EXECUTIVE SUMMARY

Uniform Formulary Beneficiary Advisory Panel (BAP)
Meeting Summary
September 25, 2019

UNIFORM FORMULARY DRUG CLASS REVIEW

I. UF CLASS REVIEWS—HIGH-POTENCY TOPICAL CORTICOSTEROIDS

A. High-Potency Topical Corticosteroids—UF/Tier 4/Not Covered recommendation

The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent for all the members of the class, except for Cordran Tape: 14 for, 2 opposed, 0 abstained, 1 absent) the following formulary recommendations for the High-Potency Topical Corticosteroids as outlined below, based on clinical and cost-effectiveness.

When considering the High-Potency Topical Corticosteroid candidates for Tier 4/not covered status, the P&T Committee considered the information outlined in the interim rule, Section 702(b)(10) of the NDAA 2018 published on December 11, 2018, and found at: https://www.federalregister.gov/documents/2018/12/11/2018-26562/tricare-pharmacy-benefits-program-reforms. The interim rule allows for complete exclusion of drugs from TRICARE pharmacy benefit coverage when certain criteria are met. Tier 4 status will apply to all users of the recommended candidates.

- UF
  - betamethasone dipropionate 0.05% ointment
  - betamethasone/propylene glycol 0.05% ointment, cream, lotion, and gel
  - clobetasol propionate 0.05% ointment, cream, solution, lotion, shampoo, spray, gel, and foam
  - clobetasol propionate/emollient 0.05% cream
  - clobetasol propionate/emollient 0.05% emulsion foam
  - desoximetasone 0.25% ointment and cream
  - fluocinonide 0.05% ointment, cream, solution, and gel
  - fluocinonide/emollient base 0.05% cream
  - halobetasol propionate 0.05% ointment
  - *Note that all the agents recommended for UF status are currently on the formulary.*
- NF
  - amcinonide 0.1% ointment (Cyclocort, and generics)
  - clobetasol propionate/emollient 0.05% foam (Olux-E, generics) *(moves from UF to NF status)*

- desoximetasone 0.05% gel (Topicort, generic) *(moves from UF to NF status)*
- diflorasone diacetate 0.05% ointment (Psorcon, Apexicon, and generics)
- diflorasone diacetate 0.05% cream (Psorcon, Apexicon, and generics
- fluocinonide 0.1% cream (Vanos, and generics)
- flurandrenolide 4 mcg/sq. cm tape (Cordran) *(moves from UF to NF status)*
- halobetasol propionate 0.05% cream (Ultravate and generics *(moves from UF to NF status)*

- Tier 4/Not Covered
  - clobetasol propionate 0.025% cream (Impoyz)
  - clobetasol propionate 0.05% shampoo/cleanser (kit) (Clodan kit)
  - diflorasone diacetate/emollient 0.05% cream (Apexicon-E)
  - halcinonide 0.1% ointment (Halog)
  - halcinonide 0.1% cream (Halog)
  - halobetasol propionate 0.05% lotion (Ultravate)
  - halobetasol propionate 0.05% foam (Lexette & authorized) *(note that Lexette foam was previously recommended for Tier 4 status in February 2019, with implementation scheduled for August 28, 2019)*
  - halobetasol propionate 0.01% lotion (Bryhali)

  For all eight products recommended for Tier 4/Not Covered status, the P&T Committee concluded that Impoyz, Clodan kit, Apexicon-E, Halog ointment and cream, Ultravate, Lexette and authorized, and Bryhali provide very little to no additional clinical effectiveness relative to the other high-potency topical corticosteroids. Overall, the P&T Committee felt that that the needs of TRICARE beneficiaries can be met by the other high-potency topical steroids.

B. High-Potency Topical Corticosteroids—Manual Prior Authorization (PA) Criteria

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for amcinonide 0.1% and diflorasone diacetate 0.05% ointments, diflorasone diacetate 0.05% cream, clobetasol propionate/emollient 0.05% foam, desoximetasone 0.05% gel, and Cordran tape in all new and current users, due to the large number of clinically and cost-effective formulary alternatives available.

The PA criteria are as follows:

1. amcinonide 0.1% ointment and diflorasone diacetate 0.05% ointment

PA criteria apply to all new and current users of amcinonide 0.1% ointment and diflorasone diacetate 0.05% ointment.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:

- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including clobetasol propionate 0.05% and fluocinonide 0.05% ointments. These agents do not require a PA.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to fluocinonide 0.05% AND desoximetasone 0.25% AND betamethasone dipropionate 0.05% ointments.
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

2. clobetasol propionate/emollient 0.05% foam

PA criteria apply to all new and current users of clobetasol propionate/emollient 0.05% foam.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:

- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including fluocinonide 0.05% solution and clobetasol propionate 0.05% solution. These agents do not require a PA.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to clobetasol propionate 0.05% solution, lotion, gel, AND foam
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

3. desoximetasone 0.05% gel

PA criteria apply to all new and current users of desoximetasone 0.05% gel.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:

- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including fluocinonide 0.05% solution and clobetasol propionate 0.05% solution. These agents do not require a PA.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to fluocinonide 0.05% solution AND gel
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days

No PA renewals allowed; patients must fill out a new PA each time

4. diflorasone diacetate 0.05% cream

PA criteria apply to all new and current users of diflorasone diacetate 0.05% cream.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:

- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including fluocinonide 0.05% and betamethasone/propylene glycol 0.05% creams. These agents do not require a PA.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to fluocinonide 0.05% AND betamethasone/propylene glycol (augmented) 0.05% AND desoximetasone 0.25% creams.
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

5. flurandrenolide 4 mcg/sq. cm (Cordran) tape

PA criteria apply to all new and current users of Cordran tape.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:

- The prescription is written by a dermatologist or plastic surgeon
- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including clobetasol propionate 0.05% ointment and fluocinonide 0.05% cream and solution. These agents do not require a PA.
- The provider acknowledges that barrier function can be accomplished by using an alternative agent (e.g., fluocinonide 0.05% cream) with an occlusive dressing. Please note occlusion increases transmission (i.e., potency); a lower potency agent should be used as an alternative to flurandrenolide tape if used with a barrier.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to clobetasol propionate 0.05% ointment OR halobetasol propionate 0.05% ointment OR betamethasone dipropionate 0.05% ointment.
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

C. High-Potency Topical Corticosteroids—UF/Tier 4/Not Covered and PA Implementation Plan

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) an effective date of 120 days from signing of the minutes in all points of service (POS), and that DHA send letters to beneficiaries who are affected by the Tier 4 decision and those affected by a change from UF to NF status.

Summary of Physician's Perspective

This subclass was reviewed due to the high degree of therapeutic interchangeability among products within the same potency sub-class and vehicle, and due to the large number of inexpensive generic products available.

Overall, 2/3 of the MHS utilization for the high potency steroids is for the cream and ointment formulations, and several of these formulations were recommended to stay on the Uniform formulary.

We did reach out to dermatologists for their input. Some of their comments were that having too many options can cause confusion and increase the risk of dosing errors; for example halobetasol is available in both a 0.05% and 0.01% formulation. Some of the providers mentioned that they only required clobetasol and fluocinonide on the formulary, (which are the two products with the highest utilization in the MHS), as long as there were different vehicles available. Others also commented that the number of products available on the formulary could be decreased, and recommended limiting the formulary to the most affordable agents.

For the formulary recommendation, determining what was needed was based on clinical reasons such as having a product from each Coopman class; including both super-high potent and high potent agents; and including a variety of vehicle formulations. The committee then assessed utilization patterns and cost,taking into account if large numbers of patients would be affected by a potential change from UF to NF. For the products recommended for UF status, they are all currently on the formulary, and represent 23 different products.

Out of the 8 products recommended for NF status, 4 are currently already designated NF. For the entire subclass, there were about 245,000 unique utilizers in the past year, and the formulary change from UF to NF for the 4 products that are currently UF will affect about 4,900 patients.

For the NF drugs, 6 products were recommended to have PAs, since there are several therapeutic alternatives which are cost effective. Although a "no grandfathering" scenario was recommended for all the PAs, it is very likely that by the time the PA is implemented, existing users would have completed their treatment course, due to the acute use of these products. Therefore the PA recommendations will are expected to effectively impact new users.

I wanted to make a few comments about Cordran tape.

- Cordran tape is currently on the UF, and in contrast to the other high potency steroids, the vast majority of the utilization is at the MTFs. It is intended for small areas that are difficult to treat, including fingertips, or to prevent the patient from scratching lesions. Cordran tape can be used for patients with keloid scars. There was a significant 1,600% price increase for the tape in 2017, and Cordran was considered for potential Tier 4/Not Covered status.

- A survey of our dermatology providers found that there were some mixed opinions on whether to move this product to Tier 4, but did recommend limiting use to dermatologists.

- The recommendation for Cordran tape was for NF status with a prior authorization. The two opposing votes for the Cordran formulary recommendation were because these P&T Committee members felt Tier 4 status was appropriate.

- The prior authorization is similar to the other topical steroid PAs, with the exception that Cordran tape must be prescribed by a dermatologist or plastic surgeon, and we do allow the provider to write in why the formulary alternatives are not acceptable, for example in the cases of patients with burns or keloids.

There are 8 products recommended for Tier 4 status; 6 of the products are currently designated as NF, one product (the Lexette foam brand) is already Tier 4 from the February 2019 meeting, and only one product (the Clodan shampoo kit) is currently UF. The Tier 4 recommendations will affect about 715 patients. However, when we looked at the total number of annual prescription fills, the majority of patients received about two fills yearly. The high potency topical steroids are not chronic medications, due to the risks associated with long term steroid use.

For the implementation period, the Committee did recommend 120 days after signing. We will send letters to the patients affected by the UF to NF changes and the Tier 4 recommendation. The patients affected by the Tier 4 change will get two letters – one at 60 days prior to implementation, and then at 30 days prior to implementation, if they are still on a Tier 4 drug. The patients affected by the PA recommendations won't receive letters, based on our review of the prescription utilization, and since the patient will likely have completed therapy by the implementation period.

Summary of Panel Questions and Comments

Mr. Hostettler mentioned that it was discussed in the March meeting that Tier 4 was to be judiciously used and 21% of the class is recommended for Tier 4. He is concerned that the Panel is setting a precedent regarding Tier 4 utilization. He also commented that the primary advantage of the available vehicle types (gels, sprays, shampoo, and tape) for this class was for patient convenience and questioned what value patient convenience is given.

CDR Hellwig responded that at least 1 of each vehicle type for this class was left on the formulary for patient convenience, including some deemed less necessary.

Mr. Hostettler asked if there are at least 2 uniform formulary products for each vehicle type as patients may not respond to the first prescription received.

Dr. Khoury had mentioned that this depends on the class, be it by Coopman Class or Stoughton Cornell Class, which is being referenced as some classes only have 1 vehicle type.

CDR Hellwig responded that tape only has 1 product. CDR Hellwig noted that prescribers were saying that they did not require all vehicle types and that some vehicle types fill the same niche such as gels and lotions.

Dr. Khoury noted that the prescribers are saying that all that is needed for treating most patients are 1 or 2 agents and that if the steroid is failing, it may be more related to the patient's disease not responding to the medication.

Mr. Hostettler commented that although some drugs had very little to no additional clinical effectiveness, there is some benefit to the patient.

Mr. Du Teil expressed his concern about more than 20% of the class moving to Tier 4. He asked why the products with "very little to no additional clinical effectiveness" were not moved to Tier 3, as opposed to Tier 4.

CDR Hellwig reiterated that some of the products are considered interchangeable and therefore provide little additional benefit over their counterparts. While there appears to be a higher percentage of Tier 4 agents than in the past, there is actually over 20 agents on the formulary which is more than most classes.

Mr. Hostettler expressed concern that there is no Tier 4 appeals process, potentially leaving physicians and patients with no options. The beneficiary would have options with an appeal process.

Dr. Khoury referenced the drug class PPIs which included designating agents Tier 4 in February. He stated that 2 out of 8 PPI agents were recommended for Tier 4 status, which is equal to 25% of the class, which is an even higher percentage than the current class in question. More important than the number of agents, is out of 245,000 unique utilizers, only 4000 of them are impacted by this Tier 4 recommendation (approximately1%). The impact this recommendation designating these agents Tier 4 on the beneficiary population is very low.

Mr. Hostettler responded that the numbers support the fact that the beneficiary impact is low. However, if you are one of the beneficiaries impacted, the recommendation could be significant. He also brought up that requiring a PA every 30 days for some of these agents would be difficult for prescriptions that come with multiple refills.

CDR Hellwig said that most patients don't get refills on this class of drugs. The mode (most common) amount of fills per prescription was 1 (average of 2 fills a year). However, there are patients with more complicated diseases that require more frequent use throughout the year.

Dr. Bertin stated that the beneficiary population he represents believes that Tier 4 is a very powerful and scary tool. Scary for the people who don't know much about drug cost issues and scary for those of us who do. He requested that formulary recommendations, especially Tier 4, be sensitive to the concerns of the beneficiaries and reiterated that Tier 4 should be used judiciously.

Dr. Bertin asked if the PA criteria was correct for clobetasol propionate/emollient 0.05% foam, where the beneficiary is required to try and fail each vehicle type (the solution, lotion, gel and foam) for 2 weeks. He also expressed concerns regarding the time it would take to complete each trial and go back to the doctor to get a new prescription. He also asked what if the patient condition did not require the use of a foam or one of the other products required by the trial.

CDR Hellwig concurred that this is correct and that there is no discernable clinical advantage of this foam type vs the other agent vehicles.

Dr. Piirainen expressed concern about the circumstance where a patient has had a PA approved already but needs a refill or additional medication for a larger area. They would have to reapply for a PA as a result of PA expirations being 30 days.

Dr. Peloquin asked if there are a lot of varying package sizes for these Non-Formulary medications as that may affect the required amounts for cases such as 2 weeks on 2 weeks off or larger required amounts.

CDR Hellwig, in response, said that the days' supply should correctly reflect the amount prescribed and is unsure if package size and quantity were considered when reviewing PA criteria. It was noted that there are no quantity limits on these products aside from tape, which is limited to 1 roll of tape. Prescribers can prescribe the necessary quantities per patient requirements.

Mr. Hostettler asked if there was discussion about extending the PA expiration past 30 days. He also stated that some patients require the medications for longer periods of time.

CDR Hellwig commented that she doesn't believe there was any discussion among the committee member for a longer PA expiration date.

Dr. Khoury mentioned that there would be concerns with using large amounts of high potency corticosteroids in a short period and in most cases an alternate course such as an oral course may be recommended past 2 weeks or for larger surface areas.

CDR Hellwig also reiterated that due to the large variety of formulary products, most patients will likely find an effective product.

Dr. Khoury noted that the PAs are monitored and audited. The PAs can be modified in the cases where clinical concerns are identified that were not previously known.

CDR Hellwig added that the pharmacy benefit group receives feedback from patients, including retail, about any difficulties they experience getting particular drugs.

Dr. Dager commented that there has been a lot of discussion regarding feedback on the PA. Has any feedback been received (complaints, other issues, etc.) received about Tier 4 drugs?

Dr. Khoury noted that the March 2019 Tier 4 recommendations were implemented on August 28th. We had yet to receive any relevant feedback that needed to be be shared with the BAP.

CDR Hellwig mentioned that a pathway was mapped out to address patient's questions and concerns regarding Tier 4.

Mr. Hostettler asked who beneficiaries can call if they have questions about Tier 4 medications.

Dr. Khoury responded that beneficiaries would most likely engage with the provider in the purchased care setting and MTF about Tier 4 products. If they had been prescribed an agent and were in need of switching, then they would be able to identify an alternative option. If it's through an MTF, that could occur through the MTF pharmacy. Additionally, patients can refer to their Pharmacy Benefits Manager (express scripts) regarding obtaining agents that are alternative to the Tier 4 designated product.

Mr. Hostettler asked about the process used to capture beneficiary Tier 4 complaints.

Mr. Ostrowski provided clarification by stating, there is no appeal process. Is there a process available for beneficiaries to comment and provide feedback? Can those comments be captured and shared with the Panel at a later date?

CAPT Norton noted that while beneficiaries cannot appeal a Tier 4 denial, beneficiaries can also write the Pharmacy Operations Division, Director of Defense Health Agency, or their congressman to file complaints and voice their concerns. As CDR Hellwig stated, the PA process/recommendations are evaluated and beneficiary feedback is taken into account as well as things such as new clinical

information on the drug, changes in marketplace, feedback from providers, comments from physicians on the BAP, etc.

CDR Hellwig did mention that Tier 4 drugs will be re-evaluated again to ensure that their designation still makes sense given any new information/feedback.

Mr. Hostettler asked for further clarification regarding the process for beneficiaries to provide feedback on PA and Tier 4 recommendations.

There were no more questions or comments from the Panel. The chair called for a vote on the UF/Tier 4/Not Covered Recommendations, Manual PA Criteria, and UF/Tier 4/Not Covered and PA Implementation Plan for the High-Potency Topical Corticosteroids.

- **High-Potency Topical Corticosteroids – UF/Tier 4/Not Covered Recommendations**

  Concur: 9 Non-Concur: 1 Abstain: 0 Absent: 0

for ***Director, DHA:***

These comments were taken under consideration prior to my final decision.

- **High-Potency Topical Corticosteroids – Manual PA Criteria**

  Concur: 9 Non-Concur: 1 Abstain: 0 Absent: 0

for ***Director, DHA:***

These comments were taken under consideration prior to my final decision.

- **High-Potency Topical Corticosteroids – UF/Tier 4/Not Covered and PA Implementation Plan**

  Concur: 9 Non-Concur: 1 Abstain: 0 Absent: 0

for ***Director, DHA:***

These comments were taken under consideration prior to my final decision.

II. MULTIPLE SCLEROSIS – INTERFERONS AND METHYL FUMARATE

A. Multiple Sclerosis – Interferons and Methyl Fumarate—UF Recommendation

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) the following for the Multiple Sclerosis agents, as outlined below, based on clinical and cost-effectiveness:

Interferons

- UF
  - interferon beta-1a IM (Avonex)
  - interferon beta-1a SC (Rebif, Rebif Rebidose)
  - interferon beta-1b SC (Betaseron)
  - interferon beta-1b (Extavia)

- NF
  - peginterferon beta-1a SC (Plegridy)

Methyl Fumarate

- UF
  - dimethyl fumarate (Tecfidera)
- NF
  - None

B. Multiple Sclerosis – Interferons and Methyl Fumarate—Manual PA Criteria

For dimethyl fumarate (Tecfidera), PA criteria have been in place since November 2013 to ensure appropriate safety monitoring. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) updating the current manual PA criteria for dimethyl fumarate (Tecfidera) in new users to only allow use for the FDA-labeled indication of MS.

1. dimethyl fumarate (Tecfidera)
Changes from August 2019 are in BOLD.

Manual PA criteria apply to new users of Tecfidera.

Manual PA Criteria: Coverage approved for patients with:
- Documented diagnosis of relapsing forms of multiple sclerosis (MS).
- Complete blood count drawn within six months prior to initiation of therapy, due to risk of lymphopenia.

- Coverage is NOT provided for concomitant use with other disease-modifying drugs of MS

Non-FDA-approved uses are not approved.
PA does not expire.

C. **Multiple Sclerosis – Interferons and Methyl Fumarate**—UF and PA Implementation Plan

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) implementation effective upon signing of the minutes in all points of service (POS).

Summary of Physician's Perspective

The MS drugs have seen an overall reduction in the use of injectables in favor of oral therapies. We did not review the entire MS class, just the interferons and methyl fumarate subclasses.

For the UF recommendation, the unanimous decision was that every drug maintains its current formulary status, therefore there is no patient disruption. Since there were no copay changes, no letters are needed.

We will continue to keep the PA for Tecfidera due to the safety concerns of PML. The only change in the PA was explicitly stating that uses other than for MS are not allowed.

Summary of Panel Questions and Comments

Mr. Hostettler asked that if the discontinue rates for all interferons are similar, then why is there a NF recommendation for Plegridy.

CDR Raisor responded that it's based on cost effectiveness.

Mr. Hostettler asked if the new PA criteria for Tecfidera would affect current users.

CDR Raisor said that it would only apply to new users. This was identified as a typo in the Manual PA for Tecfidera.

There were no more questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, and UF and PA Implementation Plan for Multiple Sclerosis – Interferons and Methyl Fumarate

- **Multiple Sclerosis – Interferons and Methyl Fumarate – UF Recommendation**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

Director, DHA:

These comments were taken under consideration prior to my final decision.

- **Multiple Sclerosis – Interferons and Methyl Fumarate – Manual PA Criteria**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

Director, DHA:

These comments were taken under consideration prior to my final decision.

- **Multiple Sclerosis – Interferons and Methyl Fumarate – UF and PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

Director, DHA:

These comments were taken under consideration prior to my final decision.

