Early Integration of DR/ER-MPH (JORNAY PM®) into a Pediatric Practice: Retrospective EMR Analysis of Children and Adolescents with ADHD

James C. Anderson IV, MD[1]

[1]Austin Regional Clinic, Austin, TX, USA

Introduction

- There remains a significant unmet need in stimulant-treated individuals with attention-deficit/hyperactivity disorder (ADHD) for all-day control of ADHD symptoms from the time of awakening until bedtime[1-3]
- DR/ER-MPH (formerly HLD200; trade name: JORNAY PM®) is an evening-dosed, delayed-release and extended-release methylphenidate that targets drug release in the colon, a less absorptive organ compared to the upper bowel[4,5], where other MPH formulations are primarily absorbed
- Colonic absorption underlies many of the distinct pharmacokinetic (PK) properties of DR/ER-MPH:
  - A smooth pharmacokinetic curve with a gradual ascending curve, without the bolus effect associated with an immediate-release (IR) component[6]
  - An extended exposure window that is predicted to be prolonged by increasing the dose[7]
  - Half of the ingested dose is absorbed after peak MPH plasma concentration is reached (ie, in the afternoon and early evening)
- DR/ER-MPH was launched in June 2019 for the treatment of ADHD in patients 6 years and older based on two pivotal Phase 3 trials that demonstrated significant improvements in symptom control and functioning versus placebo throughout the day, from early morning until evening[8,9]

Objective

- To explore findings from an early integration of DR/ER-MPH for the treatment of ADHD in a pediatric practice

Methods

- This study was a single center, retrospective, electronic medical record (EMR) analysis, with data extraction and analysis conducted between May 2021 and July 2021 from a single pediatrician's practice at the Austin Regional Clinic, Texas
  - Approximately 80% of patients at the practice have commercial insurance and ~20% of patients are covered by Medicaid
- All data extracted from the EMR were assessments that were conducted as standard of care
- Inclusion criteria were patients aged 6–18 years with a diagnosis of ADHD, with records of dose, concomitant medications, and weight for at least two visits: (1) DR/ER-MPH initiation, and (2) with an optimized dose of DR/ER-MPH (at least 3 months following DR/ER-MPH initiation)
- This study was determined by an independent IRB (WCG, Princeton, NJ) to be exempted from IRB review because of the anonymized and retrospective nature of the analysis

Data Collection

- Details retrospectively accessed from the Epic (Verona, Wisconsin) EMR included:
  - Demographics and baseline characteristics
  - Starting dose and optimized dose of DR/ER-MPH
    - As dose titration typically occurred weekly for effectiveness and tolerability, doses at least 3 months after DR/ER-MPH initiation were considered optimized doses
  - If applicable, previous stimulant medication and dose
  - Weight at the following time points:
    - DR/ER-MPH initiation
    - At least 3 months after DR/ER-MPH initiation
  - Where available, height at the following time points:
    - Pre-DR/ER-MPH (could include DR/ER-MPH initiation date or prior to initiation)
    - At least 3 months after DR/ER-MPH initiation
  - Patient/parent-reported observations based on clinician prompts
    - Improvements
    - Side effects
    - Eating
    - Appetite

Methods (cont'd)

Data Analysis

- Descriptive statistical methods were applied
- Weight and height z-scores normalized by age and sex were calculated according to the 2000 CDC growth charts for children and youth[10,11]
  - Z-scores represent the number of standard deviations (SD) that the given weight/height lies above or below the age- and sex-normalized mean
- Dose ratios were calculated for each individual using the equation:

$$\text{Dose ratio} = \frac{\text{DR/ER-MPH dose}}{\text{Prior stimulant dose}}$$

- Mean dose ratio was calculated for each prior therapy by averaging individual dose ratios

Results

Patient Baseline Characteristics and Demographics

- The first 30 patients identified in the EMR who met the inclusion criteria were included in the analysis; demographics and baseline characteristics are listed in **Table 1**
  - Patients were initiated on DR/ER-MPH from February 2020–February 2021
  - The mean amount of time that patients were on DR/ER-MPH treatment at the time of data collection was 8 months (range: 3–15)
  - The patient population was mostly (70%) male, with a mean age of 12.8 years (ranging from 6 to 18 years), and with a high rate (87%) of psychiatric comorbidities
  - The majority (70%) received previous stimulant treatment for ADHD

