Serdexmethylphenidate/Dexmethylphenidate – A Promising Treatment Option for Childhood Attention Deficit Hyperactivity Disorder (ADHD)

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Attention Deficit Hyperactivity Disorder[1,2]

- A neurodevelopmental disorder of childhood that usually lasts into adulthood; often negatively impacts the affected individual's academic and professional achievements, social interactions and daily functioning.
- The American Psychiatric Association's Diagnostic and Statistical Manual, 5th Edition (DSM-5) listed criteria for the diagnosis of ADHD. No laboratory, imaging and physical diagnostic tests are available to diagnose ADHD.
  - Three Predominant Symptoms: Inattentive, Hyperactivity-Impulsive, and Combined.
  - Symptoms must be present before age 12 and in more than one setting (i.e., both at home and in school, or social events).
  - Six or more symptoms have been present for at least 6 months and are inappropriate for developmental level.

The Multimodal Treatment Study of Children with ADHD (MTA)[3]

- First phase: 579 children aged 7 to 9.9 with ADHD Combined type participated in a 14-months open label, randomized clinical trial.
- Unequivocally established that drug therapy (psychostimulants with adequate dosing) were efficacious, safe, and well-tolerated in managing the ADHD symptoms.
- Behavioral therapy management appeared to be an option in alleviating symptoms of ADHD but is not effective as medication therapy.
- Long term effects remain to be further delineated.

FDA-approved pharmacologic treatments for ADHD[1,4,5]

- Stimulants (Amphetamine, Methylphenidate): First-line agent in controlling symptoms of ADHD with manageable side effects, most notably decreased appetite, insomnia, stunted growth (height).
  - Most are Controlled Substances class II (C-II).
- Non-stimulants (Atomoxetine, Clonidine, Guanfacine, Viloxazine): NOT controlled substances; slower onset than the stimulants, longer duration (up to 24 hours).

Serdexmethylphenidate/d-methylphenidate (SDX/d-MPH)

- SDX is a prodrug of d-MPH and gradually convert to d-MPH in the lower GI tract;[6] given with d-MPH for earlier onset of drug activity.
- Once daily dosing; may provide a rapid onset of symptom control in the morning and sustained duration of symptom control throughout the day.[6]

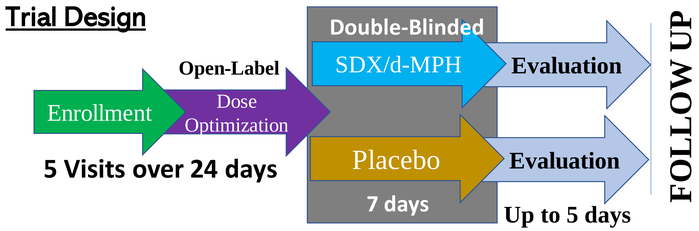
The Ideal ADHD Pharmacotherapy Agent

- Effective
- Safe and Tolerable
- Adequate but not excessive duration of activity
- Minimal drug-drug interactions
- Cost-effective

Clinical Literature Review

The NCT03292952 Trial (Kollins et al, 2021) [6]

- Doubled-blinded, randomized trial conducted in the U.S.
- **Trial Design**



- Initial daily dose of SDX/d-MPH 39.2 mg/7.8 mg, titrated to a maximum dose of 52.3 mg/10.4 mg/day during titration.[6]
- Average age 9.6 years, approximately 50% White male; average ADHD-RS-5 score 41.8 (out of 54)[6]; CGI-S score 4.9 (out of 7)[6]; 88% combined ADHD subtype
- **Trial Endpoints**

ENDPOINTS	DESCRIPTION
PRIMARY	Difference in SKAMP-C rating scale (subjective impairment of classroom behavior)[7] between start and end of testing
KEY SECONDARY	Onset of effect; Duration of treatment effects SKAMP-Deportment, SKAMP-Attention PERMP (Performance scoring) Math test over 10 minutes.[7]

- **Results**
  - **All SDX/d-MPH subjects (n=74, 71/74 dose-escalated), and all but 1 in placebo (75/76) completed randomization.**

SKAMP-C Scores, mean (SD)	SDX/d-MPH (n=74)	Placebo (n=76)
End of Randomization	17.9 (9.2)	17.9 (10.4)
End of Blinded Trial	17.0 (8.5)	14.8 (9.0)
Difference at End of Blinding (SE)	**-5.41 (0.97);** 95% CI (-7.1 to -3.71)	
Difference at Follow-up (post-hoc)	**-7.27 (0.88);** 95% CI (-9.00 to -5.53)	
Difference in ADHD-RS-5 scores	**-25.6 (8.6);** 95% CI NOT REPORTED	

- **SKAMP-D, SKAMP-A, and PREMP all showed improvement in the first 2 hours of each dose (at the end of blinded trial).**

Pharmacokinetics (Braeckman et al, 2022)[8]

- Randomized, open-labeled trial.
- Subjects: Average age 37.2 years; ~50% Black and White, all males.
- Three dosing groups (Treatment A, Treatment B, Treatment C).
- **Results**
  - **d-MPH plasma concentration peak ~ 2 hours**
  - **Appears to follow linear pharmacokinetics (doses proportional to serum levels)**
  - **Eliminated half-life ~ 10.8 hours**

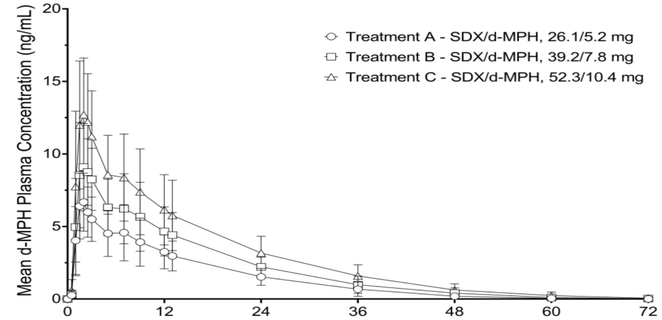


Figure. Plasma concentration-time curve for d-MPH after treatment A, B, C [8]

Adverse Drug Reactions

- SDX/d-MPH demonstrated similar rates and severity of ADRs as other psychostimulants in the same drug class.[6]
  - Most notably decreased appetite and sleep disturbance
- Medium- and long-term effects not elucidated.
- Potential drug interactions with MAO inhibitor, halogenated anesthetics, risperidone.[9]

Discussion

- SDX/d-MPH appears to be similarly effective and have safety profiles comparable to other drugs in the same class, but has only been evaluated in a short, randomized trial (7 days).
- No direct, head-to-head comparisons studies comparing against other psychostimulants in adults and/or children are currently available; whether it can be therapeutically interchanged with other agents, and its place of therapy remain to be determined.
- SDX/d-MPH has been approved in the US market in 2021 under the trade name Azstarys.[9]

Conclusion

- SDX/d-MPH appears to have a linear pharmacokinetics profile.
- SDX/d-MPH appears to be a safe and effective therapeutic option; its place of therapy in the management of ADHD symptoms will need to be determined.
- Long term efficacy and safety data are warranted.

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