III. NEWLY APPROVED DRUGS PER 32 CFR 199.21(g)(5)

A. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF/Tier 4/Not Covered Recommendation

The P&T Committee recommended (group 1: 16 for, 0 opposed, 0 abstained, 1 absent; group 2: 17 for, 0 opposed, 0 abstained, 0 absent) the following:

- UF:
  - alpelisib (Piqray) – Oncological Agent for breast cancer

- amifampridine (Ruzurgi) – Miscellaneous Neurological Agent for Lambert-Eaton myasthenic syndrome (LEMS)
- amphetamine sulfate orally disintegrating IR tablet (Evekeo ODT) – Attention Deficit Hyperactivity Disorder (ADHD)
- dolutegravir/lamivudine (Dovato) – Single-tablet regimen (STR) antiretroviral for Human Immunodeficiency Virus (HIV)
- erdafitinib (Balversa) – Oral Oncological Agent for urothelial cancer
- halobetasol propionate 0.01%/tazarotene 0.045% lotion (Duobrii) – Combination product for Plaque Psoriasis
- immunoglobulin subcutaneous injection (Cutaquig) – Immunoglobulin for Immune Deficiency Disorders
- mepolizumab injection (Nucala) – Miscellaneous Pulmonary I Agent for severe asthma and eosinophilic granulomatosis with polyangiitis (EGPA)
- methylphenidate extended-release sprinkle capsules (Jornay PM) – ADHD
- tafamidis (Vyndaqel) – Miscellaneous Neurological Agents for cardiomyopathy associated with hereditary transthyretin-mediated amyloidosis (ATTR-CM)
- triclabendazole (Egaten) – Antiinfectives: Anthelmintics for fascioliasis

- NF:
  - drospirenone (Slynd) – Progestogen-only contraceptive agent
  - galcanezumab-gnlm 100 mg injection (Emgality) – Migraine Agents: Calcitonin gene-related peptide (CGRP) inhibitors for cluster headache. *Note that the Emgality 120 mg injection formulation for prevention of migraine headache remains on the UF.*
  - risankizumab-rzaa injection (Skyrizi) – Targeted Immunomodulatory Biologic (TIB) for Plaque Psoriasis
  - rosuvastatin sprinkle capsules (Ezallor Sprinkle) – Antilipidemics-I
  - solriamfetol (Sunosi) –Wakefulness Promoting Agent

- Tier 4 (Not Covered):
  - methylphenidate extended-release sprinkle capsules (Adhansia XR) – ADHD
    - Adhansia XR was recommended for Tier 4 status as it has very little to no additional clinical effectiveness relative to similar ADHD drugs; there is a significant safety risk due to its very long duration of action (particularly in children for insomnia and weight loss) relative to other ADHD drugs; and the needs of TRICARE beneficiaries are met by alternative agents.
      - Formulary alternatives to Adhansia XR include methylphenidate ER (Aptensio XR sprinkle cap and Quillivant XR suspension), for

patients with swallowing difficulties; Concerta and generics; Ritalin LA and generics; Metadate CD and generics; dexmethylphenidate ER (Focalin XR and generics); and mixed amphetamine salts (Adderall XR and generics).

B. Newly Approved Drugs per 32 CFR 199.21(g)(5)—PA Criteria

The P&T Committee recommended (group 1: 16 for, 0 opposed, 0 abstained, 1 absent; group 2: 17 for, 0 opposed, 0 abstained, 0 absent) the following:

- ADHD: Applying manual PA criteria to new and current users of Jornay PM, requiring a trial of other clinically efficacious, safe, and cost-effective methylphenidate ER formulations with long durations of action first, including branded products targeted for patients with swallowing difficulties (i.e., Quillivant XR suspension or Aptensio XR sprinkle capsule).
- TIBs: Applying the same manual PA criteria in new users of Skyrizi that is currently in place for the other non-step-preferred TIBs. Patients must first try Humira. Additionally for Skyrizi, a trial of both Stelara and Cosentyx is required if the patient cannot be treated with Humira.
- Migraine Agents: CGRP Inhibitors for Cluster Headache: Manual PA criteria apply to the CGRP Inhibitors that are approved for prevention of migraine headache, including Emgality 120 mg injection. PA criteria will apply to new users of Emgality 100 mg syringe for cluster headache, requiring a trial of traditional preventive therapies, including verapamil, topiramate, or lithium. Use of Emgality 100 mg will not be allowed for prevention of migraine headache.
- Applying manual PA criteria to new and current users of Sunosi and Nucala.
- Applying manual PA criteria to new users of Ruzurgi, Ezallor Sprinkle, Piqray, Balversa, Vyndaqel, and Evekeo ODT.

Full PA Criteria for the Newly Approved Drugs per 32 CFR 199.21(g)(5)

1. alpelisib (Piqray)

Manual PA is required for all new users of Piqray.

Manual PA Criteria: Piqray is approved if all criteria are met:

- Patient must be ≥ 18 years old.
- Patient is diagnosed with advanced or metastatic HR positive, HER2 negative breast cancer with PIK3CA mutation as confirmed by an FDA-approved test.
- Drug is prescribed by, or in consultation with, an oncologist/hematologist.

- Female patients are post-menopausal, or if pre-menopausal, they are receiving ovarian ablation/suppression.
- Female patients of reproductive potential will use effective contraception during therapy and for one week after the last dose.
- Patient has tried and failed, or is not a candidate for, adjuvant or neoadjuvant chemotherapy.
- Patient has had disease progression while on or after endocrine-based therapy.
- Patient will receive fulvestrant injection (Faslodex) therapy along with alpelisib (Piqray).
- Patient has no history of Stevens Johnson Syndrome, Erythema Multiforme, or Toxic Epidermal Necrolysis.
- Provider is aware and has informed patient of risk of serious, life-threatening skin reactions, including Stevens Johnson Syndrome; severe hyperglycemia; gastrointestinal toxicity, including severe diarrhea; kidney injury; lung injury including pneumonitis; pancreatitis; and severe hypersensitivity reactions.
- Provider is aware and has informed patient that safety has not been established in type 1 or uncontrolled type 2 diabetic patients.
- Male patients with female partners of reproductive potential should use condoms and effective contraception during therapy and for one week after last dose.
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis:_____

Other non-FDA-approved uses are not approved.
Prior authorization does not expire.

2. amifampridine (Ruzurgi)

Manual PA is required for all new users of Ruzurgi.

Manual PA Criteria: Ruzurgi is approved if all criteria are met:
- Patient has Lambert-Eaton myasthenic syndrome (LEMS)

Non-FDA-approved uses other than LEMS in adults are not approved.
PA does not expire.

3. amphetamine sulfate orally disintegrating IR tablets (Evekeo ODT)

Manual PA is required for all new users of Evekeo ODT.

Manual PA Criteria: Evekeo ODT is approved if ALL criteria are met:

- Patient is 6-17 years of age with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) that has been appropriately documented in the medical record
- Patient has tried for at least two months and failed or has difficulty swallowing Adderall tabs (generic)
- Patient has tried for at least two months and failed or the patient has a contraindication to IR methylphenidate tablets or solution

Non-FDA-approved uses are not approved.
PA does not expire.

4. erdafitinib (Balversa)

Manual PA criteria apply to all new users of Balversa.

Manual PA Criteria: Erdafitinib (Balversa) is approved if all criteria are met:

- The patient is ≥ 18 years old
- Patient has locally advanced or metastatic urothelial carcinoma that has a susceptible FGFR3 or FGFR2 mutation confirmed with an FDA-approved test
- The patient has progressed during or following at least one line of prior platinum-containing chemotherapy (including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy)
- The drug is prescribed by or in consultation with an oncologist
- The patient will be evaluated by an ophthalmologist before starting treatment and every month for the first 4 months; then every 3 months thereafter
- The patient will be advised to seek emergent evaluation for new ocular symptoms
- The patient will be monitored for hyperphosphatemia. (Note that 33% of patients required a phosphate binder in the trial supporting FDA approval for erdafitinib)
- If the patient is female, she is not pregnant or planning to become pregnant.
- Female patients will not breastfeed.
- All patients (females AND males) of reproductive potential will use highly effective contraception during treatment and for 1 month after the last dose.

- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, the provider must list the diagnosis.

Other non-FDA-approved uses are not approved.
PA does not expire.

5. galcanezumab-gnlm 100 mg injection (Emgality)

Note that this PA applies to the Emgality 100 mg cluster headache formulation. The Emgality 120 mg migraine prophylaxis indication PA criteria is on a separate form.

Manual PA criteria apply to all new users of Emgality for episodic cluster headaches.

Manual PA Criteria: Emgality 100 mg at a dosage of 300 mg/month is approved if all criteria are met:

- Patient ≥ 18 years old and not pregnant
- The drug must be prescribed by or in consultation with a neurologist
- Patient has a diagnosis of episodic cluster headaches
- Patient has a contraindication to, intolerability to, or has failed an adequate trial of:
  - Verapamil, topiramate, or lithium
- Concurrent use with other CGRP inhibitors (e.g., Aimovig, Emgality 120 mg, Ajovy) is not allowed

Non-FDA-approved uses, including for migraine prophylaxis, chronic cluster headache, medication overuse headache, etc., are not approved.
PA expires after 6 months.

Renewal Criteria: Coverage will be approved indefinitely for continuation of therapy if there is a clinically appropriate reduction in weekly attacks (≥ 50% reduction in weekly cluster headache attack frequency) during an episode as reported by the patient.

6. mepolizumab injection (Nucala)

Manual PA is required for all new and current users of Nucala.

Manual PA Criteria: Nucala is approved if all criteria are met:

For eosinophilic asthma:

- The patient has a diagnosis of severe persistent eosinophilic asthma
- Patient must be ≥ 12 years old
- The drug is prescribed by an allergist, immunologist, or pulmonologist
- Patient has an eosinophilic phenotype asthma as defined as either
  - blood eosinophil count of > 150 cells/mcL within the past month while on oral corticosteroids OR
  - ≥ 300 cells/mcL within the past year
- The patient's asthma must be uncontrolled despite adherence to optimized medication therapy regimen, with uncontrolled asthma defined as
  - Hospitalization for asthma in the past year OR

- Required course of oral corticosteroids twice in the past year OR
- Daily high-dose inhaled corticosteroid (ICS) with inability to taper off the ICS

- The patient has tried and failed an adequate course (3 months) of at least two of the following while using a high-dose inhaled corticosteroid:
  - Inhaled long-acting beta agonist (LABA) (e.g., Serevent, Striverdi), long-acting muscarinic antagonist (LAMA) (e.g., Spiriva, Incruse), leukotriene receptor antagonist (e.g., Singulair, Accolate, Zyflo)

For eosinophilic granulomatosis with polyangiitis (EGPA):

- Patient must have diagnosis of EGPA
- The drug is prescribed by an allergist, immunologist, pulmonologist, rheumatologist, or hematologist
- Patient must be ≥ 18 years old
- The patient has had an adequate trial of at least 3 months of one of the following with an either an inadequate response to therapy, or significant side effects/toxicity or the patient has a contraindication to therapy with
  - Corticosteroids, cyclophosphamide, azathioprine, or methotrexate
- A quantity limit override for the 300 mg dose to allow three of the 100 mg syringes is approved for the EGPA indication only

Non-FDA-approved uses are not approved.
Prior authorization does not expire.

7. **methylphenidate extended-release capsules (Jornay PM)**

Manual PA is required for all new and current users of Jornay PM.

Manual PA Criteria: Jornay PM is approved if all criteria are met:

- Patient is 6 years and older with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) that has been appropriately documented in the medical record
- The patient must have tried for at least two months and failed Concerta (generic) or have difficulty swallowing pills
- The patient must have tried for at least two months and failed another long-acting methylphenidate (Methylphenidate ER/CD/LA, Quillivant XR, Aptensio XR)
- The patient must have tried for at least two months and failed or have a contraindication to Adderall XR (generic)
- The patient must have tried for at least two months an immediate release formulation methylphenidate product in conjunction with Concerta or another long-acting methylphenidate

- The provider must explain why the patient needs Jornay PM.

Non-FDA-approved uses are not approved.
PA does not expire.

8. risankizumab-rzaa injection (Skyrizi)

PA criteria apply to all new users of Skyrizi. The patient must have tried Humira, Stelara, and Cosentyx.

Manual PA Criteria: Skyrizi is approved if ALL criteria are met:

- The patient has a contraindication or has had an inadequate response to Humira, Cosentyx, AND Stelara OR
- The patient has had an adverse reaction to Humira, Cosentyx, AND Stelara that is not expected with the requested non-step-preferred TIB AND
- Patient is ≥ 18 years old
- The patient is diagnosed with moderate to severe plaque psoriasis and is a candidate for systemic therapy or phototherapy
- Patient has tried and had an inadequate response to non-biologic systemic therapy (e.g., methotrexate, aminosalicylates [e.g., sulfasalazine, mesalamine], corticosteroids, immunosuppressants [e.g., azathioprine])
- Coverage is NOT provided for concomitant use with other TIBs
- The patient has had a negative TB test result in past 12 months (or TB is adequately managed)

Non-FDA-approved uses are not approved.
PA does not expire.

9. rosuvastatin sprinkle capsules (Ezallor Sprinkle)

PA does not apply to patients 12 years of age and younger (age edit)

PA criteria apply to all new users of Ezallor Sprinkle older than 12 years of age.
Manual PA Criteria: Ezallor Sprinkle is approved if all criteria are met:

- Provider must explain why the patient requires rosuvastatin sprinkle capsules and cannot take simvastatin, atorvastatin, OR rosuvastatin tablets.

Non-FDA-approved uses are not approved.
PA does not expire.

10. solriamfetol (Sunosi)

Manual PA is required for all new and current users of Sunosi.

Manual PA Criteria: Sunosi is approved if all criteria are met:

- Patient must be ≥ 18 years old
- Sunosi is not approved for use in children, adolescents, or pregnant patients.

- Patient has a documented diagnosis of excessive daytime sleepiness associated with narcolepsy or a documented diagnosis of obstructive sleep apnea (OSA)
- For narcolepsy: Narcolepsy was diagnosed by polysomnogram or mean sleep latency time (MSLT) objective testing
- For narcolepsy: Other causes of sleepiness have been ruled out or treated including but not limited to obstructive sleep apnea
- For OSA: Patient's underlying airway obstruction has been treated with continuous positive airway pressure (CPAP) for at least 1 month prior to initiation, and the patient demonstrated adherence to therapy during this time
- For OSA: Patient will continue treatment for underlying airway obstruction (CPAP or similar) throughout duration of treatment
- Sunosi is prescribed by a neurologist, psychiatrist, or sleep medicine specialist
- The patient is not concurrently taking any of the following:
  - Central nervous system depressants, such as a narcotic analgesic (including tramadol), a benzodiazepine, or a sedative hypnotic
  - Monoamine oxidase inhibitor (MAOI) within the past 14 days
  - Modafinil, armodafinil, or stimulant-based therapy, such as amphetamine or methylphenidate
- The patient must have tried and failed and had an inadequate response to modafinil
- The patient must have tried and failed and had an inadequate response to armodafinil
- The patient must have tried and failed and had an inadequate response to stimulant-based therapy (amphetamine or methylphenidate)
- Patient and provider agree to monitor blood pressure and heart rate at baseline and periodically throughout treatment. If the patient has hypertension, the blood pressure is controlled.
- Patient does not have unstable cardiovascular disease, serious heart arrhythmias, or other serious heart problems

Non-FDA-approved uses are not approved (including but not limited to fibromyalgia, insomnia, excessive sleepiness not associated with narcolepsy, major depression, ADHD, or shift work disorder).

Prior authorization expires in 1 year. No renewal allowed. A new prescription will require a new PA to be submitted.

11. tafamidis meglumine (Vyndaqel)

Manual PA criteria apply to all new users of Vyndaqel.

Manual PA Criteria: Tafamidis (Vyndaqel) is approved if all criteria are met:

- The patient is ≥ 18 years old

- Patient has a diagnosis of wild type or hereditary transthyretin-mediated amyloidosis
- The drug is prescribed by or in consultation with a specialist who manages hereditary transthyretin amyloidosis (e.g., cardiologist, geneticist, neurologist)
- If the patient is female, she is not pregnant or planning to become pregnant
- Female patients will not breastfeed
- Female patients of reproductive potential will use highly effective contraception during treatment and for 1 month after the last dose

Non-FDA-approved uses (other than ATTR disease manifestations) are not approved.

PA does not expire.

C. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF and PA Implementation Plan

The P&T Committee recommended (group 1: 16 for, 0 opposed, 0 abstained, 1 absent; group 2: 17 for, 0 opposed, 0 abstained, 0 absent) the following:

- **New Drugs Recommended for UF or NF Status:** an effective date upon signing of the minutes in all points of service.

- **New Drugs Recommended for Tier 4 Status methylphenidate extended-release capsules (Adhansia XR):** 1) an effective date of the first Wednesday after a 120-day implementation period at all points of service, and 2) DHA send letters to beneficiaries who are affected by the Tier 4/Not Covered recommendation at 30 days and 60 days prior to implementation.

Summary of Physician's Perspective

The Committee reviewed 17 new drugs, of which 11 were recommended for UF status, with 5 recommended for NF status, and 1 Tier 4/Not Covered candidate.

Prior authorization criteria will apply to 11 of the drugs. Several drugs were recommended for PAs since criteria already apply for the class, including the oncology drugs, the TIBs, and the migraine drugs. "No grandfathering," where both new and current users will be affected by the PA, is recommended for 3 of the drugs – the ADHD drug Jornay PM, the narcolepsy drug Sunosi, and the injectable asthma drug Nucala.

There were three ADHD drugs reviewed at the meeting, Jornay PM, Evekeo ODT, and Adhansia XR.

- Jornay PM was recommended for UF status, but with a PA. It has a delayed onset of action of about 6-8 hours, and is taken at night, so that the drug's onset

of action will occur in the morning. However, it has a 14 hour duration of action, so adverse effects of insomnia and decreased appetite are a concern, especially for children. A PA was recommended because there are several cost-effective generic ADHD drugs available. The pediatrician member of the Committee recommended the PA require trials of two long-acting ADHD drugs and Adderall, plus an immediate release ADHD drug prior to the use of Jornay PM, due to the safety risks of the drug and lack of long-term data.

- Evekeo ODT was recommended for UF status, also with a PA. This drug contains 100% amphetamine which has a higher risk of adverse effects than the methylphenidate or mixed amphetamine salt products. It is only indicated for children, and several other ADHD products are available if a child has difficulty swallowing.

- Adhansia XR was recommended for Tier 4/Not covered status. This drug has a longer duration of action at 16 hours. The long duration has the risk of prolonging side effects, including lack of appetite and insomnia. The target group of patients most likely to benefit from this medication are children and adolescents ages 12-21 who need to do homework and other performance based activities (driving, extracurricular activities) into the evening hours. However there are several other methylphenidate products with durations of action of about 10-12 hours that would be appropriate for this target population.

Summary of Panel Questions and Comments

Mr. Hostettler asked how many beneficiaries are affected by Adhansia XR's Tier 4 recommendation.

CDR Hellwig stated that this is a new agent and currently there are only 3 patients utilizing the medication.

Mr. Du Teil asked if the duration of action of Adhansia XR had any bearing on the drug's designation of Tier 4 status or was there a cost consideration.

CDR Hellwig stated that there is very little data on this drug and so it is hard to determine whether the long duration of action (16 hours) will fulfill a niche patient requirement or whether it will introduce new side effects. Both duration of action and drug cost effectiveness were considered when determining Tier 4 status.

Mr. Hostettler asked for confirmation that the PA criteria for Emgality 100mg would only require a trial of one of: verapamil, topiramate, or lithium.

CDR Hellwig concurred.

Dr. Spatz stated that almost everything that had PA criteria, defined a duration of of treatment and inadequate response before moving on, with the exceptions of Skyrizi and Sunosi. He asked why "inadequate response" was not more specifically defined.

CDR Hellwig mentioned that Skyrizi is a long standing PA and that the wording was formatted to follow all other non-step preferred TIBs (Targeted Immunomodulatory Biologics). She said that the language used to determine inadequate response is looked at closer and that the intention is to prevent a physician from writing 2 prescriptions at the same time as well as having a patient from picking up a medication one day, only to try one only a few days after from a different provider. It was also mentioned that the language may have not been present on the PA criteria for Sunosi as a result of the amount of agents that must be tried first in addition to the PA expiration after 1 year. Following 1 year, the original PA criteria would again be required.

Dr. Bertin inquired about the last bulleted requirement under the PA criteria for Jornay where the provider would need to explain why the patient requires Jornay. He asked if this could explain away some of the other required criteria as it seems subjective. Can the provider provide the explanation or who makes the final decision?

CDR Hellwig explained that specific information is given to ESI for use in determining what criteria would be appropriate. Additionally, any write-in components for PA submissions are sent to pharmacist for professional judgement and review.

Mr. Hostettler pointed out that having to wait 8 months as a result of required PA criteria is a long time to wait to receive a drug that is FDA indicated for morning symptoms.

CDR Hellwig had stated that the FDA indication for Jornay PM is ADHD and has no language on approved use for morning symptoms.

Dr. Peloquin noted that some of the PA criteria are extensive and asked if PAs are being used to direct physicians on appropriate use.

CDR Hellwig responded that PAs are used to ensure the right patient is getting the drug. Safety information is included on PAs to ensure the safety of patients.

Dr. Khoury, referring to the FDA approval letters that are sent to manufacturers once a drug gains a new approval, often require up to 5 to 6 post marketing studies which are a combination of animal and, in some cases, pediatric studies that haven't been completed. These are intended to fully clarify the safety and effectiveness of the drugs. Further, some drugs receive accelerated approval without providing an overall survival benefit at the time of approval. Some drugs have failed to show an overall survival benefit, despite being approved for marketing. The number of new drugs available is overwhelming for the typical individual provider. In the past 3 years, the P&T committee has reviewed approximately 250 new drugs and I would suspect that most providers only use 5% to 10% on a regular basis. So, the PA criteria in these cases would provide additional patient safety measures for those providers that may not be fully informed of the data, efficacy, and safety of these new drugs.

There were no more questions or comments from the Panel. The chair called for a vote on the UF Recommendation, PA Criteria, and UF and PA Implementation Plan for Newly Approved Drugs.

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – UF Recommendations**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

for ***Director, DHA:***

_____ **These comments were taken under consideration prior to my final decision.**

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – PA Criteria**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

for ***Director, DHA:***

_____ **These comments were taken under consideration prior to my final decision.**

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – UF and PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

for ***Director, DHA:***

_____ **These comments were taken under consideration prior to my final decision.**

IV. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA

A. New PA Criteria

New manual PA criteria were recommended by the P&T Committee due to a variety of reasons. The new manual PAs outlined below will apply to new users for the oncology drugs Alecensa, Alunbrig, Zykadia, and Xalkori and the orthostatic hypotension product Northera and to new and current users for the prescription multivitamin Azesco and the tetracycline product doxycycline hyclate ER 80 mg.