Table 1. Demographics and Baseline Characteristics

Female, n (%)	9 (30%)
Male, n (%)	21 (70%)
Age, mean (SD)	12.8 (3.1)
Age, range	6, 18
Previous stimulant treatment, n (%)	21 (70%)
Average number of psychiatric comorbidities	2.4
Any psychiatric comorbidity, n (%)	26 (87%)
Generalized Anxiety Disorder	19 (63%)
Major Depressive Disorder	16 (53%)
Insomnia	10 (33%)
Oppositional Defiant Disorder	9 (30%)
Autism	4 (13%)
Any concomitant psychotropic medication at DR/ER-MPH initiation, n (%)	19 (76%)
Clonidine IR	8 (27%)
Escitalopram	8 (27%)
Sertraline	5 (17%)
Alprazolam	4 (13%)
Buspirone	3 (10%)
Hydroxyzine	3 (10%)
Aripiprazole	2 (7%)
Bupropion	2 (7%)
Desvenlafaxine	2 (7%)
Guanfacine ER	2 (7%)
Fluoxetine	1 (3%)
Oxcarbazepine	1 (3%)
Ziprasidone	1 (3%)

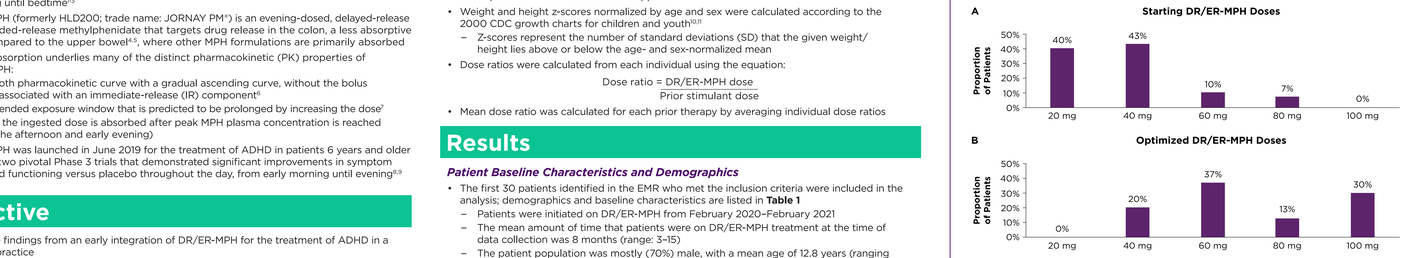
DR/ER-MPH, delayed-release and extended-release methylphenidate; ER, extended-release; IR, immediate-release; SD, standard deviation.

Dosing

- The mean (SD) starting dose was 36.7 (17.5) mg/d, with starting doses based on prior treatment history
  - Most patients initiated on DR/ER-MPH doses of 20 mg (40%) or 40 mg (43%); a smaller proportion of patients were initiated on DR/ER-MPH doses of 60 mg (10%) or 80 mg (7%) (**Figure 1A**)
- The mean (SD) optimized dose was 70.7 (22.7) mg/d
  - Optimized doses ranged between 40 mg and 100 mg (**Figure 1B**); no patients remained at 20 mg

Results (cont'd)

Figure 1. Starting (A) and Optimized (B) DR/ER-MPH Doses



DR/ER-MPH, delayed-release and extended-release methylphenidate.

- Dose ratios are presented in **Table 2**
  - Dose ratios in this patient population were similar to those calculated from the pivotal Phase 3 dose-optimization trial (NCT02493777), where patients were dose optimized for symptom control from early morning until the evening, indicating that these patients likely achieved similar symptom control over the full day[12]
  - The dose ratios herein, and in the Phase 3 trial, were higher than those predicted solely from bioavailability differences between DR/ER-MPH and other formulations, likely a result of the extended exposure window with DR/ER-MPH[6,12]

Table 2. Dose Ratios

Prior ADHD therapy[a]			Sample size	Mean prior stimulant dose (mg/day)	Mean optimal DR/ER-MPH dose (mg/day)	Mean dose ratio[b]
Stimulant Monotherapy	MPH	OROS MPH	4	31.5	70	2.3
		d-MPH XR	3	16.7	53.3	3.2
		MPH XR-ODT	1	25.9	40	1.5
		MPH-MLR	1	20	100	5
	AMP	LDX	2	30	50	1.8
		AMP XR-ODT	4	15.7	85	5.4
Stimulant Combination	MPH	OROS MPH + IR MPH	2	52.5	100	1.9
		d-MPH XR + d-MPH IR	1	22.5	100	4.4
		d-MPH IR BID	1	10	40	4
	AMP	AMP EROS BID	2	16.9	90	5.3
No Previous ADHD Treatment			10	-	68	-

