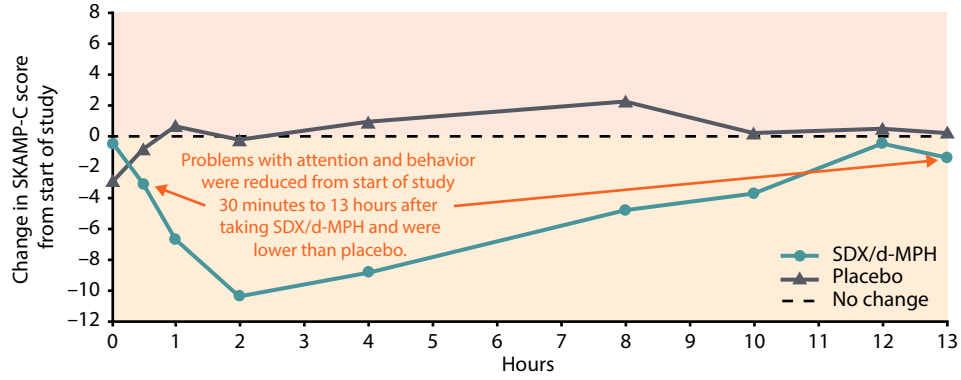
- The primary outcome (the main thing being measured in the clinical study) was safety and tolerability of SDX/d-MPH assessed throughout the 12-month duration of the study
- During the treatment phase, the ADHD-RS-5 and the Clinical Global Impressions–Severity (CGI-S) scores were used to measure the symptoms and severity of ADHD
- ADHD-RS-5 rates the 18 potential symptoms of ADHD
- CGI-S is a clinical assessment used to evaluate overall ADHD severity

What did the results show?

1 Study 1 (laboratory classroom study)

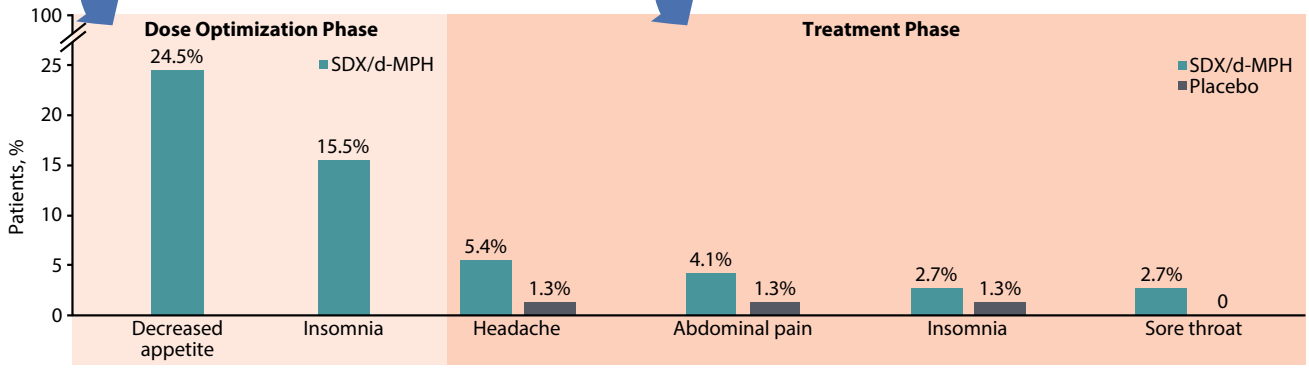
- SDX/d-MPH treatment showed an improvement in the children's attention and classroom behavior compared with placebo
- SKAMP assessment scores were lower in children treated with SDX/d-MPH compared with those given placebo, indicating more improvement in symptoms for a child with ADHD
- PERMP assessments showed an improvement in children treated with SDX/d-MPH as compared with children treated with placebo

13 HOURS SDX/d-MPH was shown to be effective from 0.5- to 13-hours after the medication was given.



67.1% During the dose-optimization phase, 67.1% of all patients reported side effects (the unintended and unwanted effects of the medication), the most common being decreased appetite (24.5%) and insomnia (15.5%).

31.1% During the treatment phase, 31.1% of those taking SDX/d-MPH versus 14.5% of those taking placebo reported side effects; the most common side effects with those taking SDX/d-MPH versus those given placebo were headache (5.4% versus 1.3%), abdominal pain (4.1% versus 1.3%), insomnia (2.7% versus 1.3%), and sore throat (2.7% versus 0).