1. **Antibiotics: Tetracyclines – Doxycycline hyclate extended-release 80 mg – Oral tetracycline antibiotic for acne vulgaris or rosacea**

PA criteria were recommended for this new 80 mg ER doxycycline hyclate available from a single manufacturer. The P&T Committee reviewed the oral tetracycline class in February 2017 and agreed there is little evidence to support advantages of the newer doxycycline products over the traditional generic formulations in terms of salt (monohydrate versus hyclate), dosage form (tablet versus capsule versus scored tablets), or release mechanisms (IR versus ER versus DR). Cost-effective generic formulations of doxycycline hyclate (i.e., 50 mg and 100 mg immediate release) are available on the UF without a PA required.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new and current users of doxycycline hyclate ER 80 mg tablets.

Manual PA Criteria: Doxycycline hyclate extended-release 80 mg is approved if all criteria are met:

- This agent has been identified as having cost-effective alternatives. The provider must describe why this drug is required as opposed to available alternatives.

Non-FDA-approved uses are not approved.
PA does not expire.

2. **Oral Oncologic Agents: alectinib (Alecensa), brigatinib (Alunbrig), ceritinib (Zykadia), and crizotinib (Xalkori)**

PA criteria have not previously been required for the non-small cell lung cancer (NSCLC) drugs; however, PA is in place for several oncological drug classes. The P&T Committee reviewed four oral oncologic agents, Alecensa, Alunbrig, Zykadia, and Xalkori. PA criteria were recommended for these four products in new users in order to ensure prescribing in accordance with FDA-approved indications or National Comprehensive Cancer Network (NCCN) Guideline-endorsed off-label indications.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new users.

a) alectinib (Alecensa), brigatinib (Alunbrig), and ceritinib (Zykadia)

Manual PA Criteria: Alecensa, Alunbrig, or Zykadia is approved if all criteria are met:

- The patient has *metastatic* anaplastic lymphoma kinase (*ALK*)-positive NSCLC as detected by an FDA-approved test AND
- The drug is prescribed by or in consultation with a hematologist/oncologist OR
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, the provider must list the diagnosis.

Other non-FDA-approved uses are not approved.

Prior authorization does not expire.

b) crizotinib (Xalkori)

Manual PA Criteria: Xalkori is approved if all criteria are met:

- Patient has metastatic anaplastic lymphoma kinase (ALK)-positive NSCLC as detected by an FDA-approved test OR
- Patient has NSCLC with ROS1 rearrangement AND
- The drug is prescribed by or in consultation with a hematologist/oncologist OR
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, the provider must list the diagnosis.

Other non-FDA-approved uses are not approved

Prior authorization does not expire.

3. Vitamins: Prenatal – Prenatal multivitamin (Azesco)

Azesco is a prenatal multivitamin manufactured by a single manufacturer that requires a prescription prior to dispensing. The primary ingredients of Azesco are 13 mg of iron and 1 mg of folic acid. Prescription prenatal multivitamins are included in the TRICARE pharmacy benefit for women younger than age 45. This agent was identified as having numerous cost-effective alternatives (including Prenatal Vitamins Plus Low I, Prenatal Plus, Preplus, Prenatal, Prenatal Vitamins, Prenatal Multi+ DHA, Prenatal Vitamin + Low Iron, and Prenatal Plus DHA) that are available on the UF, where a PA is not required.

he P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new and current users of Azesco.

Manual PA Criteria: Azesco is approved if all criteria are met:

- This agent has been identified as having cost-effective alternatives. The provider must describe why this drug is required as opposed to available alternatives.

Non-FDA-approved uses are not approved.

PA does not expire.

4. Cardiovascular Agents Miscellaneous: Droxidopa (Northera)

Droxidopa (Northera) is an alpha/beta agonist approved in February 2014 for neurogenic orthostatic hypotension (NOH). The product labeling for Northera contains a black box warning that it may cause or exacerbate supine hypertension. A consensus statement from the American Autonomic Society and the National Parkinson Foundation for NOH was published in 2017 and recommends treatments including midodrine, fludrocortisone, and pyridostigmine, in addition to droxidopa. No one pharmacologic treatment is preferred over another in the guidelines. PA

criteria were recommended for Northera to ensure appropriate use of clinically and cost-effective alternative therapies for neurogenic orthostatic hypotension first.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for droxidopa in new users.

Manual PA Criteria: Northera is approved if all criteria are met:

- Patient is ≥ 18 years of age
- Patient has been diagnosed with symptomatic Neurogenic Orthostatic Hypotension (NOH) due to primary autonomic failure (Parkinson's disease [PD], multiple system atrophy [MSA], and pure autonomic failure [PAF]), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy
- The drug is prescribed by or in consultation with a cardiologist or a neurologist
- The patient has tried two other medications (e.g., fludrocortisone, pyridostigmine, or midodrine) and failed to respond to therapy
- Patient has initiated non-pharmacological measures including but not limited to elevation of the head of the bed, orthostatic compression garments, increased salt intake, and appropriate physical training

Non-FDA-approved uses are not approved.
PA does not expire.

D. New PA Criteria—PA Implementation

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) new PAs for Alecensa, Alunbrig, Zykadia, Xalkori, Azesco, Northera, and doxycycline hyclate ER 80 mg become effective 90 days after the signing of the minutes. DHA will send letters to beneficiaries affected by the new PA requirements for Azesco and doxycycline hyclate extended-release 80 mg if applicable, as new and current users will be subject to the PA.

Summary of Physician's Perspective

There were drugs from four classes where new PA criteria were recommended.

Doxycycline 80 mg: This product is for a new 80 mg dosage strength by one manufacturer that is not cost effective compared to the most commonly dispensed 50 mg and 100 mg strengths. There is already step therapy in the tetracycline class, so the PA criteria reflect what is already in place for the non-step preferred products. We currently don't have any utilization of this drug.

NSCLC drugs (Alecensa, Alunbrig, Zykadia, Xalkori): This is part of our ongoing process of reviewing the oncology drugs to determine which ones do not have PAs in place. These drugs are all approved for non-small cell lung cancer, and PA was recommended to ensure the appropriate patients receive the drugs, based on FDA indications. These new PA's allow off-label uses that are included in the

NCCN guidelines be considered as part of the PA review, before having the provider file an appeal.

Azesco: This product is a prescription prenatal vitamin that is over 12,000 times more expensive than the other prescription prenatal vitamins. Legend prenatal vitamins are part of the TRICARE pharmacy benefit, so having the PA is the most appropriate option to ensure this product is not used in the DoD. Currently as of Sept 18, 2019 we haven't had any utilization in DOD.

Droxidopa (Northera): This drug has not previously been reviewed by the P&T Committee, since it has been on the market since 2014. The recommended PA criteria are in alignment with what is recommended in the professional treatment guidelines for neurogenic orthostatic hypotension. There is only limited evidence for this drug, and it is marginally effective with a risk of adverse events. The PA criteria recommended here are similar to what other health plans have and will apply to new users only.

Summary of Panel Questions and Comments

Mr. Hostettler asked if the PA criteria for Doxycycline Hyclate and Azesco meant that it would be difficult to get these products approved.

Dr. Khoury responded saying that those are the current PA criteria and if there are concerns that we haven't captured, they will be captured in comments/feedback from providers.

Mr. Hostettler also noted that Azesco (Prenatal Vitamin) seemed like a Tier 4 candidate.

Dr. Khoury responded it is unusual because it requires a prescription and it is a vitamin not a drug. Otherwise, it would be considered potentially for not covered status.

Mr. Hostettler asked for confirmation that Droxidopa PA criteria is for new users only.

CDR Raisor concurred.

Dr. Bertin asked about pharmacist review of Tetracycline and Azesco and whether they are being told to deny PA at that level.

Dr. Khoury responded the language is not telling the physician that the PA request will be denied. The PAs, with that language, are specifically meant to ensure the pharmacist has a discretion if the patient has a legitimate reason to request the drug not captured in the form.

Dr. Pirrainen, referencing the oncology agents, asked if PA review would have to be in consultation with an Oncologist or Hemotologist, in the case where a provider

were prescribing off label.

CDR Raisor stated that it was the intent of the committee was to have it in consultation with or written by a specialist.

There were no more questions or comments from the Panel. The chair called for a vote on the New Manual PA Criteria and PA Implementation Plan for the New Manual PA Criteria.

- **New Manual PA Criteria**

  Concur: 9 Non-Concur: 1 Abstain: 0 Absent: 0

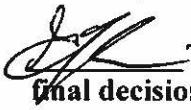
  for ***Director, DHA:***

   These comments were taken under consideration prior to my final decision.

- **New Manual PA Criteria – PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

  for ***Director, DHA:***

   **These comments were taken under consideration prior to my final decision.**

V. UTILIZATION MANAGEMENT—UPDATED MANUAL PA CRITERIA

A. Updated PA Criteria

Updates to the step therapy and manual PA criteria for several drugs were recommended by the P&T Committee due to a variety of reasons, including expanded FDA indications, pediatric uses, clinical trial data, or to be consistent with existing PAs for the drug class. The updated manual PAs outlined below will apply to new users.

The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) updates to the manual PA criteria for Xyrem, Dupixent, Symdeko, Doptelet, Benlysta, Tibsovo, Otezla, Humira, Xermelo, Firdapse, and Inbrija.

The updates are as follows:

Updated Criteria for reasons other than new FDA indications

1. **Gastrointestinal-2 Agents: telotristat ethyl (Xermelo)** – Manual PA criteria for Xermelo were first recommended in May 2017. Manual PA criteria for Xermelo were updated to reflect the TELECAST trial, which allowed for use in carcinoid syndrome diarrhea in persons having less than 4 bowel movements per day with or without concurrent somatostatin analog therapy.

2. **Neurological Agents Miscellaneous: amifampridine (Firdapse)** – Manual PA criteria for Firdapse for treating LEMS were first recommended in May 2019. Ruzurgi is another amifampridine formulation (see section VI B on page 14). Although the package labeling for Ruzurgi states it is approved for pediatric patients, the clinical trial used to gain FDA approval was conducted in adult patients with a mean age of 52 years, and the maximal dosing is higher with Ruzurgi than Firdapse (100 mg vs. 80 mg, respectively). Ruzurgi is cost-effective compared to Firdapse. Manual PA criteria for Firdapse were updated to require a trial of the cost-effective amifampridine agent Ruzurgi first in new patients.

3. **Parkinson's Agents: levodopa inhalation powder (Inbrija)** – Manual PA criteria for Inbrija were first recommended in May 2019. Manual PA criteria were updated to remove the 1-year expiration date and renewal criteria, as the other Parkinson's drugs have PAs that do not expire.

New FDA-Approved Indications or Age Ranges

1. **ADHD-Wakefulness Promoting Agents: Wakefulness Promoting Agents: sodium oxybate (Xyrem)** – Manual PA criteria were updated to reflect a new FDA-approved indication for use in children ≥ 7 years of age for the treatment of cataplexy in patients with narcolepsy.

2. **Corticosteroids – Immune Modulators: Atopic Dermatitis: dupilumab (Dupixent)** – Manual PA criteria were updated for the new indication for add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.

3. **Cystic Fibrosis Agents: tezacaftor/ivacaftor (Symdeko)** – Manual PA criteria were updated to reflect a new indication for treatment of patients ≥ 6 years of age in the treatment of cystic fibrosis.

4. **Hematological agents: Platelets: avatrombopag (Doptelet)** – Manual PA criteria were updated to reflect a new indication for thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment.

5. **Immunosuppressives: belimumab (Benlysta)** – Manual PA criteria were updated to reflect a new indication for the treatment of patients as young as 5 years of age with

active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy.

6. **Oncological Agents: Acute Myelogenous Leukemia: ivosidenib (Tibsovo)** – Manual PA criteria were updated to reflect a new indication for the treatment of adult patients with newly diagnosed acute myelogenous leukemia (AML) who are aged 75 years or older who have comorbidities that preclude use of intensive induction chemotherapy.

7. **Targeted Immunomodulatory Biologics (TIBs) – Non-Tumor Necrosis Factor (TNF) Inhibitors: apremilast (Otezla)** – Manual PA criteria were updated to reflect a new indication for treatment of adult patients with oral ulcers associated with Behçet's disease. Note that for Behçet's disease, a trial of adalimumab (Humira) is not required first.

8. **Targeted Immunomodulatory Biologics (TIBs) – Tumor Necrosis Factor (TNF) Inhibitors: adalimumab (Humira)** – Manual PA criteria for Humira were updated to allow for off-label use in pediatric patients for plaque psoriasis. In the European Union, Humira is approved in the pediatric population for plaque psoriasis, and data exists to support its use in this age group. Note that pediatric patients are not required to use the DoD's step-preferred Humira first for plaque psoriasis given that it is currently off-label in the United States.

E. Updated PA Criteria—Implementation Plan

The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) updates to the current PA criteria for Firdapse, Xermelo, Inbrija, Xyrem, Symdeko, Benlysta, Otezla, Tibsovo, Dupixent, Doptelet, and Humira in new users become effective 30 days after the signing of the minutes.

F. Weight Loss Agents: liraglutide 3 mg (Saxenda)—Updated PA Criteria

The P&T Committee was briefed on trends in the current utilization and spend for the weight loss agents, which were reviewed in November 2017. Generic phentermine is the most utilized weight loss agent, while liraglutide 3 mg injection (Saxenda) is the second most utilized weight loss agent, but ranks first in total cost per patient. A review of Saxenda claims data found that the majority of patients did not meet the criteria for a trial of other branded weight loss drugs first. The P&T Committee recommended updating the manual PA criteria for liraglutide 3 mg (Saxenda) to streamline the PA form and more closely reflect the original intent of the November 2017 P&T Committee meeting.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) updating the manual PA criteria for new and current users of Saxenda who do not have a diagnosis of diabetes. Previous trials of other weight loss drugs must be documented prior to use of Saxenda.

G. Weight Loss Agents: liraglutide 3 mg (Saxenda)—Implementation Plan

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) an effective date 60 days after the signing of the minutes in all points of service.

Summary of Physician's Perspective

The majority of the PA updates made at this meeting were very straightforward, and do represent that the Committee continually monitors the drugs that we have PAs on and provides updates when needed.

Firdapse - Earlier in this meeting another amifampridine product, Ruzurgi was presented as a newly approved drug, and given UF status with a PA required. Ruzurgi and Firdapse contain the same active ingredient. The recommendation for the Firdapse PA update is to require a trial of Ruzurgi first. Ruzugri actually allows more flexibility, since the package insert provides instructions for making a suspension for small children and also for patients with feeding tubes. Although Ruzurgi is only approved for children aged 6 to 17 years, the clinical trial was conducted in adults, and providers are willing to use this drug in adults. This fact is supported by a review of MHS utilization for Ruzurgi which shows that there are six patients on the drug, and 4 of these 6 patients are over the age of 18 years. The PA update will only apply to new users. Currently we have 8 patients on Firdapse.

Weight loss drugs – Saxenda: When we reviewed the medication profiles of the MHS patients taking Saxenda, we found that they did not satisfy the PA criteria recommended back in November 2017 requiring a trial of the other branded weight loss drugs first. Therefore the recommendation is that patients currently on Saxenda will be required to go through the PA again, but only if they do not have a diagnosis of diabetes. Our data pull can show patients who have an ICD-10 code for diabetes. Therefore the "no grandfathering" will only apply to patients without diabetes; this will affect about 786 patients. We are not affecting patients receiving Saxenda who have a diagnosis of diabetes, which is about 295 patients. We will send letters to the patients without a diabetes diagnosis, informing them of the PA requirements.

Summary of Panel Questions and Comments

Mr. Hostettler asked for confirmation that the new manual PA criteria for Tibsovo was meant to say 75 and above.

CDR Raisor concurred saying at least 75.

Mr. Hostettler, in regards to weight loss agents' updated PA criteria, asked how many agents patients have to go through if they have diabetes.

Dr. Khoury responded that patients would need to try and fail or have a contraindication to 4 agents.

There were no more questions or comments from the Panel. The chair called for a vote on the Updated Manual PA Criteria, and the PA Implementation Plan for the referenced drugs and the Weight Loss Agents.

- **Updated Manual PA Criteria**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

Director, DHA:

_____ These comments were taken under consideration prior to my final decision.

- **Updated PA Criteria – PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

Director, DHA:

_____ These comments were taken under consideration prior to my final decision.

- **Weight Loss Agents – Updated Manual PA Criteria**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

Director, DHA:

_____ These comments were taken under consideration prior to my final decision.

- **Weight Loss Agents – PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

Director, DHA:

_____ These comments were taken under consideration prior to my final decision.

Informational Item—SUMMARY OF RECOMMENDATIONS AND BENEFICIARY IMPACT August 2019

Table of Implementation Status of UF Recommendations/Decisions Summary

DoD PEC Drug Class	UF Drugs	NF Drugs	Tier 4/Not Covered Drugs	Implement Date	Notes and Unique Users Affected
High-Potency Topical Corticosteroids	*Note that all are currently UF* • betamethasone dipropionate 0.05% ointment • betamethasone/propylene glycol 0.05% ointment, cream, lotion, gel • clobetasol propionate 0.05% ointment, cream, solution, lotion, shampoo, spray, gel, foam • clobetasol propionate/emollient 0.05% cream • clobetasol propionate/emollient 0.05% emulsion foam • desoximetasone 0.25% ointment, cream • fluocinonide 0.05% ointment, cream, solution, gel • fluocinonide/emollient base 0.05% cream • halobetasol propionate 0.05% ointment	• amcinonide 0.1% ointment (Cyclocort, generics) • clobetasol propionate/emollient 0.05% foam (Olux-E, generics) *moves from UF to NF* • desoximetasone 0.05% gel (Topicort, generic) *moves from UF to NF* • diflorasone diacetate 0.05% ointment, cream (Psorcon, Apexicon, generics) • fluocinonide 0.1% cream (Vanos, generics) • flurandrenolide 4 mcg/sq. cm (Cordran) tape *moves from UF to NF* • halobetasol propionate 0.05% cream (Ultravate, generics) *moves from UF to NF*	• clobetasol propionate 0.025% cream (Impoyz) • clobetasol propionate 0.05% shampoo/cleanser (kit) (Clodan kit) • diflorasone diacetate/emollient 0.05% cream (Apexicon-E) • halcinonide 0.1% ointment (Halog) • halcinonide 0.1% cream (Halog) • halobetasol propionate 0.05% lotion (Ultravate) • halobetasol propionate 0.05% foam (Lexette & authorized generic) • halobetasol propionate 0.01% lotion (Bryhali)	Pending signing of the minutes / 120 days	• Manual PA criteria applies to all new and current users for the following products: ▪ amcinonide 0.1% ointment ▪ diflorasone diacetate 0.05% ointment ▪ diflorasone diacetate 0.05% cream ▪ clobetasol propionate/emollient 0.05% foam ▪ desoximetasone 0.05% gel ▪ flurandrenolide 4 mcg/sq. cm (Cordran) tape • Note the Lexette foam was previously recommended for Tier 4 status at the February 2019 meeting, which was implemented on August 28, 2019. Unique Users Affected (Tier 4 candidates) Mail – 195 MTF – 18 Retail – 502 Total – 715 (UF to NF changes) Mail – 1,061 MTF – 1,318 Retail – 2,533 Total – 4,912

DoD PEC Drug Class	UF Drugs	NF Drugs	Tier 4/Not Covered Drugs	Implement Date	Notes and Unique Users Affected
Multiple Sclerosis: Interferons and Methyl Fumarate	**Interferons** ▪ Interferon beta-1a (Avonex) ▪ Interferon beta-1a (Rebif, Rebif Rebidose) ▪ Interferon beta-1b (Betaseron) ▪ Interferon beta-1b (Extavia) **Methyl Fumarate** ▪ dimethyl fumarate (Tecfidera)	**Interferons** peginterferon beta-1a (Plegridy)	▪ None	Upon signing of the minutes	▪ The MS subclasses of Glatiramer, symptomatic agents, and Oral Miscellaneous were not reviewed ▪ Updated manual PA criteria for all users of dimethyl fumarate (Tecfidera); off-label uses are not allowed Unique Users Affected – Not applicable, no change to formulary status.

Drugs with Prior Authorization Criteria—Unique Utilizers Affected

Drug	MTF	Mail Order	Retail	Total
Weight Loss Agents – liraglutide 3 mg injection (Saxenda)	45	177	575	786
Vitamins: Prenatal – Prenatal multivitamin (Azesco)	0	0	0	0
Antibiotics: Tetracyclines – Doxycycline hyclate extended-release 80 mg	0	0	0	0

Appendix II **09/25/2019 BAP Meeting**

Brief Listing of Acronyms Used in this Summary

Abbreviated terms are spelled out in full in this summary; when they are first used, the acronym is listed in parentheses immediately following the term. All of the terms commonly used as acronyms in the Panel discussions are listed below for easy reference. The term "Pan" in this summary refers to the "Uniform Formulary Beneficiary Panel," the group who's meeting in the subject of this report.

- ADHD – Attention Deficit Hyperactivity Disorder
- AIDS – Acquired Immune Deficiency Syndrome
- ALL – Acute Lymphoblastic Leukemia
- AML – Acute Myeloid Leukemia
- BIA – Budget Impact Analysis
- CFR – Code of Federal Regulations
- CMA – Cost Minimization Analysis
- DHA – Defense Health Agency
- DMARDs – Disease Modifying Anti-Rheumatic Drugs
- DoD- Department of Defense
- ER – Extended Release
- FDA – Food & Drug Administration
- G – Grams
- GI-2 – Gastrointestinal-2
- GLP1RA – Glucagon-Like Peptide-1 Agonists
- HAE – Hereditary Angiodema
- HD – Extended Release
- HER2 – Human Epidermal Growth Factor Receptor
- HFA – Hydrofluoroalkane
- HIV – Human Immunodeficiency Virus
- ICS/LABAs – Inhaled Corticosteroids/Long-Acting Beta Agonists
- INSTI – Integrase Strand Transfer Inhibitors
- JIA – Juvenile Idiopathic Arthritis
- MAOI – Monamine Oxidase Inhibitors
- MHS – Military Health Systems
- mL- milliliter
- MTF – Military Treatment Facility
- NDAA – National Defense Authorization Act
- NDC – National Drug Codes
- NF – Non-Formulary
- NKI – Neurokinin
- NNRT1 – Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
- NPH – Neutral Protamine Hagedorn
- OIC – Opioid-Induced Constipation

- PA- Prior Authorization
- PAMORAs – Peripherally-Acting MU Opioid Receptor Agonists
- PEG – Percutaneous Endoscopic Gastronomy
- P&T – Pharmacy & Therapeutics
- pJLA – Plyarticular Juvenile Idiopathic Arthritis
- PPIs – Proton Pump Inhibitors
- PrEP – Pre-Exposure Prohylaxis
- SGLT2 – Sodium Glucose Co-Transporter
- SQ – Subcutaneously
- SU – Sulfoylurea
- TIBs – Targeted Immunomodulatory Biologics
- TNF – Anti-Tumor Necrosis Factor
- TRICARE – Healthcare Network
- UF – Uniform Formulary
- VMAT2 – Vesicular Monoamine Transporter 2
- XR – Extended Release

Private Citizen Comments

Ironshore Pharmaceuticals and Development, Inc.
a subsidiary of Highland Therapeutics

TO: Colonel Paul J. Hoerner, USAF
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101

FROM: Ironshore Pharmaceuticals Inc.