[a]Included branded and generic formulations; [b]Mean of individual dose ratios; ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; AMP EROS, amphetamine extended-release oral suspension (Adzenys ER®); AMP XR-ODT, amphetamine extended-release orally disintegrating tablet (Adzenys XR-ODT®); BID, twice a day; d-MPH IR, dexmethylphenidate immediate release (Focalin®); d-MPH XR, dexmethylphenidate extended release (Focalin XR®); DR/ER-MPH, delayed-release and extended-release methylphenidate (JORNAY PM®); ER, extended-release; IR MPH, immediate-release methylphenidate (Ritalin®); LDX, lisdexamfetamine dimesylate (Vyvanse®); MPH, methylphenidate; MPH-MLR, methylphenidate multilayer bead extended release (Aptensio XR®); MPH XR-ODT, methylphenidate extended-release orally disintegrating tablets (Cotempla XR-ODT®); OROS MPH, osmotic release oral system methylphenidate (Concerta®).

- Six patients were previously on a regimen that required a second stimulant dose taken in the afternoon; all 6 were optimized to a single stimulant dose with DR/ER-MPH (ie, required no afternoon stimulant dose) (**Table 3**)
- Ten patients were previously on a combination of stimulants and non-stimulants (either clonidine IR or guanfacine ER); all 10 remained on the non-stimulant with DR/ER-MPH (**Table 3**)

Table 3. Previous Combination Regimens

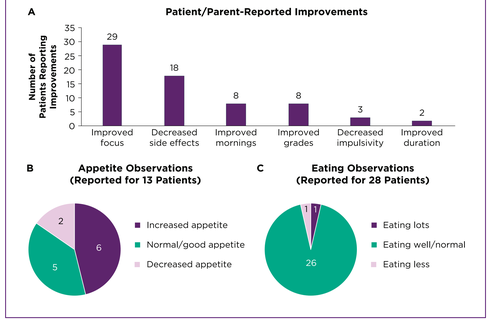
Previous regimen	Current regimen
Stimulant Combination (ER + ER, ER + IR, or IR + IR) ± Non-stimulant	
Stimulant combination[a], n = 2	DR/ER-MPH, n = 2
Stimulant combination[b] + Clonidine IR QHS, n = 3	DR/ER-MPH + Clonidine IR QHS[d], n = 3
Stimulant combination[c] + Guanfacine ER QHS, n = 1	DR/ER-MPH + Guanfacine ER QHS, n = 1
Stimulant + Non-stimulant	
Stimulant + Clonidine IR QHS, n = 2	DR/ER-MPH + Clonidine IR QHS[d], n = 2
Stimulant + Guanfacine ER QHS, n = 1	DR/ER-MPH + Guanfacine ER QHS, n = 1
Non-stimulant	
Clonidine IR QHS, n = 3	DR/ER-MPH + Clonidine IR QHS[d], n = 3

[a]ER + IR, n=2.
[b]ER + ER, n=1; ER + IR, n=1, IR + IR, n=1.
[c]ER + ER, n=1.
[d]3 patients were prescribed Clonidine IR PRN (unchanged between previous and current regimen).
ER, extended-release; IR, immediate-release; PRN, as needed; QHS, at bedtime.

Patient/Parent-Reported Improvements, Appetite Observations, Eating Observations, and Side Effects

- The following were reported regarding patient/parent-reported improvements, changes/levels in appetite and eating, and any side effects with optimized doses of DR/ER-MPH:
  - Most patients reported multiple improvements (**Figure 2A**), with almost all (97%) reporting improved focus
  - Of the 13 patients for which appetite observations were noted, most reported increased (46%) or normal/good appetite (17%), with 2 patients (15%) reporting decreased appetite (**Figure 2B**)
  - Of the 28 patients for which eating observations were noted, the majority (93%) reported they were eating well/normally; 1 patient (4%) each noted increased and decreased eating (**Figure 2C**)
  - One of the patients who reported decreased appetite (stimulant-naïve) and the one patient who reported decreased eating were prescribed cyproheptadine to improve appetite/eating
  - No side effects beyond the two cases of decreased appetite and one case of decreased eating were noted in the EMR

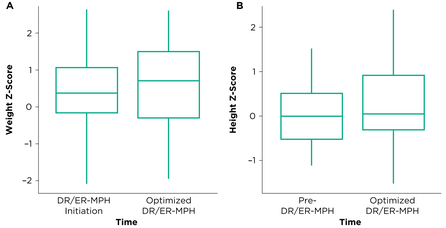
Figure 2. Patient/Parent-Reported Improvements (A), Appetite Observations (B), and Eating Observations (C)