Taylor & Francis
Taylor & Francis Group

2 Study 2 (12-month safety study)

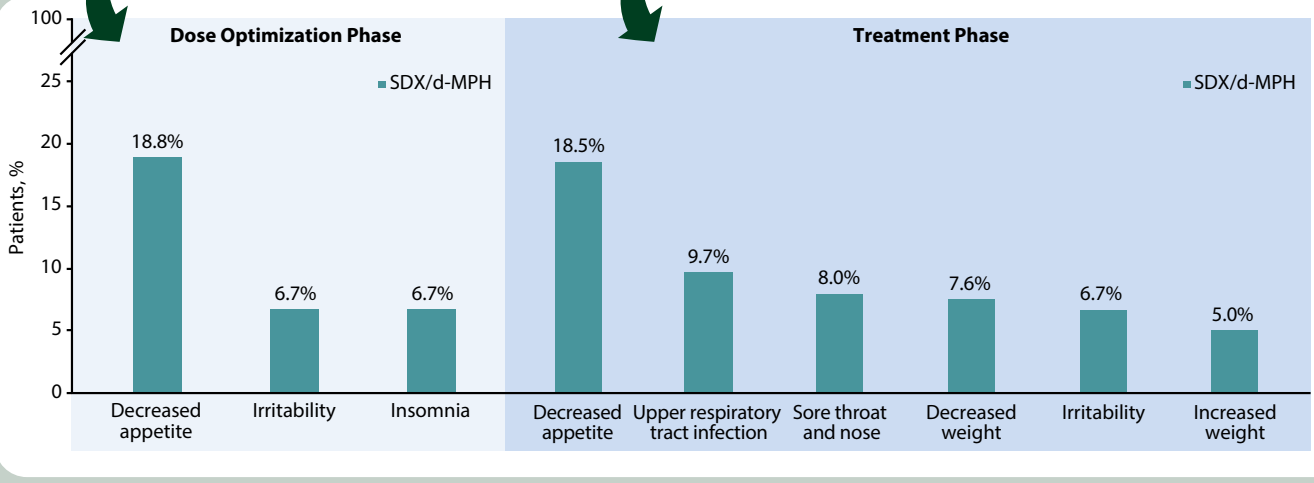
There were no new safety issues that were found. Side effects were similar to those seen in the classroom study and with studies of other MPH-containing medications.

54.3%

During the dose-optimization phase, 54.3% reported side effects, the most common being decreased appetite (18.8%) and irritability and insomnia (both 6.7%).

60.1%

During the treatment phase, 60.1% reported side effects, the most common being decreased appetite (18.5%), upper respiratory tract infection (9.7%), sore throat and nose (8.0%), decreased weight (7.6%), irritability (6.7%) and increased weight (5%).



The ADHD-RS-5 and CGI-S assessments showed an overall reduction in ADHD symptoms and severity that was maintained during the 12-month study period.

What do the results of the studies mean?

Study 1 (laboratory classroom study)

SDX/d-MPH showed a noticeable improvement in ADHD symptoms compared with placebo in children and adolescents aged 6 to 12 years. SDX/d-MPH was shown to be effective as soon as 30 minutes after it was taken and lasted up to 13 hours after after taking the medication. SDX/d-MPH was found to be as safe as other MPH medications used to treat ADHD.

Study 2 (12-month safety study)

After 12 months of use, SDX/d-MPH was found to be safe and remained effective in reducing ADHD symptoms throughout 12 months of treatment.

10.2217/fnl-2023-0026

Some potential weaknesses of this analysis

- In the real-world setting, as compared with a well-controlled clinical study setting such as this, children with ADHD may also have other health and behavioral problems, but children with those other problems were not included in this study. There is a possibility that in a real-world setting, the outcomes with SDX/d-MPH treatment may be slightly different
- In the classroom study, children could have received a placebo, but in the 12-month open-label study, no placebo was given. So, it is unknown if the mere action of taking a medication, but not the medication itself, could have made the children feel better

Where can readers find more information on this study and ADHD?

Original publication citation

Kollins SH, Braeckman R, Guenther S, Barrett AC, Mickle TC, Oh C, Marraffino A, Cutler AJ, Brams MN. A randomized, controlled laboratory classroom study of serdexmethylphenidate and d-methylphenidate capsules in children with attention-deficit/hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* 31(9), 597–609 (2021). doi: 10.1089/cap.2021.0077.

The study number is NCT03292952, and additional information on the study can be found at ClinicalTrials.gov (https://www.clinicaltrials.gov/study/NCT03292952).

Original publication citation

Childress AC, Marraffino A, Cutler AJ, Oh C. Safety and tolerability of serdexmethylphenidate/dexmethylphenidate capsules in children with attention-deficit/hyperactivity disorder: a 12-month, open-label safety study. *J. Child Adolesc. Psychopharmacol.* 33(2), 51–58 (2023). doi: 10.1089/cap.2022.0076.

The study number is NCT03460652, and additional information on the study can be found at ClinicalTrials.gov (https://www.clinicaltrials.gov/study/NCT03460652).

Educational resource

For more information on ADHD, visit these websites: American Psychiatric Association (https://www.psychiatry.org/) and National Institute of Mental Health – Attention-Deficit/Hyperactivity Disorder (https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd).

For more information on SDX/d-MPH (trade name Azstarys®) visit: (https://azstarys.com/).

Acknowledgments

The authors thank the patients in both studies and staff at the participating study sites.

Financial disclosure

Clinical research was funded by Zevra Therapeutics Inc (previously KemPharm Inc). Funding for editorial and writing assistance in the form of proofreading, copyediting, and fact-checking was provided by Corium LLC (Boston, MA, USA). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed in the original articles.

Competing interests disclosure

A full list of authors' disclosures can be found in the original articles. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed in the original articles. Full disclosure information for the authors can be found here:
https://www.liebertpub.com/doi/10.1089/cap.2021.0077 and https://www.liebertpub.com/doi/10.1089/cap.2022.0076.

Writing disclosure

Plain language summary graphic design, writing, and editorial support were provided by Sandra Muller; Charlette Tiloke, PhD and Gautam Bijur, PhD; and Mary C. Wiggin, respectively; of Ashfield MedComms, an Inizio company, and were funded by Corium LLC. The authors had full control of this summary and provided their final approval of all content.