DATE: September 18, 2019

RE: JORNAY PM™ (methylphenidate HCl Extended-Release Capsules)
Prior Authorization Criteria

Dear Colonel Hoerner,

On behalf of Ironshore Pharmaceuticals, the manufacturer of JORNAY PM™ (methylphenidate HCl Extended-Release Capsules), I appreciate the opportunity to comment on the Prior Authorization Criteria recommended by the Pharmacy & Therapeutics Committee in its August 8th Recommendations to the Uniform Formulary Beneficiary Advisory Panel (BAP). The recommended criteria are as follows:

- Patient is 6 years and older with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) that has been appropriately documented in the medical record
- The patient must have tried for at least two months and failed Concerta (generic) or have difficulty swallowing pills
- The patient must have tried for at least two months and failed another long-acting methylphenidate (Methylphenidate ER/CD/LA, Quillivant XR, Aptensio XR)
- The patient must have tried for at least two months and failed or have a contraindication to Adderall XR (generic)
- Must have tried for at least two months an immediate release formulation methylphenidate product in conjunction with Concerta or another long-acting methylphenidate
- Please explain why the patient needs Jornay PM.

This recommendation requires patients to have tried and failed on four different Uniform Formulary products/regimens for at least 2 months each prior to JORNAY PM being approved for use for the patient. We respectfully request that the criteria be modified to give the clinicians more latitude in determining the timeline for assessing efficacy in their patients. While we understand that JORNAY PM typically would not be used first-line or even second-line, we request the Committee consider revising the criteria to appropriate age and diagnosis plus failure on no more than two stimulants available within the ADHD Category.

Clinical Considerations: Early morning functioning is a significant unmet need in many patients affected by ADHD, and JORNAY PM is the only ADHD stimulant medication with FDA-approved labeling demonstrating early morning symptom control (see attached publications). This is important both for patients who have challenges with the morning routine and those who start school very early in the morning and are unable to take traditional ADHD medication early enough for it to have full effect at the beginning of the school day. Children in single parent military households – where spouses have been deployed – may benefit greatly from this early morning symptom control. JORNAY PM was developed using a novel drug delivery technology that incorporates a delayed-release layer that limits release of the drug overnight, and an extended-release layer which provides a

long, slow release of drug throughout the day. This unique evening dosing provides efficacy from the time of awakening without sacrificing efficacy later in the afternoon and evening.

Thus, in our view it is unduly burdensome to require children to try and fail on four different medications/medication combinations (with differing potential side effects) over the course of 8 months before being able to try JORNAY PM. First, each medication failure has real consequences for these children; they may suffer from significant side effects, have trouble at school, and/or fall behind in classwork because they aren't able to concentrate. Further, during this trial period, they may well continue to have problems maintaining positive peer and family relationships. In addition, this 4-step process creates an unnecessary burden for families. Each medication change typically requires two doctor's visits – one to get the medication and then a 30-day follow-up – that's 8 appointments before they can get JORNAY PM. Often it is difficult to schedule doctor appointments after school or on weekends, so each visit may mean missed school for children who may already struggle academically. Moreover, the impact of an 8-month period on the life of a child should not be discounted – that is almost an entire school year where a child may struggle socially, emotionally, and academically.

To best serve DoD Tricare beneficiaries, we ask that DoD consider taking steps to simplify the number of step edits to no more than two, which still allows for trial of the first-line agent but limits the number of trials, so that access (and patient success) does not become unachievable or is unduly delayed.

Cost Considerations: We understand the need to contain costs associated with prescription drugs, and for this reason we offered a significant additional discount beyond the Federal Ceiling Price to the Tricare Retail Pharmacy Program per a Uniform Formulary Additional Discount Program (UF ADP) offer. While we fully intended to submit a BPA offer of additional discount, we did not submit this offer based on our understanding at the time that we could not do so prior to execution of an FSS Interim Agreement with the Department of Veterans Affairs (VA). Once our FSS Interim Agreement is in place (and we are currently working with VA to facilitate its award) we intend to offer an additional FSS discount to DoD per a BPA.

Thank you for your time and consideration,

L Warrington

Lewis Warrington, MD
Vice President, Medical Affairs

W Scott Evangelista

W. Scott Evangelista
President, Ironshore Pharmaceuticals

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JORNAY PM™ safely and effectively. See full prescribing information for JORNAY PM.

JORNAY PM (methylphenidate hydrochloride) extended-release capsules, for oral use, CII
Initial U.S. Approval: 1955

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

INDICATIONS AND USAGE

JORNAY PM is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. (1)

DOSAGE AND ADMINISTRATION

- JORNAY PM should be taken only in the evening. (2.2)
- Recommended starting dose for patients 6 years and above is 20 mg daily in the evening. (2.2)
- Adjust the timing of administration between 6:30 p.m. and 9:30 p.m. to optimize the tolerability and the efficacy the next morning and throughout the day.
- Dosage may be increased weekly in increments of 20 mg per day up to a maximum daily dose of 100 mg. (2.2)
- Patients are advised to take JORNAY PM consistently either with food or without food. (2.2)
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce. (2.2)
- To avoid substitution errors and overdosage, do not substitute for other methylphenidate products on a milligram-per-milligram basis. (2.3)

DOSAGE FORMS AND STRENGTHS

- Extended-Release Capsules: 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg. JORNAY PM exhibits both delayed-release and extended-release properties. (3, 11)

CONTRAINDICATIONS

- Known hypersensitivity to methylphenidate or product components. (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI) or use of an MAOI within the preceding 14 days. (4)

WARNINGS AND PRECAUTIONS

- *Serious Cardiovascular Reactions:* Sudden death has been reported in association with CNS stimulants at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions:* Use of CNS stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to JORNAY PM use. (5.4)
- *Priapism:* Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* CNS stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth:* Monitor height and weight at appropriate intervals in pediatric patients. (5.7)

ADVERSE REACTIONS

Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions for pediatric patients and adults are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.

Additional adverse reactions (≥5% and twice the rate of placebo) in pediatric patients 6 to 12 years treated with JORNAY PM: headache, psychomotor hyperactivity, and mood swings. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ironshore Pharmaceuticals Inc. at 1-877-938-4766 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including JORNAY PM™, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), (9.3)]*.

1 INDICATIONS AND USAGE

JORNAY PM is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating pediatric patients and adults with CNS stimulants, including JORNAY PM, assess for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse, dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate for the need for JORNAY PM use *[see Boxed Warning, Warnings and Precautions (5.1) and Drug Abuse and Dependence (9)]*.

2.2 General Dosing Information

JORNAY PM is given orally once daily in the evening. JORNAY PM should not be taken in the morning.

The recommended starting dose of JORNAY PM for patients 6 years and older is 20 mg once daily in the evening. The dose may be titrated weekly in increments of 20 mg. Daily doses above 100 mg have not been studied and are not recommended.

Initiate dosing at 8:00 p.m. Adjust the timing of administration between 6:30 p.m. and 9:30 p.m. to optimize the tolerability and efficacy the next morning and throughout the day. In clinical trials of patients aged 6 to 12 years, the most common dosing time (>70% of patients) was 8:00 p.m., with an allowed range between 6:30 p.m. and 9:30 p.m. Following determination of the optimal administration time, advise patients to maintain a consistent dosing time.

Patients who miss their dose of JORNAY PM at the regularly scheduled time should take it as soon as they remember that same evening. If a patient remembers the missed dose the following morning, they should skip the missed dose and wait until their next scheduled evening administration.

Advise patients to take JORNAY PM consistently, either with food or without food.

JORNAY PM may be taken whole, or the capsule may be opened, and the entire contents sprinkled onto applesauce. If the patient is using the sprinkled administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken at the same time.

Pharmacological treatment of ADHD may be needed for extended periods. Periodically re-evaluate the long-term use of JORNAY PM and adjust dosage as needed.

2.3 Switching from Other Methylphenidate Products

If switching from other methylphenidate products, discontinue that treatment, and titrate with JORNAY PM using the titration schedule described above.

Do not substitute JORNAY PM for other methylphenidate products on a milligram-per-milligram basis because these products have different pharmacokinetic profiles from JORNAY PM and may have different methylphenidate base composition *[see Description (11) and Clinical Pharmacology (12.3)]*.

2.4 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or, if necessary, discontinue the drug. JORNAY PM should be periodically discontinued to assess the child's condition. If improvement is not observed after appropriate dosage adjustment over a one-month period, discontinue drug.

3 DOSAGE FORMS AND STRENGTHS

JORNAY PM (methylphenidate hydrochloride) extended-release capsules exhibit both delayed-release and extended-release properties and are available in the following dose strengths:

- 20 mg capsules with ivory opaque body and light green opaque cap;
- 40 mg capsules with ivory opaque body and blue-green opaque cap;
- 60 mg capsules with white opaque body and powder blue opaque cap;
- 80 mg capsules with white opaque body and light blue opaque cap; and
- 100 mg capsules with white opaque body and dark blue opaque cap.

All capsules are imprinted with the dose in black on the body and "IRONSHORE" in black on the cap, except for the 100 mg capsule, on which "IRONSHORE" is imprinted in white.

4 CONTRAINDICATIONS

JORNAY PM is contraindicated in patients:

- With a history of hypersensitivity to methylphenidate or other components of JORNAY PM. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products *[see Adverse Reactions (6)]*.

- Receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of a monoamine oxidase inhibitor, because of the risk of hypertensive crisis *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk for medication abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Drug Abuse and Dependence (9.2, 9.3)]*.

5.2 Serious Cardiovascular Reactions

Sudden death, stroke, and myocardial infarction have been reported in adults treated with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious cardiac problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia,

coronary artery disease, and other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with JORNAY PM.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants may cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such occur, consider discontinuing JORNAY PM. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared with 0 in placebo-treated patients.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric patients and adults. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

CNS stimulants, including JORNAY PM, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Long-term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or nonmedication-treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in

height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including JORNAY PM. Patients not growing or gaining height or weight as expected may need to have their treatment interrupted.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Drug Dependence *[see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*
- Hypersensitivity to methylphenidate or other components of the JORNAY PM *[see Contraindications (4)]*
- Hypertensive crisis when used concomitantly with monoamine oxidase inhibitors *[see Contraindications (4) and Drug Interactions (7.1)]*
- Serious Cardiovascular Reactions *[see Warnings and Precautions (5.2)]*
- Blood Pressure and Heart Rate Increases *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Priapism *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (5.6)]*
- Long-term Suppression of Growth *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD

Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia.

Clinical Trials Experience with JORNAY PM in Pediatric Patients (6 to 12 years) with ADHD

The safety of JORNAY PM was evaluated in 280 patients (6 to 12 years of age) who participated in two controlled clinical studies of patients with ADHD *[see Clinical Studies (14)]*.

Study 1, conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week open-label dose-optimization phase in which all patients received JORNAY PM (n=125; mean dose 50 mg), followed by a 1-week, double-blind controlled phase in which patients were randomized to continue JORNAY PM (n=65) or switch to placebo (n=54). During the open-label JORNAY PM treatment phase, adverse reactions reported in > 5% of patients included: any insomnia (41%), decreased appetite (27%), affect lability (22%), headache (19%), upper respiratory tract infection (17%), upper abdominal pain (9%), nausea or vomiting (9%), increased diastolic blood pressure (8%), tachycardia (7%), and irritability (6%). Three patients discontinued treatment because of adverse reactions of affect lability, panic attacks, and agitation and aggression. Because of the trial design (6-week open-label active treatment phase followed by a 1-week, randomized, double-blind, placebo-controlled withdrawal), the adverse reaction rates described in the double-blind phase are lower than expected

in clinical practice. No difference occurred in the incidence of adverse reactions between JORNAY PM and placebo during the 1-week, double-blind, placebo-controlled treatment phase.

Study 2 was a 3-week, placebo-controlled study of JORNAY PM (n=81; mean dose 52mg) in pediatric patients 6 to 12 years.

Most Common Adverse Reactions (incidence of ≥ 5% and at a rate at least twice placebo): any insomnia, decreased appetite, headache, vomiting, nausea, psychomotor hyperactivity, and affect lability or mood swings.

One patient in the JORNAY PM group discontinued from the study due to mood swings.

Table 1 provides the incidence of adverse reactions reported in Study 2 (incidence of 2% or more and at least twice placebo) among pediatric patients 6 to 12 years in a 3-week clinical trial.

Table 1: Adverse Reactions Occurring in ≥2% of JORNAY PM-treated Pediatric Patients and Greater than Placebo in a 3-Week ADHD Study (Study 2)

Body Organ System	Adverse Reaction	JORNAY PM (N=81)	Placebo (N=80)
Psychiatric disorders	Any insomnia	33%	9%
	Initial insomnia	14%	5%
	Middle insomnia	11%	4%
	Terminal insomnia	11%	1%
	Insomnia, not specified	4%	1%
	Affect lability/ Mood swings	6%	1%
Metabolism and nutrition disorders	Decreased appetite	19%	4%
Nervous system disorders	Headache	10%	5%
	Psychomotor hyperactivity	5%	1%
Cardiovascular	Blood pressure diastolic increased	7%	4%
Gastrointestinal disorders	Vomiting	9%	0%
	Nausea	6%	0%
Infections and infestations	Nasopharyngitis	3%	1%
	Pharyngitis streptococcal	3%	0%
Injury, poisoning and procedural complications	Contusion	3%	0%
Musculoskeletal and connective tissue disorders	Back pain	3%	0%
Skin and subcutaneous tissue disorders	Rash	2%	0%

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably

estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole

Eye Disorders: Diplopia, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Hyperpyrexia

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus, Rashes, Eruptions, and Exanthemas

Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal, Severe hepatic injury

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis

Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Libido changes, Mania

Urogential System: Priapism

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

7 DRUG INTERACTIONS

7.1 MAO Inhibitors

Do not administer JORNAY PM concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAO inhibitors and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to JORNAY PM during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.

Risk Summary

Published studies and postmarketing reports on methylphenidate use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes *[see Data]*. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 2 and 9 times the maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m^2 basis, respectively. However, spina bifida was observed in rabbits at a dose 31 times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre-and post-

natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 3.5 times the MRHD given to adolescents *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

CNS stimulant medications, such as JORNAY PM, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Human Data

A limited number of pregnancies have been reported in published observational studies and postmarketing reports describing methylphenidate use during pregnancy. Due to the small number of methylphenidate-exposed pregnancies with known outcomes, these data cannot definitely establish or exclude any drug-associated risk during pregnancy. Methodological limitations of these observational studies include small sample size, concomitant use of other medications, lack of detail regarding dose and duration of exposure to methylphenidate and nongeneralizability of the enrolled populations.

Animal Data

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 31 times the maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (9 times the MRHD given to adolescents on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (6 times the MRHD given to adolescents on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD given to adolescents on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JORNAY PM and any potential adverse effects on the breastfed infant from JORNAY PM or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of JORNAY PM in pediatric patients less than 6 years have not been established.

The safety and effectiveness of JORNAY PM have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical studies in pediatric patients 6 to 12 years, pharmacokinetic data in adults, and safety information from other methylphenidate-containing products *[see Clinical Studies (14) and see Clinical Pharmacology (12.3)]*.

The long-term efficacy of methylphenidate in pediatric patients has not been established.

Long-Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including JORNAY PM. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.7)]*.

Juvenile Animal Toxicity Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 2.5 times the maximum recommended human dose (MRHD) of 100 mg/day given to children on a mg/m^2 basis.

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal Day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with ≥ 50 mg/kg/day (approximately ≥ 2.5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis), and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (0.25 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

JORNAY PM has not been studied in patients older than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

JORNAY PM contains methylphenidate, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration, which can result in overdose and death *[see Overdosage (10)]*.

To reduce the abuse of CNS stimulants including JORNAY PM, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on

proper storage and disposal of CNS stimulants *[see How Supplied/Storage and Handling (16)]*, monitor for signs of abuse while on therapy, and re-evaluate the need for JORNAY PM use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants including JORNAY PM.

Dependence

Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants, including JORNAY PM. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include: dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

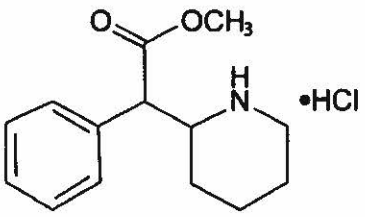
10.2 Management of Overdose

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdosage with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosages. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

11 DESCRIPTION

JORNAY PM contains methylphenidate hydrochloride, a central nervous system (CNS) stimulant.

Methylphenidate hydrochloride is a white, odorless crystalline powder. Its aqueous solutions are acidic. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. The chemical name of methylphenidate hydrochloride is *d,l* (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its molecular formula is $C_{14}H_{19}NO_2$•HCl and the molecular weight is 269.77. Its structural formula is



The molecular formula of the free base is $C_{14}H_{19}NO_2$ and its molecular weight is 233.31.

JORNAY PM extended-release capsules contain beads with two functional film coatings (outer delayed-release and inner extended-release) surrounding a drug core coated with methylphenidate hydrochloride. The outer, delayed-release coating delays the initial release of methylphenidate while the inner extended-release coating controls the release throughout the day. JORNAY PM is available as extended-release capsules for oral use in five strengths. Each capsule contains 20 mg, 40 mg, 60 mg, 80 mg, or 100 mg of methylphenidate hydrochloride, which is equivalent to 17.4 mg, 34.8 mg, 52.2 mg, 69.6 mg, or 87.0 mg of methylphenidate free base, respectively.

JORNAY PM capsules also contain the following inactive ingredients: dibutyl sebacate, diglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer Type B, microcrystalline cellulose, monoglycerides, polysorbate 80, and talc. The capsule shell of 20 and 40 mg strength capsules is made of FD&C Blue #1, hypromellose, titanium dioxide, yellow iron oxide, and black ink for the imprint. The capsule shell of 60 and 80 mg strength capsules is made of FD&C Blue #1, hypromellose, titanium dioxide, and black ink for the imprint. The capsules shell of 100 mg strength capsule is made of black iron oxide, FD&C Blue #1, hypromellose, red iron oxide, titanium dioxide, and black ink, and white ink for the imprint.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant. The exact mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprising the *d*- and *l*-isomers. The *d*-isomer is more pharmacologically active than the *l*-isomer. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

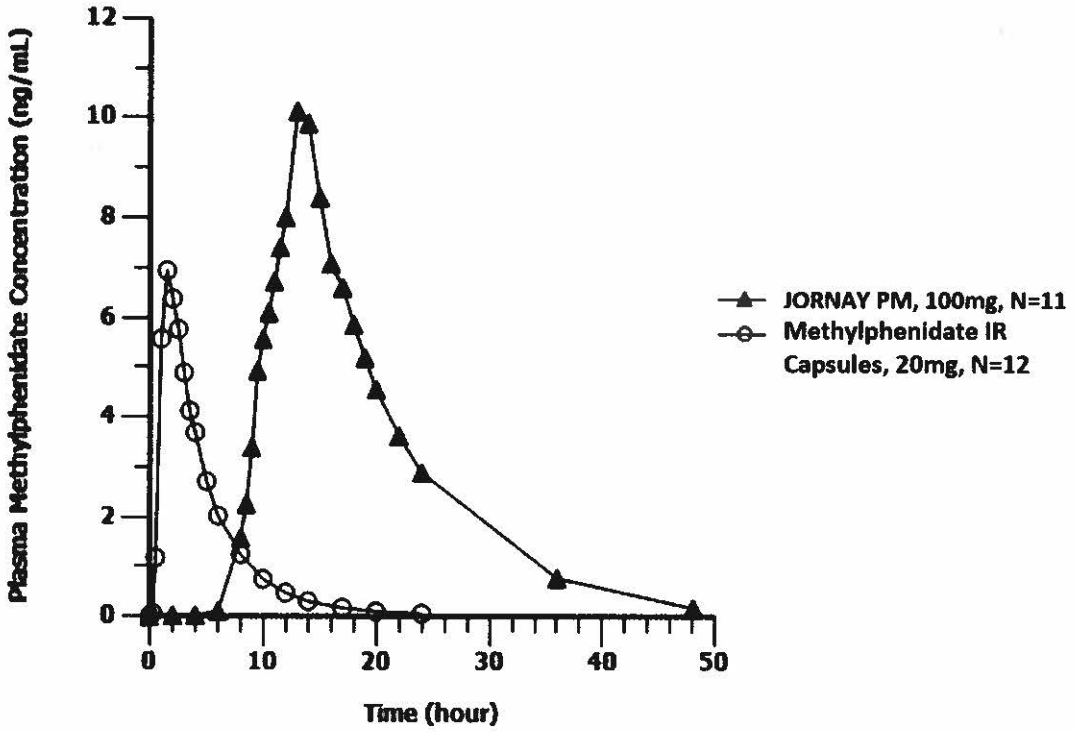
12.3 Pharmacokinetics

The pharmacokinetics of methylphenidate was dose-proportional between 20 mg and 100 mg dose level.