Weight and Height Trajectories

- Weight and height z-scores (normalized by sex and age) were calculated and plotted in **Figure 3**
  - Median (interquartile range [IQR]) weight z-scores increased from 0.38 (–0.16, 1.06) at DR/ER-MPH initiation to 0.71 (–0.31, 1.50) with optimized DR/ER-MPH
- Chart notes indicated that one patient was actively trying to lose weight by exercise and diet; the patient's weight (z-score) decreased from 72 kg (2.64) at DR/ER-MPH initiation to 58.5 kg (1.73) with optimized DR/ER-MPH
- One weight measurement at DR/ER-MPH initiation and 12 weight measurements on optimized DR/ER-MPH were taken at home, which reflects the reality of telemedicine during the COVID-19 pandemic
- Height measurements were not an inclusion criterion; nonetheless, 13 patients had height records before DR/ER-MPH (including at DR/ER-MPH initiation) and with optimized DR/ER-MPH (at least 3 months following DR/ER-MPH initiation)
  - Median (IQR) height z-scores increased from 0 (–0.53, 0.51) pre-DR/ER-MPH to 0.05 (–0.32, 0.92) with optimized DR/ER-MPH (**Figure 3**)

Figure 3. Weight (A, n = 30) and Height (B, n = 13) Z-Score Box Plots



The top and bottom of the box indicate the third and first quartiles, respectively, with the center of the box indicating the median. The top and bottom whiskers indicate the maximum and minimum, respectively.
DR/ER-MPH, delayed-release and extended-release methylphenidate.

Conclusions

- This retrospective database analysis in a typical pediatric clinic setting with patients with multiple comorbidities corroborated Phase 3 trial results, where patients on an optimized dose of DR/ER-MPH achieved significant reductions in ADHD symptoms versus placebo from early morning until evening with a safety profile consistent with other MPHs
  - Clinician-noted benefits were reported with a single appropriately titrated dose of DR/ER-MPH, with no requirement for an afternoon stimulant dose, and few side effects were reported
- The positive appetite/eating reports and increased weight trajectory reported herein indicate that DR/ER-MPH may have a milder suppressant effect on appetite/weight compared to other stimulants, possibly due to its lack of an IR component and resulting smooth pharmacokinetic profile with no peaks and troughs during the day[6,13]
- These positive findings warrant investigation in prospective and/or real-world data evidence studies to see if the results from this small retrospective study at a single pediatric practice are generalizable to a larger population of patients with ADHD

Disclosures

James C. Anderson IV, MD: Speaker Bureau: Ironshore Pharmaceuticals Inc., Supernus Pharmaceutials, Inc.

Acknowledgements

Under the guidance of the author, writing support was provided by Michelle Po, PhD, of Highland Therapeutics Inc., the parent company of Ironshore Pharmaceuticals. Cassandra Uchida, PhD, and Marina Komolova, PhD, of Highland Therapeutics Inc. and Lewis Warrington, MD, and Karl Weddige, PhD, both of Ironshore Pharmaceuticals Inc. all reviewed content for scientific accuracy.

References

1. Brown TE, et al. *Prim Care Companion CNS Disord*. 2019;21(3):18m02397. **2.** Sallee FR. *J Child Adolesc Psychopharmacol*. 2015;25(7):588-565. **3.** Faraone SV, et al. *J Child Adolesc Psychopharmacol*. 2017;27(8)715-722. **4.** Watts PJ, et al. *Drug Dev Ind Pharm*. 1997;23(9):893-913. **5.** Vertzoni M, et al. *Eur J Pharm Sci*. 2019;134:153-175. **6.** Liu T, et al. *J Child Adolesc Psychopharmacol*. 2019;29(3):181-191. **7.** Gomeni R, et al. *J Clin Psychopharmacol*. 2020;40(4):350-358. **8.** Pliszka SR, et al. *J Child Adolesc Psychopharmacol*. 2017;27(6):474-482. **9.** Childress AC, et al. *J Child Adolesc Psychopharmacol*. 2020;30(1):2-14. **10.** Kuczmarski RJ, et al. *Vital Health Stat 11*. 2002;246:1-190. **11.** Flegal KM, et al. *Natl Health Stat Report*. 2013;63:1-3. **12.** Childress AC, et al. *Clin Ther*. 2020;42(12):2332-2340. **13.** Gomeni, R., et al. Poster presented at: American Professional Society of ADHD and Related Disorders Annual Meeting; January 2021; Virtual.

Developed and published with support from Ironshore Pharmaceuticals & Development, Inc.

Poster presented at the Journal of Clinical Psychiatry and The Primary Care Companion for CNS Disorders Perpetual Poster Session, 2021.