Absorption

The pharmacokinetics of methylphenidate after a single, 100 mg oral dose of JORNAY PM administered in the evening at 9 pm were studied in healthy adults. The initial absorption of methylphenidate into plasma is delayed such that no more than 5% of total drug is available within the first 10 hours after dosing. After the lag period, the absorption of methylphenidate occurs in a single peak with a median T_{max} 14.0 hours, followed by a gradual decline throughout the rest of the day.

Figure 1: **Arithmetic Mean Plasma Methylphenidate Concentrations following a Single, Oral, 100 mg Dose of JORNAY PM (Methylphenidate Hydrochloride Extended-Release Capsule) or Methylphenidate Immediate-Release Oral Product Administered in a Crossover Manner to Healthy Adult Subjects**



The relative bioavailability of JORNAY PM (given once a day) compared to the same daily dose of a methylphenidate immediate-release oral product (given 3 times a day) in adults is 73.9%.

Food Effects

Compared to the fasted state, JORNAY PM taken with a high-fat meal at night exhibited similar mean AUC $_{0-\infty}$, a 14% lower mean C_{max}, and a median T_{max} extended by approximately 2.5 hours. After JORNAY PM was taken at night, a morning meal had no effect on the pharmacokinetics of methylphenidate.

The pharmacokinetic parameters were similar when JORNAY PM was taken as a whole capsule or when sprinkled on applesauce.

Elimination

The apparent half-life of methylphenidate in adults following oral administration of JORNAY PM was approximately 5.9 hours.

Metabolism

In humans, methylphenidate is metabolized primarily by de-esterification to α-phenyl-piperidine acetic acid (PPAA). The metabolite has little pharmacologic activity.

Excretion

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Alcohol Effect:

In vitro testing showed that approximately 97% of methylphenidate was released from JORNAY PM capsules in 2 hours in the presence of 40% alcohol. The increase in methylphenidate release rate was not observed in the presence of 5 to 20% alcohol. No *in vivo* studies have been conducted to assess the effect of alcohol on drug exposure.

Specific populations:

Pediatric Patients

The pharmacokinetics of methylphenidate after a single, 54 mg oral dose of JORNAY PM administered in the evening at 9 pm were studied in two separate studies in adults and in children and adolescent patients with ADHD between 8 and 17 years of age. The plasma methylphenidate concentration curves were qualitatively similar in healthy adult volunteers, children 8 to 12 years, and adolescents with ADHD. Body weight dose normalized AUC and C_{max} were similar in children, adolescents, and adults. However, there were differences in mean PK parameters between children, adolescents, and adults; children were exposed to higher levels of methylphenidate when provided the same dose of JORNAY PM (C_{max}: children = 11.6 ng/mL, adolescents = 7.2 ng/mL, adults = 6.0 ng/mL; AUC_t: children = 206 ng·hr/mL, adolescents = 106 ng·hr/mL, adults = 83.4 ng·hr/mL).

Patients with Renal Impairment:

There is no experience with the use of JORNAY PM in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of JORNAY PM.

Patients with Hepatic Impairment

There is no experience with the use of JORNAY PM in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 1.5 times the maximum recommended human dose (MRHD) of 100 mg/day given to children on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 2 times the MRHD (children) on a mg/m^2 basis.

In a 24-week carcinogenicity study in the transgenic mouse strain p53$^{+/-}$, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis:

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility:

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 6-times the maximum recommended human dose of 100 mg/day given to adolescents on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of JORNAY PM was established in two clinical studies of JORNAY PM in pediatric patients 6 to 12 years of age (N = 278) who met DSM-5 criteria for ADHD inattentive, hyperactive-impulsive, or combined inattentive/hyperactive-impulsive subtypes.

Study 1 (NCT#02493777), conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week, open-label, dose-optimization phase in which all patients (n = 117) received JORNAY PM (once each evening; flexible dosing from 20 mg to 100 mg), followed by a 1-week, double-blind, placebo-controlled withdrawal phase in which patients were randomized to continue JORNAY PM (n=64; mean dose 67 mg) or switch to placebo (n=53). After 1 week of double-blind treatment, patients were evaluated in an analog classroom over a 12-hour period using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. Possible scores range from 0 (normal/ no impairment) to 78 (maximal impairment). The primary efficacy endpoint was the model-adjusted average of all post-dose SKAMP combined scores measured during the 12-hour analog testing period from 8:00 a.m. to 8:00 p.m. The secondary efficacy measure was the morning subscale of the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R AM), to measure manifestations of ADHD in the early morning. This clinician-rated scale is based on parent interview using three questions and assesses manifestations of ADHD during the early morning period. Possible scores range from 0 (no ADHD manifestations) to 9 (severe ADHD manifestations).

The primary efficacy endpoint, the model-adjusted average of all post-dose SKAMP combined scores measured during the 12-hour analog testing period, was statistically significantly better (lower) for JORNAY PM compared with placebo (Table 2). JORNAY PM showed improvement over placebo at time points (9 and 10 a.m., and 12, 2, 4, 6 and 7 p.m.) on the next day after the evening dosing. Figure 2 shows the LS mean and standard error of SKAMP combined scores at each of the individual time points from 8:00 a.m. to 8:00 p.m. The secondary efficacy endpoint, the PREMB-R AM, was also statistically significantly better (lower) for JORNAY PM versus placebo.

Study 2 (NCT#02520388) was a 3-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in pediatric patients, 6 to 12 years of age. Patients were randomized to an evening dose of 40, 60, or 80 mg JORNAY PM (n=81) or placebo (n=80). The primary efficacy measure was the ADHD Rating Scale (ADHD-RS-IV) Total Score, measuring severity of manifestations throughout the day. Possible scores range from 0 (no ADHD manifestations) to 54 (severe symptoms of both ADHD subtypes). Normative scores range 18 to 29 in ADHD. The secondary efficacy measure was the Before School Functioning Questionnaire (BSFQ), a clinician-rated 20-item questionnaire assessing ADHD manifestations on a severity scale of 0 to 3. BSFQ is intended to assess early morning before school activities from the time the child awakens and some behaviors not specific to early morning. Possible scores range from 0 (no difficulty) to 60 (severe difficulty).

After 3 weeks of treatment, the ADHD-RS-IV total scores were statistically significantly better (lower) for JORNAY PM than placebo (Table 2). The secondary efficacy endpoint, the BSFQ, was also statistically significantly better (lower) for JORNAY PM versus placebo.

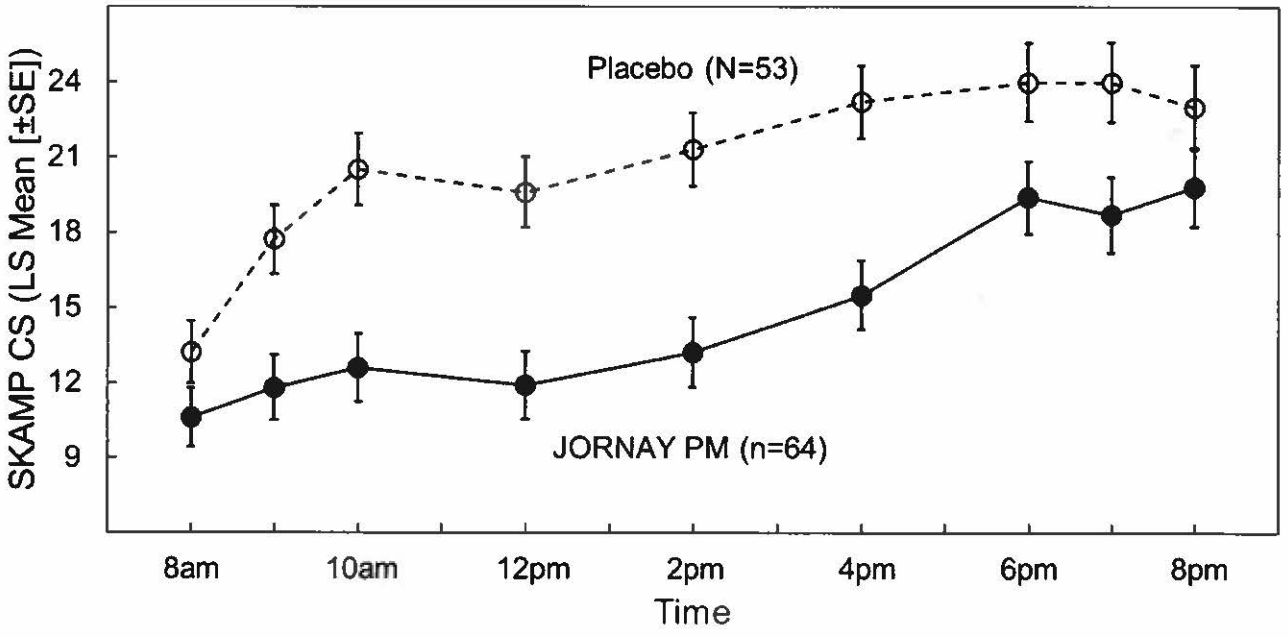
Table 2 summarizes the primary endpoint results for Study 1 and Study 2.

Table 2: Summary of Primary Efficacy Results in Pediatric Patients (6 – 12 years) with ADHD (Studies 1 and 2)

Study Number	Measure (Primary Endpoint)	Treatment Group (#ITT Subjects)	Mean Baseline Score (SD)	LS Mean (SE)	Placebo-subtracted Difference (95% CI)
Study 1	**SKAMP CS Average**	JORNAY PM (64)	NA	14.8 (1.17)	-5.9 (-9.1, -2.7)
		Placebo (53)	NA	20.7 (1.22)	
Study 2	**ADHD-RS-IV**	JORNAY PM (81)	43.1 (7.33)	24.1 (1.50)	-7.0 (-11.4, -2.7)
		Placebo (80)	43.5 (6.84)	31.2 (1.60)	

ITT: Intent-to-treat. SE: Standard Error. SD: Standard Deviation. CI: Confidence Interval. NA: Not Available.
CS: Combined Score (sum of items 1-13)

Figure 2: Study 1—LS Mean SKAMP Combined Score on Day after Final Treatment, as Measured in an Analogue Classroom, N=117



LS = Least Squares; CS = Combined Score (sum of items 1-13); N= Sample Size; SE = Standard Error

16 HOW SUPPLIED/STORAGE AND HANDLING

JORNAY PM (methylphenidate hydrochloride) extended-release capsules are available as follows:

20 mg Capsules – ivory opaque body and light green opaque cap (imprinted with "20 mg" in black on the body and "IRONSHORE" in black on the cap)
Bottles of 100.....NDC 71376-201-03
40 mg Capsules – ivory opaque body and blue-green opaque cap (imprinted with "40 mg" in black on the body and "IRONSHORE" in black on the cap)

Bottles of 100.....NDC 71376-202-03
60 mg Capsules – white opaque body and powder blue opaque cap (imprinted with "60 mg" in black on the body and "IRONSHORE" in black on the cap)
Bottles of 100.....NDC 71376-203-03
80 mg Capsules – white opaque body and light blue opaque cap (imprinted with "80 mg" in black on the body and "IRONSHORE" in black on the cap)
Bottles of 100..... NDC 71376-204-03
100 mg Capsules – white opaque body and dark blue opaque cap (imprinted with "100 mg" in black on the body and "IRONSHORE" in white on the cap)
Bottles of 100.....NDC 71376-205-03

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Protect from humidity.

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired JORNAY PM by a medicine take-back program or by an authorized collector registered with the Drug Enforcement Administration. If no take-back program or authorized collector is available, mix JORNAY PM with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard JORNAY PM in the household trash.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/Potential for Abuse and Dependence

Advise patients that JORNAY PM is a federally controlled substance, and it can be abused or lead to dependence *[see Drug Abuse and Dependence (9.1, 9.2, 9.3)]*. Instruct patients that they should not give JORNAY PM to anyone else. Advise patients to store JORNAY PM in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired JORNAY PM through a medicine take-back program if available *[Warnings and Precautions (5.1), Abuse and Dependence (9.2, 9.3), How Supplied/Storage and Handling (16)]*.

Dosage and Administration Instructions

Advise patients that JORNAY PM is taken once daily in the evening. Advise patients that JORNAY PM should not be taken in the morning. It should be taken consistently, either with food or without food, and patients should establish a routine pattern of administration time.

For patients who take JORNAY PM sprinkled over applesauce, the contents of the entire capsule should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. When initiating treatment with JORNAY PM, provide dosage escalation and administration instructions *[see Dosage and Administration (2)]*.

Advise patients that if they forget to take JORNAY PM at their regularly scheduled time, they may take it as soon as they remember that same evening. If a patient remembers the following morning that they forgot to take their JORNAY PM dose the evening before, advise the patient to wait until their next scheduled evening administration.

Serious Cardiovascular Risks

Advise patients that there is a potential for serious cardiovascular risks including sudden death, myocardial infarction, stroke, and hypertension with JORNAY PM use. Instruct patients to contact a healthcare provider

immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Blood Pressure and Heart Rate Increases

Advise patients that JORNAY PM can cause elevations in blood pressure and heart rate *[see Warnings and Precautions (5.3)]*.

Psychiatric Risks

Advise patients that JORNAY PM, at recommended doses, can cause psychotic or manic symptoms, even in patients without a prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Priapism

Advise patients, caregivers, and family members of the possibility of painful or prolonged penile erections (priapism). Instruct the patient to seek immediate medical attention in the event of priapism *[see Warnings and Precautions (5.5)]*.

Circulation Problems in Fingers and Toes [peripheral vasculopathy, including Raynaud's phenomenon]

- Instruct patients about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change from pale, to blue, to red.
- Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.
- Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking JORNAY PM.
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Suppression of Growth

Advise patients, caregivers, and family members that JORNAY PM can cause slowing of growth and weight loss *[see Warnings and Precautions (5.7)]*.

Alcohol Effect

Advise patients to avoid alcohol, while taking JORNAY PM. Consumption of alcohol while taking JORNAY PM may result in a more rapid release of the dose of methylphenidate *[see Clinical Pharmacology (12.3)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to JORNAY PM during pregnancy *[see Use in Specific Populations (8.1)]*.

Packaged by:
Patheon Puerto Rico, Inc.
Manatí, Puerto Rico, 00674 USA

Manufactured for:
Ironshore Pharmaceuticals, Inc.
Cherry Hill, NJ, 08002 USA

MEDICATION GUIDE
JORNAY PM (JOR-nay)
(methylphenidate hydrochloride)
extended-release capsules, CII

What is the most important information I should know about JORNAY PM?

JORNAY PM can cause serious side effects, including:

- **Abuse and dependence.** JORNAY PM contains methylphenidate. JORNAY PM, other methylphenidate containing products, and amphetamines, have a high chance for abuse and can cause physical and psychological dependence. Your healthcare provider should check you or your child for signs of abuse and dependence before and during treatment with JORNAY PM.
  - Tell your healthcare provider if you or your child has ever abused or been dependent on alcohol, prescription medicines, or street drugs.
  - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **Heart-related problems, including:**
  - sudden death, stroke, and heart attack in adults
  - sudden death in children who have heart problems or heart defects
  - increased blood pressure and heart rate

  Your healthcare provider should check you or your child carefully for heart problems before starting JORNAY PM. Tell your healthcare provider if you or your child has any heart problems, heart defects, or high blood pressure.

  Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with JORNAY PM.

  Call your healthcare provider right away or go to the nearest hospital emergency room right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with JORNAY PM.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior and thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

  Tell your healthcare provider about any mental problems you or your child has, or about a family history of suicide, bipolar illness, or depression.

  Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with JORNAY PM, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What is JORNAY PM?

JORNAY PM is a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in people 6 years of age and older. JORNAY PM may help increase attention and decrease impulsiveness and hyperactivity in people 6 years of age and older with ADHD.

It is not known if JORNAY PM is safe and effective in children under 6 years of age.

JORNAY PM is a federally controlled substance (CII) because it contains methylphenidate that can be a target for people who abuse prescription medicines or street drugs. Keep JORNAY PM in a safe place to protect it from theft. Never give your JORNAY PM to anyone else, because it may cause death or harm them. Selling or giving away JORNAY PM may harm others, and is against the law.

Who should not take JORNAY PM?

Do not take JORNAY PM if you or your child is:

- allergic to methylphenidate hydrochloride, or any of the ingredients in JORNAY PM. See the end of this Medication Guide for a complete list of ingredients in JORNAY PM.
- taking or has taken within the last 14 days, a medicine used to treat depression called a monoamine oxidase inhibitor (MAOI).

Before taking JORNAY PM, tell your or your child's healthcare provider about all medical conditions, including if you or your child:

- have heart problems, heart defects, or high blood pressure

- have mental problems including psychosis, mania, bipolar illness, or depression, or have a family history of suicide, bipolar illness, or depression
- have circulation problems in fingers or toes
- are pregnant or plan to become pregnant. It is not known whether JORNAY PM will harm your unborn baby.
  - There is a pregnancy registry for females who are exposed to JORNAY PM during pregnancy. The purpose of the registry is to collect information about the health of females exposed to JORNAY PM and their baby. If you or your child becomes pregnant during treatment with JORNAY PM, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants. You can register by calling 1-866-961-2388.
- are breastfeeding or plan to breastfeed. JORNAY PM passes into breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with JORNAY PM.

Tell your healthcare provider about all of the medicines that you or your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

JORNAY PM and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted during treatment with JORNAY PM.

Your healthcare provider will decide whether JORNAY PM can be taken with other medicines.

Especially tell your healthcare provider if you or your child takes medicine to treat depression, including MAOIs.

Know the medicines that you or your child takes. Keep a list of the medicines with you to show your healthcare provider and pharmacist when you or your child get a new medicine.

Do not start any new medicine during treatment with JORNAY PM without talking to your or your child's healthcare provider first.

How should JORNAY PM be taken?

- Take JORNAY PM exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose and timing of the JORNAY PM dose if needed.
- **Take JORNAY PM by mouth 1 time each day in the evening between 6:30 p.m. and 9:30 p.m.**
- Take JORNAY PM at the same time each evening. JORNAY PM **should not** be taken in the morning.
- JORNAY PM can be taken with or without food, but take it the same way each time.
- JORNAY PM capsules may be swallowed whole, or if JORNAY PM capsules cannot be swallowed whole, the capsules may be opened and sprinkled onto applesauce. Make sure to sprinkle all the JORNAY PM onto the applesauce. The JORNAY PM dose should not be divided.
  - swallow **all** the applesauce and medicine mixture right away
  - **do not** chew the applesauce and medicine mixture
  - **do not** store the applesauce and medicine mixture
- Your healthcare provider may sometimes stop JORNAY PM treatment for a while to check for ADHD symptoms.
- If a dose of JORNAY PM is missed, it should be taken as soon as you remember the same evening. If you do not remember until the next morning you should not take the dose. Wait until that evening to take the next scheduled dose. **A missed dose should not be taken in the morning.**
- If you or your child takes too much JORNAY PM, call your healthcare provider or go to the nearest hospital emergency room right away.

What should be avoided during treatment with JORNAY PM?

- Avoid drinking alcohol during treatment with JORNAY PM. This may cause a faster release of the JORNAY PM medicine.

What are possible side effects of JORNAY PM?

JORNAY PM can cause serious side effects, including:

- See **"What is the most important information I should know about JORNAY PM?"**
- **Painful and prolonged erections (priapism).** Priapism has happened in males who take products that contain methylphenidate. If you or your child develops priapism, get medical help right away.
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon). Signs and symptoms may include:**
  - fingers or toes may feel numb, cool, or painful
  - fingers or toes may change color from pale, to blue, to red

Tell your healthcare provider if you or your child has numbness, pain, skin color change, or sensitivity to temperature in the fingers or toes.

Call your healthcare provider right away if you or your child has any signs of unexplained wounds appearing on fingers or toes during treatment with JORNAY PM.

- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with JORNAY PM. JORNAY PM treatment may be stopped if your child is not gaining weight or height.

The most common side effects of methylphenidate products in children, adolescents, and adults with ADHD include:

- decreased appetite
- trouble sleeping
- nausea
- vomiting
- indigestion
- stomach pain
- weight loss
- anxiety
- dizziness
- irritability
- mood swings (affect liability)
- increased heart rate
- increased blood pressure

The most common side effects of JORNAY PM, in children age 6 to 12 with ADHD include:

- trouble sleeping
- decreased appetite
- restlessness (psychomotor hyperactivity)
- headache
- nausea
- mood swings
- vomiting

These are not all the possible side effects of JORNAY PM.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JORNAY PM?

- Store JORNAY PM at room temperature between 68°F to 77°F (20°C to 25°C).
- Store JORNAY PM in a safe place, like a locked cabinet. Protect from humidity.
- Dispose of remaining, unused, or expired JORNAY PM by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix JORNAY PM with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away JORNAY PM in the household trash.

Keep JORNAY PM and all medicines out of the reach of children.

General information about the safe and effective use of JORNAY PM.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use JORNAY PM for a condition for which it was not prescribed. Do not give JORNAY PM to other people, even if they have the same symptoms. It may harm them, and it is against the law.

You can ask your doctor or pharmacist for information about JORNAY PM that is written for healthcare professionals.

What are the ingredients in JORNAY PM?

Active Ingredient: methylphenidate hydrochloride

Inactive Ingredients: dibutyl sebacate, diglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer Type B, microcrystalline cellulose, monoglycerides, polysorbate 80, and talc.

The capsule shell of 20 and 40 mg strength capsules contains FD&C Blue #1, hypromellose, titanium dioxide, yellow iron oxide, and black ink for the imprint. The capsule shell of 60 and 80 mg strength capsules contains FD&C Blue #1, hypromellose, titanium dioxide, and black ink for the imprint. The capsules shell of 100 mg strength capsule contains black iron oxide, FD&C Blue#1, hypromellose, red iron oxide, titanium dioxide, black ink, and white ink for the imprint.

Manufactured for Ironshore Pharmaceuticals, Inc.:

For more information about JORNAY PM go to www.jornaypm.com or call 1-877-938-4766

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Early Morning Functioning in Stimulant-Treated Children and Adolescents with Attention-Deficit/Hyperactivity Disorder, and its Impact on Caregivers

Floyd R. Sallee, MD, PhD

Abstract

Objective: The purpose of this study was to examine the temporal occurrence and severity of inadequate attention-deficit/hyperactivity disorder (ADHD) symptom control throughout the day, and, more specifically, the frequency and severity of associated functional impairments and their apparent emotional impact on parents and caregivers during the early morning routine before school, in children and adolescents with ADHD currently treated with stable doses of stimulant medications.
Methods: Information was obtained from 201 primary caregivers of children and adolescents with ADHD using a self-administered, on-line quantitative research survey.
Results: Inadequately controlled ADHD symptoms were rated as most severe during the evening homework time and the early morning routine. The majority of caregivers reported early morning ADHD symptoms and impairment of early morning functioning (EMF) as moderate to severe. Caregiver reactions to their child's early morning ADHD symptoms and unwanted behaviors included feeling overwhelmed, exhausted, and constantly stressed.
Conclusions: Control of EMF impairments from inadequately controlled ADHD symptoms is a significant unmet need in children and adolescents with ADHD treated with stable morning doses of stimulant medications. Current orally administered stimulant treatment options have not addressed this challenge.

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is among the most common childhood psychiatric conditions (Pliszka and AACAP Work Group on Quality Issues 2007) with an estimated prevalence range of 5.9–7.1% in children and adolescents (Willcutt 2012). According to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-V), the essential diagnostic feature of ADHD is a persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning or development (American Psychiatric Association 2013). In order to meet the diagnostic criteria for ADHD, there must be clear evidence of interference with, or the reduced quality of, social, academic, or occupational functioning attributable to the symptoms (American Psychiatric Association 2013). A host of studies have associated ADHD in children and adolescents with significant behavioral consequences including psychopathology, school and occupational failure, family and peer difficulties, emotional problems, and low self-esteem (Shaw et al. 2012). Additionally, ADHD has also been shown to have negative effects on families as a whole, such as disturbed interpersonal relationships, less perceived family cohesiveness and greater conflict, depression in parents, and higher incidences of divorce and separation (Wymbs et al. 2008; Chang et al. 2013; Gau and Chang 2013). Accordingly, the American Academy of Child and Adolescent Psychiatry Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder recommends that a well-thought-out and comprehensive treatment plan for patients with ADHD should consist of psychopharmacologic and/or behavior therapy (Pliszka and AACAP Work Group on Quality Issues 2007).

Behavioral symptoms in children with ADHD have been shown to fluctuate across the day (Antrop et al. 2005). Stimulant-based medications such as methylphenidate (MPH) and amphetamines (AMP) have been the cornerstone of ADHD pharmacotherapy for several decades (Pliszka and AACAP Work Group on Quality Issues 2007), and their temporal effects on behavioral symptoms in children and adolescents have been assessed at different times throughout the day. The earliest temporal assessments of stimulant treatment effect focused on adequate control of ADHD symptoms in school. In the last decade, the temporal effects of stimulant medications in controlling ADHD symptoms have evolved in parallel with the evolution of numerous long-acting, extended-

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release (ER) stimulant medications; to include both in-school and after-school symptom control.

Although it is known that many home-based difficulties for children and adolescents with ADHD occur before the school day begins (Whalen et al. 2006) and that the time from awakening to arrival at school may represent up to 20% of the day (~2–3 hours) for children and adolescents with ADHD and their families (Wilens et al. 2010), little is known about the specific nature of early morning functioning (EMF) impairments in stimulant-treated children and adolescents with ADHD or the impact of these impairments on caregivers.

Recent interest has now begun to focus on the issue of inadequately controlled ADHD symptoms that occur during the early morning hours before the school day begins and to date, three pharmacotherapy-based efficacy studies have addressed the effects of different MPH formulations on EMF in children and adolescents with ADHD (Sangal et al. 2006; Wilens et al. 2010; Döpfner et al. 2011). The earliest of the published studies was a randomized, double-blind, crossover trial designed to assess the effects of three-times-daily administration of immediate-release (IR) MPH (before 8:00 a.m., at or near noon, and between 4:00 and 5:00 p.m.) versus twice daily atomoxetine on sleep parameters in 85 children and adolescents ages 6–14 with ADHD (Sangal et al. 2006). The 13 item Daily Parent Rating of Evening and Morning Behavior (DPREMB) scale was among the study's secondary outcome measures and included caregiver ratings of core ADHD symptoms and behavioral problems typically experienced by children with ADHD in the early morning (4 items) and late afternoon/evening (9 items) (Michelson et al. 2002). The results of the study pertaining to improvements in EMF demonstrated that atomoxetine was shown to have significant beneficial treatment effects on two of the four EMF items as compared to the thrice-daily IR MPH regimen. The mean changes from baseline on the DPREMB for the morning subscale score were −1.18 for atomoxetine and −0.41 for IR MPH, which was statistically significant favoring atomoxetine ($p<0.001$). When looking specifically at the treatment effect for the IR-MPH group on the DPREMB (morning) parent-rated questions, "How difficult was it to get your child out of bed this morning?", "How much difficulty did your child have getting ready this morning?", "How much was your child arguing or struggling excessively this morning?", and "How irritable and quick was your child to lose his or her temper this morning?", the mean change scores compared with baseline values ranged from 0.03 (worsening) to −0.22 (minor improvement). In summary, oral administration of IR-MPH before 8:00 a.m. did not demonstrate statistically significant improvements in early morning ADHD symptoms and behaviors in children and adolescents when compared with baseline values (Sangal et al. 2006).

The second study (Döpfner et al. 2011), was a non-interventional, non-controlled, multicenter, prospective, observational, postmarketing surveillance study, which assessed the efficacy of a once-daily modified-release MPH formulation in 822 children and adolescents with ADHD ages 6–17 years. Although the time of dosing was not specified, most once-daily ADHD medications are administered in the morning immediately after awakening or at breakfast time. As a secondary measure, this study used the parent version of the Day Profile of ADHD Symptoms (DAYAS-P) questionnaire, a new rating scale that assesses the daily profile of ADHD externalizing symptoms from early morning until bedtime (Breuer et al. 2011). Data from the DAYAS-P questionnaire indicated that treatment resulted in statistically significant improvement ($p<0.001$) in the total score for morning/before-school symptoms and behavioral problems from visit 1 (1.37 ± 0.77) to visit 3 (1.02 ± 0.72), and for the ADHD symptom score for the morning before school from visit 1 (1.38 ± 0.71) to visit 3 (1.02 ± 0.78), although the Cohen's d for effect size for both ratings was rather low (0.51 and 0.47, respectively) (Döpfner et al. 2011).

Only one randomized, placebo-controlled study has focused exclusively on inadequately controlled ADHD symptoms and associated EMF impairments in children ages 6–12 years with ADHD by examining the efficacy of a transdermal MPH formulation (MTS) administered once-daily between 6:00 and 7:00 a.m. (Wilens et al. 2010). The study's primary outcome measures include the ADHD-Rating Scale (ADHD-RS) and ADHD-AM-RS (for the time period 6:00–9:00 a.m. only). This study also included a new clinician-rated and completed 20 item questionnaire (the Before-School Functioning Questionnaire [BSFQ]) as a secondary outcome measure. The questionnaire was generated from commonly reported areas of dysfunction in the early morning (6:00–9:00 a.m.), before-school activities associated with ADHD symptomatology, such as breakfast, hygiene, time awareness, and getting to school. The psychometric properties of the BSFQ have recently been validated by Faraone et al. (2015). Results of the study demonstrated significant reductions with MTS compared to placebo for the ADHD-RS total score ($p<0.001$), ADHD-AM-RS ($p=0.003$), and BSFQ total score ($p=0.001$). Of the 20 before-school items that comprised the BSFQ, only three did not show statistically significant differences ($p<0.05$) between the transdermal MPH- and placebo-treated groups ("Did your child have difficulty with: being quiet; awaiting his/her turn; and getting to school?"). There was a 69% reduction in the subjects' total score for transdermal MPH versus a 23% reduction for transdermal placebo. The items that had the largest difference in favor of transdermal MPH versus placebo included listening, following directions, attention, distraction, and hygiene ($p<0.01$) (Wilens et al. 2010).

When viewed collectively, the results from the two aforementioned pharmacologic studies with orally administered MPH suggesting that the acute treatment has benefits for inadequately controlled early morning ADHD symptoms and associated behaviors are inconclusive. These mixed results also suggest the need for further research on EMF impairments in stimulant-treated children and adolescents with ADHD. Further, these three studies appear to suggest a need for a more formalized assessment of EMF, as well as a need for further exploration regarding the mechanisms by which pharmacotherapies may improve some aspects of early morning ADHD symptoms and functioning, as opposed to others.

In addition to pharmacotherapeutic efficacy studies, one large, on-line, parent-completed questionnaire survey study conducted in Europe was designed to examine the impact of ADHD on their children's/adolescent's everyday activities, general behavior, and family relationships, and to assess the effect of stimulant medications on the behaviors of their children and adolescents with ADHD during times of day when parents have the closest contact with their children and adolescents, such as the early morning (Coghill et al. 2008). Survey results demonstrated that a significantly higher percentage of children and adolescents ages 6–18 years with ADHD receiving stimulant medication experienced impaired functioning during their morning routine (from 7:00 to 8:00 a.m.; waking up, getting ready for school) compared with unmedicated children and adolescents with ADHD (55% vs. 36%, respectively; $p<0.05$). Additionally, parents reported that children and adolescents with ADHD receiving 12 hour stimulant medications experienced greater levels of functional impairments during the morning routine than those receiving 6–8 hour stimulant medications. Coghill et al. noted a possible limitation of the study in that traditionally in

Europe, the most severely symptomatic and impaired ADHD children and adolescents are the ones who are treated with stimulant medications (in general) and further, that longer acting stimulant medications (12 hour) are often reserved for the most severely ill patients whereas the 6–8 hour medications are typically utilized for less severely ill ADHD patients. Therefore, this stratification of ADHD patient symptom severity assignment to stimulant treatment and use of modified-release formulations specifically for the most highly symptomatic patients, may account for the apparent diminished benefit of stimulant treatment on early morning ADHD symptoms reported by the authors. Importantly, this large quantitative research survey study clearly detected evidence of early morning ADHD symptomatology and related EMF impairments in children and adolescents treated with stimulant medications. In aggregate, the survey's EMF findings add further evidence to pharmacologic studies in suggesting that morning administration of oral stimulant medications may not provide meaningful clinical control of early morning ADHD symptoms, so as to improve functioning during the school-age child's early morning routines (Coghill et al. 2008).

In summary, a review of the current ADHD clinical literature would suggest that despite recent formulation advances in oral stimulant medications designed to provide increasingly longer duration of treatment benefit throughout the day, very little is known about the specific prevalence, frequency, and severity of inadequately controlled ADHD symptoms and related EMF impairments that likely occur during the early morning routine in stimulant-treated children and adolescents.

The objectives of this parent self-report-based, quantitative research survey were to determine the temporal occurrence and severity of inadequately controlled ADHD symptoms throughout the day in children and adolescents with ADHD who are currently treated with stable doses of stimulant medications. More importantly, the survey allowed for a quantitative exploration of the temporal occurrence, frequency, and severity of inadequately controlled ADHD symptoms specifically related to the early morning hours of the day, before school; as well as detailed descriptions of related functional impairments, unwanted behaviors and their apparent emotional impact on parents and caregivers.

Methods

Survey development and description

This self-administered, anonymous, on-line quantitative research survey was conducted between December 31, 2012 and January 24, 2013. An on-line, primary caregiver-completed questionnaire was designed with input from experts in the field of child and adolescent psychiatry to determine from parent self-reports if inadequately controlled ADHD symptoms exist in children and adolescents with ADHD who are currently treated with stable doses of stimulant medications. Second, parents were asked to define these inadequately controlled ADHD symptoms, if present, with respect to their temporal occurrence and severity. Of particular interest were the detailed responses of those parents who identify the "Early Morning Routine," defined in the survey as "from the moment the child/adolescent awakens to the time they leave for school" and including activities such as getting out of bed, getting dressed, brushing teeth, sitting down for breakfast, having breakfast, and getting ready to leave the household, as a problematic time period for the inadequate control of ADHD symptoms. Caregivers who identified inadequately controlled ADHD symptoms during the Early Morning Routine (Likert severity rating > 2) were asked to continue the survey by answering a series of multiple choice and open-ended questions. This portion of the survey allowed respondents to provide detailed descriptions of related functional mpairments and unwanted behaviors that manifest from these inadequately controlled ADHD symptoms. Additionally, it allowed for assessment of their ADHD symptom severity and frequency of early morning ADHD symptom occurrence across the weekdays when school was in session.

The survey contained 32 primary questions and 30 subquestions for a total of 62 questions. On average, the time taken for primary caregivers of children/adolescents with ADHD to complete the survey was 20 minutes.

This study was sponsored by Ironshore Pharmaceuticals & Development, Inc. and conducted by Repass & Partners, an experienced market research firm. The survey did not contain any option for any of the 18 standard types of protected health information (PHI) data to be collected. Surveys were completed voluntarily and anonymously. Caregiver respondents were blinded as to the research sponsor, and the survey was conducted in accordance with and adherence to The Marketing Research Association's (MRA) Code of Marketing Research Standards (Marketing Research Organization 2013).

Sampling strategy

Parent/primary caregiver research respondents were derived from nationally representative consumer research panels consisting of both presumed or known households of children and adolescents with ADHD ($n = 10{,}750$). To ensure that 200 surveys were completed, an additional invitation was sent to households with unknown child/adolescent-ADHD diagnostic status ($n = 142{,}999$). Primary caregivers who volunteered to participate in the survey first completed a screening questionnaire to ensure that the following requisite inclusion criteria were met prior to beginning the general survey: 1) Must be the parent (≥65% of completed surveys) or primary caregiver for a child/adolescent 6–17 years of age diagnosed with ADHD and 2) that child or adolescent's primary ADHD medication must be a stimulant medication and 3) the dosage of the stimulant medication must have been stable for at least 3 months prior to taking the survey. Caregivers who were employed by a physician, a hospital, a pharmaceutical manufacturer, or a pharmacy or marketing research firm were not eligible to participate.

Eligible respondents were subsequently screened to assess for the presence of inadequately controlled ADHD symptoms at any time throughout the day. If inadequately controlled ADHD symptoms were present, the caregiver was asked to identify in which of the following temporal periods of the day did the symptoms manifest and at what severity level (Likert scale 1–10): 1) The Early Morning Routine, 2) During the School Day, 3) Afternoon Homework Time, 4) Dinner Time, 5) Evening Homework Time, and 6) Bedtime.

Results

A total of 2013 caregivers volunteered to participate in the survey and 290 (14.0%) met the requisite screening criteria and entered into the formal survey; 280 respondents (97.0%) identified at least one temporal period of the day when their child's/adolescent's ADHD symptoms were inadequately controlled and 264 caregivers (91.0%) specifically identified the Early Morning Routine as a time period when inadequately controlled ADHD

symptoms manifested with at least mild severity (Likert scale ≥ 2). A total of 201 caregivers completed the entire survey, including the specific details for how the Early Morning Routine was impacted by these inadequately controlled ADHD symptoms; therefore, this is the number that was used for the majority of the analyses.

Adult respondent and child/adolescent patient demographic information is presented in Tables 1 and 2, respectively. Among respondents, 45.3% (91/201) were between the ages of 36 and 45, 33.3% (67/201) had completed college, 25.9% (52/201) reported earning $50,000–75,000 per year, and 72.6% (146/201) reported being the mother of a child/adolescent with ADHD. Almost half (46.3%, 93/201) reported that there were two children/adolescents living in the household, and 50.1% (236/471) reported that the age of all children/adolescents living in the household was between 6 and 12 years and that 55.0% (259/471) of all the children/adolescents living in the household were male. The majority (87.1%, 175/201) reported that only one child/adolescent in the household was receiving stimulant treatment for ADHD. As for the child/adolescent patients reported on by caregivers in completed surveys, 71.1% (143/201) were male, 59.7% (120/201) were 6–12 years of age, and the mean age was 11.3 years. The majority had been diagnosed with the combined subtype of ADHD (78.6%, 158/201) and smaller numbers were diagnosed with the inattentive (12.9%, 26/201) and hyperactive-impulsive (8.5%, 17/201) subtypes. Two thirds (67.0%, 135/201) of the children and adolescents reported on by their caregivers had been diagnosed with one or more of nine comorbidities examined. The most frequently diagnosed comorbid conditions for these children and adolescents with ADHD were learning disability (37.8%, 76/201), anxiety (31.3%, 63/201), and oppositional defiant disorder (ODD) (24.4%, 49/201). Subgroup analyses of caregiver respondent ratings indicated that early morning ADHD symptom scores were higher for Medicaid patients than for those with commercial insurance, for children (6–12) than for adolescents (13–17), for children diagnosed with comorbid ODD than for those without, and for children taking a supplemental ADHD medication in addition to their primary stimulant medication than for those who were not.

TABLE 1. ADULT RESPONDENT DEMOGRAPHIC INFORMATION

	n (%)
Age of respondent (years)	
18–25	1/201 (0.5)
26–35	62/201 (30.8)
36–45	91/201 (45.3)
46–55	40/201 (19.9)
56–65	7/201 (3.5)
Education level of respondent	
High school	31/201 (15.4)
Trade/Technical school	12/201 (6.0)
Some college	63/201 (31.3)
College graduate	67/201 (33.3)
Masters/Advanced degree	28/201 (13.9)
Income level of respondent	
<$30,000	35/201 (17.4)
$30,000–$49,999	45/201 (22.4)
$50,000–$74,999	52/201 (25.9)
$75,000–$99,999	32/201 (15.9)
$100,000–$124,999	17/201 (8.5)
≥$125,000	19/201 (9.5)
Refused to answer/Did not know	1/201 (0.5)
Respondent relationship to child/adolescent with ADHD	
Mother	146/201 (72.6)
Father	36/201 (17.9)
Other	19/201 (9.5)
Total number of children/adolescents in the household	
1	45/201 (22.4)
2	93/201 (46.3)
3	32/201 (15.9)
4	19/201 (9.5)
≥5	12/201 (6.0)
Age of all children/adolescents in the household (years)	
<6	74/471 (15.7)
6–12	236/471 (50.1)
13–17	161/471 (34.2)
Gender of all children/adolescents in the household	
Male	259/471 (55.0)
Female	212/471 (45.0)
Number of children/adolescents in the household taking ADHD medication	
1	175/201 (87.1)
2	24/201 (11.9)
3	2/201 (1.0)

ADHD, attention-deficit/hyperactivity disorder.

MPH HCl ER was the most frequently reported primary ADHD medication (30.3%, 61/201), and 59.7% (120/201) of these children/adolescents with ADHD were not receiving any supplemental ADHD medications. Of those who did receive supplemental ADHD medications, AMP and dextroamphetamine mixed salts, IR (9.0%, 18/201), MPH HCl IR (7.0%, 14/201), and MPH HCl ER (7.0%, 14/201) were the most frequently used. Almost one third of subjects were reported to have been taking their primary ADHD medication for 6–12 months (30.8%, 62/201), and an equal number had been receiving their primary ADHD medication for >2 years. Approximately two thirds of the patients (67.2%, 135/201) received their primary ADHD medication once daily and 65.7% (132/201) were taking their primary stimulant medication 7 days a week during the school year for ADHD symptom management. Most (33.3%, 103/309) of the patients were administered this medication at 7 a.m., whereas 6 p.m. to midnight and 8 a.m. were the second and third most common administration times of day, respectively (16.5%, 51/309 and 13.9%, 43/309). For those patients receiving supplemental medication, most (23.4%, 26/111) were administered with this medication between 6 p.m. and midnight. Regarding frequency of follow-up with the physician charged with treating patients with ADHD, most (87/201, 43.3%) were followed up more than three times per year.

When asked to rate the overall severity of treated patient ADHD symptoms on a 10 point scale where 1 indicated no ADHD symptoms and 10 indicated significant ADHD symptoms, respondents reported an average score of 5.45 (Fig. 1). Symptoms of ADHD were regarded as most severe during the Early Morning Routine (6.45) and Evening Homework (6.46) times of day. The average level of overall functional impairment caused by ADHD symptoms during the Early Morning Routine time of day was rated by respondents as 6.09 on a 10 point scale, where 1 indicated mild impairment and 10 indicated severe impairment (Fig. 2). More specifically, 59.7% (120/201) of caregivers reported overall ADHD symptoms throughout the day as moderate to severe (ADHD symptom score 5–10) and concordantly, 75.6% (152/201) of parents reported impairment of EMF as moderate to severe (Early Morning Impairment of Functioning score 5–10).

Almost three quarters of respondents reported that easy distractibility (74.1%, 149/201) and failure to listen (72.6%, 146/201)

TABLE 2. CHILD/ADOLESCENT PATIENT DEMOGRAPHIC INFORMATION

	n (%)
Gender	
Male	143/201 (71.1)
Female	58/201 (28.9)
Age	
6–12	120/201 (59.7)
13–17	81/120 (40.3)
ADHD subtype	
Hyperactive/impulsive	17/201 (8.5)
Inattentive	26/201 (12.9)
Combined	158/201 (78.6)
Primary ADHD medication	
Methylphenidate HCl, ER	61/201 (30.3)
Amphetamine, dextroamphetamine mixed salts, ER	51/201 (25.4)
Methylphenidate HCl, IR	25/201 (12.4)
Lisdexamfetamine dimesylate	25/201 (12.4)
Dexmethylphenidate HCl, IR, and ER	18/201 (9.0)
Amphetamine, dextroamphetamine mixed salts, IR	18/201 (9.0)
Methylphenidate transdermal	3/201 (1.5)
Supplemental ADHD medication	
Methylphenidate HCl, ER	14/201 (7.0)
Amphetamine, dextroamphetamine mixed salts, ER	13/201 (6.5)
Dexmethylphenidate HCl, IR, and ER	4/201 (2.0)
Lisdexamfetamine dimesylate	2/201 (1.0)
Amphetamine, dextroamphetamine mixed salts, IR	18/201 (9.0)
Methylphenidate HCl, IR	14/201 (7.0)
Guanfacine HCl, ER	7/201 (3.5)
Atomoxetine HCl	4/201 (2.0)
Methylphenidate transdermal	1/201 (0.5)
Other	4/201 (2.0)
None	120/201 (59.7)
Length of time taking primary ADHD medication	
3–6 months	25/201 (12.4)
6–12 months	62/201 (30.8)
1–2 years	52/201 (25.9)
>2 years	62/201 (30.8)
Number of times per day taking primary medication	
Once	135/201 (67.2)
Twice	49/201 (24.4)
Three or more	17/201 (8.5)
Time of day taking primary medication ($n=201$ responses with multiple times)	
Midnight–5 a.m.	10/309 (3.2)
6 a.m.	37/309 (12.0)
7 a.m.	103/309 (33.3)
8 a.m.	43/309 (13.9)
9 a.m.–noon	28/309 (9.1)
1–5 p.m.	37/309 (12.0)
6 p.m.–midnight	51/309 (16.5)
Time of day taking supplemental medication ($n=81$ responses with multiple times)	
Midnight–5 a.m.	8/111 (7.2)
6 a.m.	7/111 (6.3)
7 a.m.	24/111 (21.6)
8 a.m.	13/111 (11.7)
9 a.m.–noon	17/111 (15.3)
1–5 p.m.	16/111 (14.4)
6 p.m.–midnight	26/111 (23.4)
Days per week taking ADHD medication during the school year	
7	132/201 (65.7)
6	10/201 (5.0)
5	50/201 (24.9)
4	4/201 (2.0)
1–3	5/201 (2.5)
Frequency of routine follow-up with ADHD physician	
Less than once a year	11/201 (5.5)
Once a year	23/201 (11.4)
Twice a year	44/201 (21.9)
Three times a year	36/201 (17.9)
More than three times a year	87/201 (43.3)

ADHD, Attention-deficit/hyperactivity disorder; ER, extended-release; IR, immediate-release.

were the ADHD symptoms that appeared most frequently during Early Morning Routine time of day (Fig. 3). When asked about unwanted behaviors that appeared frequently during the Early Morning Routine time of day, roughly half of the respondents reported that being impulsive/acting without thinking (49.3%, 99/201) and failure to finish things (48.8%, 98/201) were the most frequent (Fig. 4). Respondents reported that they often felt overwhelmed and exhausted (40.8%, 82/201) as a result of patient ADHD symptoms during the Early Morning Routine time of day, and a higher percentage reported sometimes feeling constantly stressed (46.8%, 94/201), raising their voices more than they wanted to (43.8%, 88/201), feeling inadequate as a caregiver (43.8%, 88/201), and punishing his/her child/adolescent more and praising the child/adolescent less (43.8%, 88/201; Fig. 5). Approximately one third (34.3%, 69/201) of respondents reported that the challenges of the Early Morning Routine, associated with their child's/adolescent's inadequately controlled ADHD symptoms, had a somewhat negative effect on their relationship with the patient and 7.5% (15/201) stated that it had a very negative effect on their relationship with the patient. However, some parents stated that it had a very positive impact (10%, 20/201), somewhat positive impact (21.4%, 43/201), or no impact (26.9%, 54/201) on their overall relationship with the patient. When asked about their satisfaction with their child's/adolescent's current ADHD medication in providing meaningful symptom relief during the Early Morning

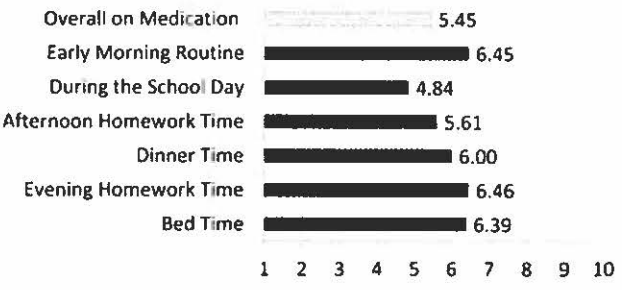

FIG. 1. Attention-deficit/hyperactivity disorder (ADHD) symptom severity, overall and times of day, using a scale of 1–10 where 1 means no ADHD symptoms and 10 means significant ADHD symptoms.

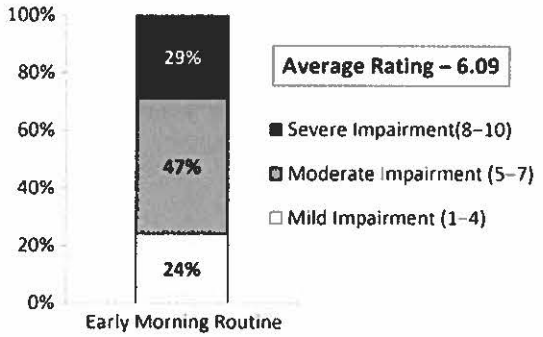

FIG. 2. Overall impairment of functioning from attention-deficit/hyperactivity disorder symptoms during the Early Morning Routine, using a scale of 1–10 where 1 means "Mild Impairment" and 10 means "Severe Impairment." The average rating of impairment was 6.09.

Routine time of day, most (38.8%, 78/201) reported that they were only somewhat satisfied, 10.9% (22/201) were not very satisfied, 3.0% (6/201) were not at all satisfied, 35.8% (72/201) were very satisfied, and 11.4% (23/201) were extremely satisfied. A majority of respondents (79.1%, 159/201) reported discussing patient EMF impairments with the patient's physician, and almost half (48.3%, 97/201) reported that they had previously woken up early in order to administer ADHD medication to their child/adolescent in an attempt to help mitigate early morning ADHD symptoms.

Discussion

The temporal occurrence of inadequately controlled ADHD symptoms, specifically during the Early Morning Routine, has only recently received attention in clinical trials involving stimulant medications. Inadequately controlled early morning ADHD symptoms in stimulant-treated children and adolescents can be attributed to the delayed onset of clinically meaningful symptom control afforded by oral stimulant medications that are dosed subsequent to awakening.

To our knowledge, this is the first quantitative research survey directly assessing parent/caregiver perceptions of: 1) The relative prevalence and severity of inadequately controlled early morning ADHD symptoms, 2) their impact on early morning behaviors and EMF, and 3) their apparent emotional impact on the parent and 4)

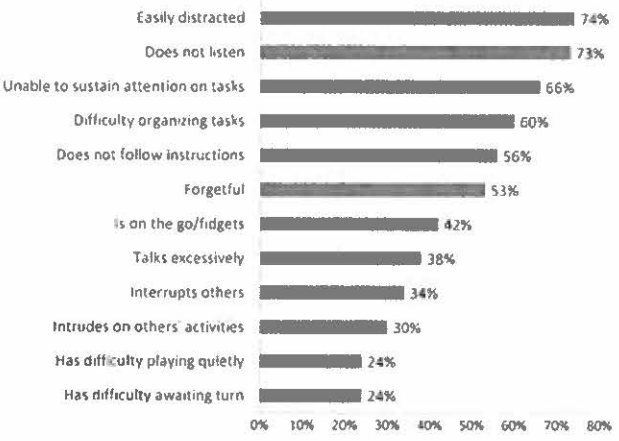

FIG. 3. Attention-deficit/hyperactivity disorder symptoms appearing frequently during the Early Morning Routine.

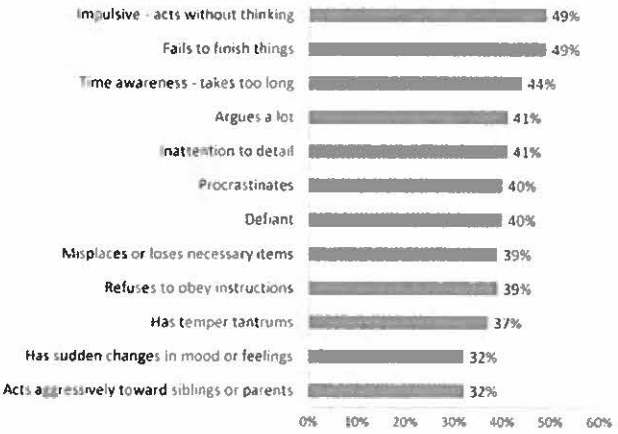

FIG. 4. Unwanted behaviors appearing frequently during the Early Morning Routine.

on the parent–child relationship. As such, this research survey produced several important quantitative findings. First, survey data indicated that caregivers regarded the Early Morning Routine as a period frequently associated with moderate to severe ADHD-symptom-related functional impairments in children and adolescents with ADHD, despite morning administration of stable doses of stimulant medications. Second, caregivers reported a host of negative emotional feelings as a result of their child's inadequately controlled early morning ADHD symptoms. Third, approximately one third of caregivers reported that their child's ADHD symptom-related functional impairments during the Early Morning Routine contributed to a somewhat negative relationship with their child. Interestingly, caregivers overwhelmingly acknowledged that they had discussed EMF impairments with the child or adolescent's treating physician, and more than half expressed room for improvement regarding satisfaction with the current medication regimen during this time of day.

Limitations

The current study had several limitations. Survey instruments such as the one developed for the current study may lack some of the specificity of formally validated ADHD assessment tools used to assess symptom severity and functional impact. Furthermore, the surveys were completed through the anonymity of the Internet, were not subject to immediate assessment, and could not offer the opportunity for clarification provided by questionnaires administered during one-on-one research interviews. Survey data are collected in real world circumstances and unlike clinical trials, cannot be fully controlled. The study also did not include an untreated ADHD control group to serve as a comparator, which could have provided some additional insight regarding EMF impairments in children and adolescents with ADHD who were not treated with stimulant medications. It should be noted, however, that parental/primary caregiver surveys can be an important tool for evaluating the impact of EMF impairments on children and adolescents with ADHD and their caregivers in "real-world" settings, and that such information is difficult to obtain from clinical trials. Additionally, the detailed survey data reported in this study represent an important addition to the sparse clinical literature regarding EMF impairments in children and adolescents with ADHD treated with a stimulant medication, as well as the potential impact of impaired EMF on the parent–child relationship.

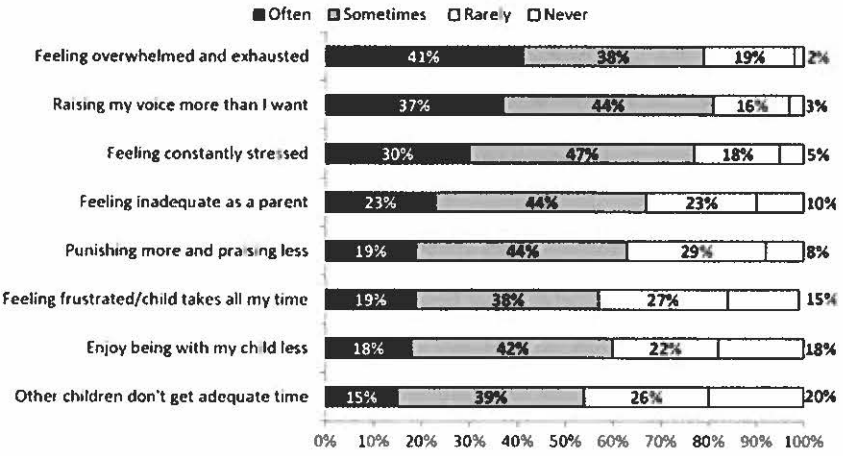

FIG. 5. Caregiver reactions to attention-deficit/hyperactivity disorder symptoms during the Early Morning Routine.

Conclusions

The issue of ADHD symptom control in the early morning time period is a meaningful issue to parents and caregivers, as almost half (48.3%) of caregivers indicated they had woken up early to administer their child's ADHD medication, and 79.1% of caregivers had previously discussed their child's early morning functional impairments with their doctor. The results from this quantitative research survey study strongly suggest that despite early morning administration of stable doses of existing formulations of stimulant medications, parents/primary caregivers of children and adolescents with ADHD report a high prevalence of inadequately controlled, early morning ADHD symptoms, and the severity of these early morning symptoms and related functional impairments are moderate to severe for a majority of their children. Importantly, they also noted that oftentimes their relationship with their child or adolescent with ADHD was negatively affected by these inadequately managed ADHD symptoms. These results further suggest that pharmacologic management of EMF impairments caused by ADHD symptoms remains a significant unmet need in children and adolescents with ADHD following the morning administration of stimulant medications. Finally, formulation research to explore development of additional stimulant-based treatment options for children and adolescents with ADHD should most likely include a focus on drug delivery mechanisms designed to provide clinically meaningful control of early morning ADHD symptoms and commensurate improvements in overall functioning during the early morning routines of school-age children. Finally, we concur with the observations of Faraone et al. (2015) that, given the clinical and practical impact of ADHD on morning symptoms and functioning, a scale specifically developed and validated to measure morning behaviors impaired by the symptoms of ADHD should be used in future trials of ADHD medications for youth.

Clinical Significance

Despite improvements in drug delivery systems for ADHD medications, EMF remains an issue in many children and adolescents with ADHD (Whalen et al. 2006). Current stimulant formulations cannot offer meaningful control of ADHD symptoms for at least 1 hour following oral ingestion (Swanson et al. 2003). This study confirms that the early morning routine continues to be a problematic time of the day for children and adolescents with ADHD treated with stimulant medication and their families.

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Disclosures

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Original Research

Early Morning Functional Impairments in Stimulant-Treated Children with Attention-Deficit/Hyperactivity Disorder Versus Controls: Impact on the Family

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Abstract

Objective: Children with attention-deficit/hyperactivity disorder (ADHD) frequently manifest early morning functional (EMF) impairments before school. We conducted a quantitative research survey to assess the impact of these EMF impairments on the family unit (caregiver, spouse/partner, and siblings).

Study Design: We developed an online survey questionnaire to collect data from 300 primary caregivers of children with ADHD and 50 primary caregivers of children who did not have ADHD.

Results: Although the ADHD children we surveyed were currently treated with stable doses of stimulants as their primary ADHD medication for at least 3 months, their parents reported high levels of EMF impairments in the child, which had a substantial negative effect on the emotional well-being of parents, on parents' functioning during the early morning routine, and on the level of conflict with siblings. The impact of EMF impairments on family functioning was mediated by the severity of the index child's impairments.

Conclusions: EMF impairments exert a pervasive and significantly negative emotional and functional burden on not only the primary caregiver but also on the spouse/partner and siblings. This work suggests that adequate ADHD symptom control during the early morning period may be an unmet need for school-age children with ADHD being treated with stimulants. More work is needed to confirm this finding and determine the degree to which symptom control at other times of day is also an unmet need.

Keywords: ADHD, morning, family, siblings, parents, functioning

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a common, persistent, and impairing psychiatric disorder affecting many children aged 3–17 years worldwide (Faraone et al. 2015a). Although much is known about how ADHD impacts patients and their families (Faraone et al. 2015a), little is known about the effects of ADHD during particular times of the day, especially on early morning functioning (EMF).

The EMF of children with ADHD, especially on school days, deserves special attention for several reasons. Between waking and arriving at school, children must appropriately sequence and complete a series of complex behaviors (e.g., dressing, eating, self-hygiene/brushing teeth, and gathering school books) in the context of other family members who may also be engaged in the same or similar goal-directed activities. Completing these behaviors requires time management, working memory, and self-regulation skills as well as social skills and cooperation that are frequently impaired by ADHD symptoms (Whalen et al. 2006). When children fail to efficiently complete their morning routine, it puts them at risk for being late to school and forgetting to take homework and other materials to school. These issues may lead to academic and social difficulties.

Inadequate control of ADHD symptoms during the early morning routine before school can also be significantly disruptive

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to siblings and parents who must also be prepared and depart the home for their own scheduled activities in a timely manner.

A study by Barkley and Cunningham (1979) showed that ADHD impaired early morning organization, self-care, preparation for the school day, and transportation to school. Whalen et al. (2006) showed that children's ADHD symptoms led to less effective parenting behaviors, especially before school. Sallee (2015) surveyed 201 primary caregivers of youth with ADHD treated with stable doses of stimulant medication. Despite being maintained on stimulant medications, 75% of the caregivers rated their child's early morning routine before school as a period associated with moderate-to-severe symptoms of the disorder and related functional impairments. Many caregivers also experienced negative emotions related to their child's early morning impairments. The caregivers experienced stress while getting their child ready for school as well. About half said that these symptoms and impairments were harmful to the parent–child relationship. The authors concluded that early morning ADHD symptoms and EMF impairments were inadequately controlled for many youth with ADHD treated with stable morning doses of stimulant medications.

Given that EMF impairments may produce downstream adverse impacts on the entire day for the affected child as well as other family members, several studies assessed the efficacy of ADHD treatments for EMF impairments. Two placebo-controlled clinical trials assessed EMF impairments using the Before-School Functioning Questionnaire (BSFQ), which has documented reliability, internal homogeneity, and concurrent validity (Faraone et al. 2015b). Wilens et al. (2013) randomized ADHD youth to receive either continued stimulant treatment plus guanfacine extended release (GXR) in the morning (GXR AM) or evening (GXR PM), or continued stimulant treatment plus placebo. Parent-rated BSFQ scores indicated that EMF impairments improved with both GXR AM and PM. A crossover study of ADHD youth compared the methylphenidate transdermal system (MTS) with a placebo transdermal system (PTS) (Wilens et al. 2010). Compared to the PTS, MTS significantly reduced the investigator-rated BSFQ total score, but not the child self-rated BSFQ total score. The Daily Parent Rating of Evening and Morning Behavior (DPREMB) (Faraone et al. 2015a) was used by Michelson et al. (2002) in a double-blind study of atomoxetine treatment. Atomoxetine was not better than placebo for improving four early morning behaviors reported by parents. In contrast, two studies using a revised version of the same scale (DPREMB-R) reported greater improvements in EMF for atomoxetine versus placebo in randomized controlled clinical trials (Sutton et al. 2003; Kelsey et al. 2004), and two trials showed that, compared with stimulant treatment, atomoxetine was more effective for treating EMF impairments (Sangal et al. 2006; Whalen, et al. 2010).

The few data available on EMF and ADHD suggest that it is a considerable source of impairment for children with ADHD as well as stress within their families, and current pharmacotherapies show variable efficacy. However, no prior study has assessed EMF impairments and its effects on both the stimulant-treated child with ADHD and their family using a controlled study. Such a study of stimulant-treated children is needed to determine if EMF impairments are an unmet need for the pharmacotherapy of ADHD. We did not include children treated with nonstimulants due to cost considerations and the fact that only a small minority of ADHD youth are treated with nonstimulants as their primary ADHD medication.

To fill this gap in the literature, we conducted a survey of primary caregivers of children with and without ADHD. We had several goals: (1) to assess the nature and severity of EMF impairments associated with stimulant-treated ADHD and (2) to assess the prevalence, frequency, and impact of EMF impairments on the caregiver, spouse/partner, and siblings of stimulant-treated ADHD children and adolescents. We hypothesized that compared with families not having children with ADHD, those having children with ADHD, who expressed at least mild ADHD symptoms in the morning, would, despite being treated with stimulants, show higher levels of EMF impairments and these impairments would have deleterious effects on the family. We also tested the hypothesis that the impact on the family would be mediated by the severity of the EMF impairments.

Methods

Survey participants were 300 caregivers of children diagnosed with ADHD and 50 caregivers of children not diagnosed with ADHD. Potential survey participants were drawn from the Lightspeed GMI US Panel ($N = 1,269,000$). The Lightspeed GMI panel is constructed so that its consented panel members are generally representative of the U.S. population in terms of age, gender, income, ethnicity, geography, employment, and educational levels in the household (see Appendix). GMI collects a wide range of valuable consumer information about habits, characteristics, behaviors, and medical conditions that aid in survey targeting. To improve survey productivity, our panel sample for parents of ADHD children was initially drawn from the subset of GMI US panel members who had previously identified that they had a child with ADHD aged 6–17 years (targeted sample, $n = 17,130$). Once that subset was exhausted, survey invitations were sent to the subset of GMI US panelists with children aged 6–17 years ($n = 253,800$). Lightspeed GMI also provided the survey programming and online hosting for the project.

As an incentive for participation, those who completed the survey were awarded points as participation incentives. The number of points awarded is based on a proprietary formula that factors in survey length and difficulty of recruiting. A longer survey has a higher point value incentive than a shorter one. A survey with a difficult-to-recruit audience awards more points than an easier-to-recruit survey. After accumulating points, members are able to redeem them for items within Lightspeed GMI's rewards catalog. Examples of items panel members can redeem points for include the following: PayPal and Amazon e-certificates, gift cards, vouchers, cash, electronics, and home and personal care products.

Inclusion in the ADHD group required four criteria: (1) being self-identified as the primary caregiver of an ADHD child aged 6 to 17 years; (2) the child with ADHD was taking stimulant medication as his or her primary ADHD medication; (3) he or she was taking a stable dose of their primary stimulant medication for 3 months or more; and (4) the caregiver rated that the severity of the child's ADHD symptoms throughout the entire day and during the early morning routine, as two or more on a scale of 1 (no symptoms) to 10 (significant symptoms). We selected ADHD children showing at least mild evidence of ADHD in the morning because our goal was to determine if the expression of ADHD symptoms in the morning was associated with impairments in stimulant-treated children.

The study was conducted in April of 2016. Caregiver respondents were blinded as to the research sponsor. The survey was conducted in accordance with and adherence to the Marketing Research Association Code of Standards. Potential respondents were invited to participate through an email message. The survey invitation did not specifically refer to ADHD or/and EMF; so it did

not bias participation toward families struggling with this domain of problems. The exact wording of the invitation was, "Today we are conducting a marketing research study concerning healthcare for your family. Your opinions are important to us. Please continue with the survey." The survey, which was administered as an online questionnaire, required about 20 minutes for completion. It did not contain any option for any of the 18 standard types of PHI data to be collected and thus did not require IRB approval. Surveys were completed voluntarily and anonymously.

For the ADHD families, if there was more than one child with ADHD in the household, respondents were instructed to select the ADHD child who had the most severe ADHD symptoms. For the non-ADHD sample, respondents were instructed to select the child whose birthday was next. We refer to these selected children as the "index" children. The questions asked to caregivers of ADHD and non-ADHD youth were slightly different. For example, regarding concerns for safety, the former were asked the following question: "How often do your child's inadequately controlled ADHD symptoms during the early morning routine (before school) cause you concern for their safety and well-being in the home?" and the latter were asked the following question: "How often does your child's behavior during the early morning routine (before school) cause you concern for their safety and well-being in the home?"

We compared ADHD and non-ADHD families using logistic regression with ADHD status as the outcome and the demographic and family impact measures as independent variables. We first tested for demographic differences and included significant demographic predictors as covariates in all models. Because the family impact measures are conceptual outcomes, a more standard approach would have been to use these outcomes as dependent variables. However, doing so creates analytic problems due to the extreme nonnormality of the data and the strong assumptions we would need to analyze ordinal data. Logistic regression requires minimal assumptions and provides a valid method of establishing the statistical significance of the association.

To test the hypothesis that the impact on the families of ADHD youth was mediated by the severity of the EMF impairments, we included the severity of EMF impairments in the index child as a covariate in models testing for the association of ADHD family status and family impact. Our measure of severity was the answer to the following question: "On a scale from 1 to 10, where 1 means "Mildly Impaired" and 10 means "Very Severely Impaired", how severe is that child's functional impairment (or difficulty to function) during the early morning routine?."

Results

The families with and without ADHD children did not differ in age of the index child (11.6 vs. 11.9; $z=0.5$, $p=0.6$), or relationship of the caregiver to the child ($X^2[3]=1.6$, $p=0.7$). The index children in the ADHD group were more likely to be male (68% vs. 44%; $z=3.2$, $p=0.001$). Thus, all the following analyses are statistically corrected for sex of the index child. Forty-six percent of the ADHD youth were taking an amphetamine formulation and 54% were taking a methylphenidate formulation. Twenty-seven percent had been taking their medication for 3 to 6 months; 21% for 6 months to a year; 21% for one to 2 years; and 31% for more than 2 years.

EMF impairments among ADHD children

Overall, 77% of caregivers rated the severity of EMF impairment in their child with ADHD as moderate-to-severe (severity rating of 5–10 on a 10-point severity scale). On the same severity scale from 1 to 10, where 1 means "Mildly Impaired" and 10 means "Very Severely Impaired," ADHD children were rated as having higher mean levels of EMF impairment compared with controls (6.2 vs. 1.5; $z=6.7$, $p<0.001$). This shows that ADHD children who express some ADHD symptoms in the morning are at risk for EMF impairments. Consistent with this, the median number of school days each week that the child had EMF impairments was greater for youth with ADHD (4 days per week vs. 1 day per week; $z=5.8$, $p<0.001$).

We asked parents about 10 maladaptive behaviors occurring during the EMF period. Seven of these impairments were significantly more common among youth with ADHD compared with those without ADHD, and only 2% of youth with ADHD demonstrated none of these frequent maladaptive behaviors compared with 52% of non-ADHD youth (Fig. 1). Seventy-eight percent of the parents of ADHD youth had discussed the issue of EMF impairments with their doctor.

We asked the parents of the children with ADHD if they, or another adult in the household, ever woke their child with ADHD up earlier than their normal waking time to administer ADHD medication and then let them go back to sleep, so that the medication could provide more effective ADHD symptom control in the early morning. Fifty-seven percent indicated that they had used this strategy a median of 4 days per week during the school year. Seventy-eight percent of those who used this strategy indicated that its impact was either very positive or somewhat positive.

Impact of EMF impairments on parents and siblings

As shown in Figure 2, the child's EMF impairments had a substantial and statistically significant negative impact on the emotional well-being of the caregivers of youth with ADHD. In response to EMF impairments, the caregivers of youth with ADHD were significantly more likely than caregivers of non-ADHD youth to report raising their voice more often, and feeling overwhelmed and exhausted, constantly stressed, inadequate as a parent, frustrated their child with ADHD consumed all their time, and guilty they were neglecting their other children.

Compared with caregivers of youth without ADHD, the caregivers of youth having ADHD were more likely to report that EMF impairments led to more stress from sibling conflict, greater disruption of the child's breakfast, greater disruption of the caregiver's morning routine, and a greater likelihood of being late for their own morning activities (all p's <0.001). We found similar results when assessing the effects of the child's EMF impairments on the spouses/partners of the caregivers. During the early morning period, the caregivers of youth with ADHD reported significantly more conflict with their spouses/partners, more disruption of their spouse's/partner's early morning routine, and that the child's EMF impairments kept the spouses/partners from being on time (all p's <0.01).

Parents were asked how often EMF impairments caused them concern for the index child's safety and well-being inside and outside the home. The same question was also asked if such ADHD-related EMF of the index child also affected the safety and well-being of the siblings. As Figure 3 shows, concerns about index child and sibling safety were significantly and substantially higher among the parents of children with ADHD (all p's <0.001).

We also assessed the impact of the index child's EMF on the morning routines of their siblings. Compared with the parents not having an ADHD child, those with an ADHD child were more

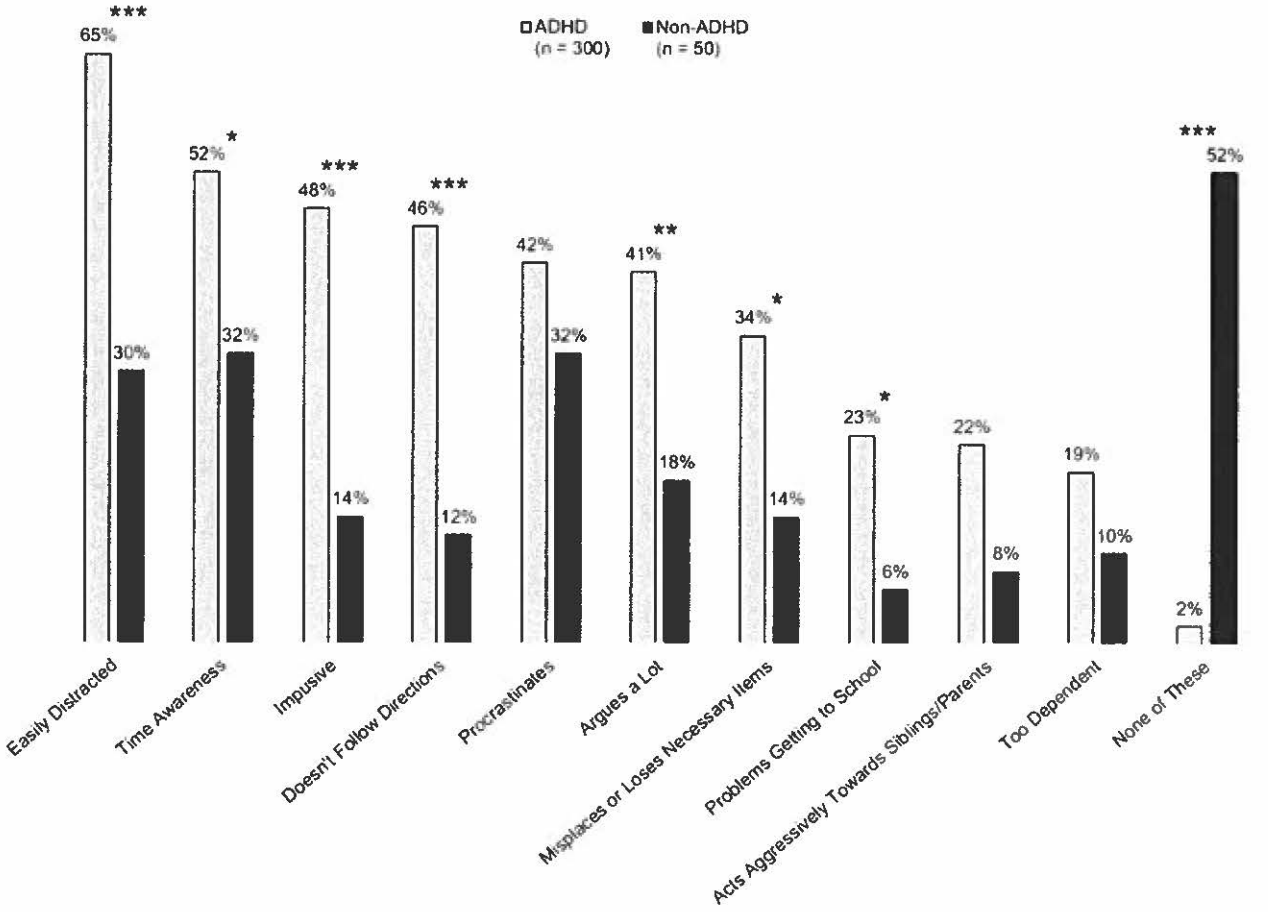

FIG. 1. ADHD child's maladaptive behaviors and EMF impairments occurring "frequently." Caregivers were given a list of EMF behaviors and asked to indicate which ones occurred "frequently." $^{*}p<0.05$, $^{**}p<0.01$, and $^{***}p<0.001$ vs. non-ADHD. ADHD, attention-deficit/hyperactivity disorder; EMF, early morning functioning.

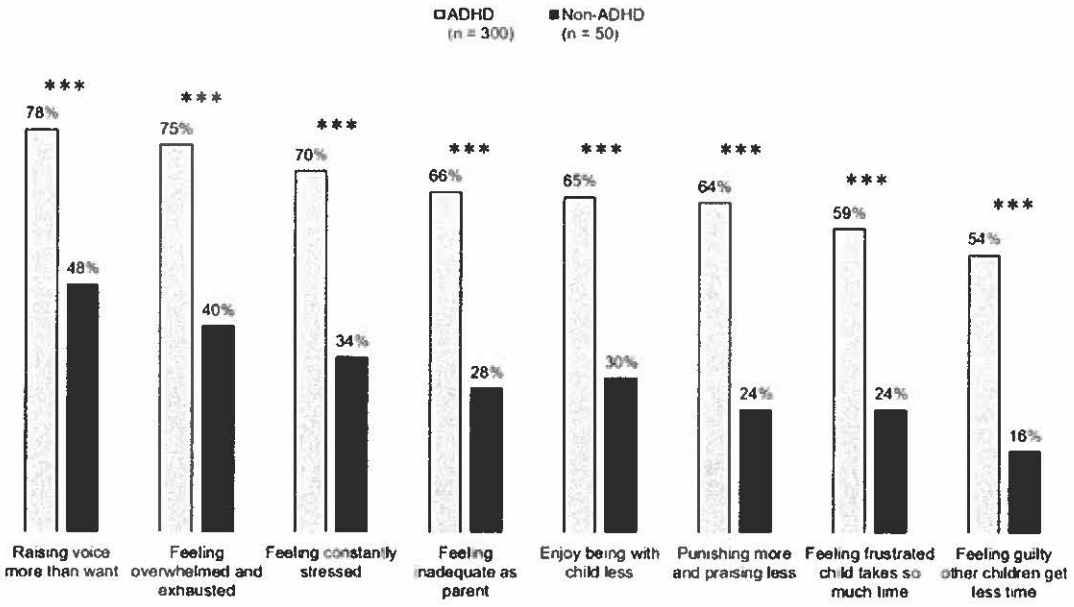

FIG. 2. Parent feelings toward their child's impaired EMF occurring "sometimes" or "often." Caregivers rated behaviors on a four-point scale: "never occurs," "rarely occurs," "sometimes occurs," and "often occurs." $^{***}p<0.001$ vs. non-ADHD. ADHD, attention-deficit/hyperactivity disorder; EMF, early morning functioning.

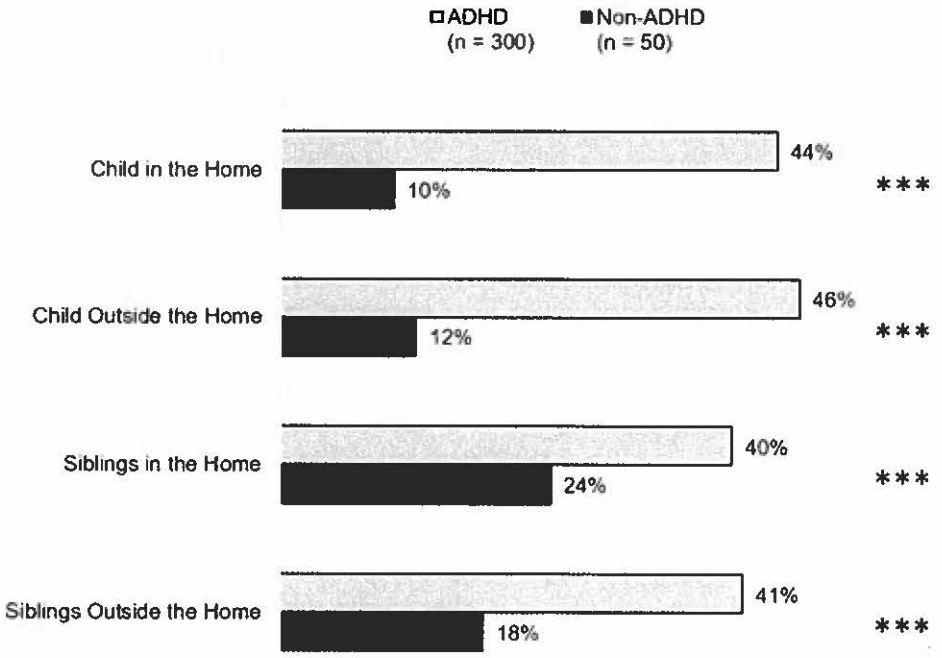

FIG. 3. Parent concern about their child's/sibling's safety occurring "often" or "very often." Caregivers rated behaviors on a five-point scale: "never," "rarely," "sometimes," "often," and "very often." ***$p<0.001$ vs. non-ADHD. Note: 258 ADHD families had siblings and 34 non-ADHD families had siblings. ADHD, attention-deficit/hyperactivity disorder.

likely to report significant or very significant disruptions of the siblings' morning routines (42% vs. 18%, $p<0.001$), disruptions causing siblings to be late ($p<0.001$), disruption of the family breakfast ($p<0.001$), and conflict with siblings ($p<0.05$). Fifty-two percent of parents with ADHD children reported that sibling complaints about the index child's EMF impairments or disruption of the sibling's morning routine occurred often or very often compared with 18% of control families ($p<0.001$).

Mediation of impact on family by severity of EMF impairments in the child

We added the severity of the EMF impairments in the index child as a covariate in all the models testing for the association of ADHD family status and family impact. For all these models except one, the association between ADHD family status and impact on the family lost significance when EMF impairment was a covariate (all p's >0.05). The exception was the model testing for the impact on parental stress due to conflicts among siblings in the early morning ($p=0.04$). To determine if the severity of EMF impairments associated with ADHD was predictive of impact on the family, we conducted regression analyses limited to the ADHD families that predicted the family impact variables from the severity of the ADHD child's EMF impairments. We found significant correlations between the EMF impairment severity of the ADHD child and all the family impact variables (all p's <0.001; correlations ranging from 0.44 to 0.68).

Discussion

Although the ADHD children we surveyed had been treated with stimulant medications as their primary ADHD medication for at least 3 months, they still had elevated levels of EMF impairments compared with controls. This shows that ADHD children who express some ADHD symptoms in the morning are at risk for EMF impairments. These impairments diminished the emotional well-being of parents, interfered with the parental early morning routine, and increased the level of conflict among siblings and between caregiver and their spouse/partner. These findings confirm the survey findings reported by Sallee (2015), who also studied stimulant-treated youth with ADHD.

The impact of EMF impairments on the family was substantial. The parents in ADHD families were highly likely to report feeling adverse emotions, more conflict with spouses/partners, and greater disruption of the parental morning routine. The EMF impairments of ADHD children were also associated with higher levels of conflict with siblings and disruption of their morning routines. These findings are consistent with prior work indicating that families of patients with ADHD experience elevated levels of distress that impact family functioning (Whalen et al. 2006). Of particular concern, almost half of the parents of youth with ADHD expressed concern about the safety of their child and that of their other children due to the EMF impairments related to the child with ADHD. This finding is especially notable for clinicians given that children with ADHD are at significantly higher risk for a variety of types of accidents (Swensen et al. 2004) and the injury rates from accidents are reduced by medication treatment (Dalsgaard et al. 2015).

Consistent with our hypothesis, mediation analyses showed that the differences in family functioning between the families with and without ADHD were mediated (or could be accounted for) by the severity of EMF impairments in the index child. This finding, to some extent, reflects that nature of the questions about family impact, which asked about the effect of EMF impairments on family functioning (see Supplementary Data; Supplementary Data are available online at www.liebertpub.com/cap). Thus, the mediation analyses confirm that parents were responding as requested, that is,

they were reporting problems in the family caused by the EMF impairments of the index child. These findings show that the adverse family functioning results were not simply due to the presence of ADHD in the child, but were, in fact, associated with the index child's EMF impairments. As further support for this idea, within the ADHD families, we found significant correlations between the EMF impairment severity of the ADHD child and all the family impact variables.

Our conclusions are tempered by several methodological limitations. We used an online survey to collect data rather than in person, structured interviews. The use of the former may have decreased the sensitivity of our assessments. It is, however, unlikely that the use of online methodology would have created spurious findings. Our survey had not previously been tested for either reliability or validity. Low reliability and validity would have added noise to the analyses and made it difficult to find statistical significance. Thus, negative findings should be interpreted with caution. In contrast, low reliability and validity would not explain the pattern of significant differences we found across many measures. Our design does not allow us to conclude if EMF impairments were due to delayed onset of stimulant effects or to underdosing or overall partial response.

We did not confirm the parental reports of their children's ADHD diagnoses and only collected EMF data from one parent. That means that some findings could be accounted for by method variance, that is, the parents may not have been able to discriminate EMF problems from global impairment and safety concerns. Without behavioral data or multiple respondents, we cannot with certainty separate child dysfunction from parental concern. Thus, using multiple respondents would have been ideal. Despite these concerns, single respondent surveys have a strong precedent for survey research, for example, it has been used by the Center for Disease Control (Visser et al. 2014). Moreover, using one parent to provide information about the psychiatric and functional status of children has a strong precedent in prior literature.

Because we only recruited families having children with ADHD who were stimulant treated, our findings may not generalize to families that have children with ADHD who are untreated or who are treated through other modalities. Like other surveys, our data are restricted to parent retrospective reports, not observations of actual behaviors. To most accurately assess the effects of ADHD on EMF impairments, the best design would be to include behavioral samples at early morning and at other times of the day and to evaluate whether our findings are specific to EMF or are, perhaps, simply a reflection of functional impairments throughout the day. Although the panel from which respondents were selected was representative of the U.S. population, given the low response rate, it is possible that our sample is biased in unknown ways. Thus, we cannot be sure to which populations our results will generalize. Our population cannot be biased, however, with regard to EMF because the email used to recruit respondents did not indicate a specific interest in ADHD children and adolescents with "problems in the morning" or "EMF Impairment" (or similar wording). Further evidence for lack of bias regarding EMF impairment is the fact that our 77% rate of caregiver-reported moderate-to-severe EMF impairment severity is similar to the rate of 76% reported by Sallee (2015).

Conclusions

Within the constraints of these limitations, our findings show that the primary caregivers of stimulant-treated children and adolescents with ADHD report that inadequately controlled early morning ADHD symptoms and EMF impairments persist despite treatment. EMF impairments exert a pervasive and significantly negative emotional and functional burden, not only on the primary caregiver but also on the spouse/partner and siblings. This work, especially when considered in the context of similar findings by Sallee (2015), suggests that adequate ADHD symptom control during the early morning period may be an unmet need for school-age children with ADHD being treated with stimulant medications. More work is needed to confirm this finding, and to determine the degree to which symptom control at other times of day is also an unmet need.

Clinical Significance

What are the clinical implications of the fact that stimulant-treated children show evidence of EMF impairments that impact their family? One approach is seen in the data presented. About half the parents indicated that they had woken up their child with ADHD earlier than normal to administer ADHD medication and then let them go back to sleep, so that the medication would provide control in the early morning. Most who used this strategy said it had a very positive or somewhat positive effect. Thus, this is an option clinicians could communicate to parents. The early morning routine also provides a well-defined target for behavioral family therapy or, for adolescents, cognitive behavior therapy. Using organizational charts and reinforcing clearly defined early morning behaviors could alleviate many of these problems. This suggests that psychosocial treatment programs should develop modules aimed at EMF impairments.

Disclosures

In the past year, S.V.F received consulting income, travel expenses, and/or research support from Ironshore, Arbor, Shire, Akili Interactive Labs, Alcobra, VAYA, and Neurovance and research support from the National Institutes of Health (NIH). His institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards, or participated in continuing medical education programs sponsored by Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. S.V.F receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health*, Oxford University Press: *Schizophrenia: The Facts*, and Elsevier: ADHD: *Non-Pharmacologic Interventions*. R.A.B. is currently a consultant to Ironshore Pharmaceutical & Development, Inc. He has previously been a paid consultant to and/or speaker for Eli Lilly Co., Shire, Janssen, Medici, and Novartis. He receives book, rating scale, newsletter, and/or video royalties from Guilford Press, Premier Educational Seminars, Inc., J & K Seminars, and the American Psychological Association press. He also receives royalties for online CE courses he has written or recorded for ContinuingEdCourses.net and PsychContinuingEd.com. R. J. S. is a member of the Scientific Advisory Board of Ironshore Pharmaceuticals & Development, Inc. ("Ironshore"), has received consulting income or equity from ehave and Purdue Pharma and funding from Canadian Institutes for Health Research, Ontario Mental Health Foundation, and Ontario Brain Institute. His institution holds the rights for cognitive rehabilitation software for ADHD. In the past, he received consulting fees or was on the Advisory Board, or participated in medical education programs sponsored by the North American and Canadian Scientific Advisory Board of Strattera (Lilly).

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(Appendices follow →)

Appendix

Lightspeed GMI US Panel Demographic Profile (N = 1,269,000)

The profile of Lightspeed GMI US Panel participants overall reflects the demographic makeup of the United States. Key panel profile characteristics are shown below.

	%
Gender	
Male	31
Female	69
Household income	
Less than $25K	37
$25K–$49.9K	26
$50K–$74.9K	16
$75K–$99K	10
$100K+	12
Age	
18–24	19
25–34	28
35–44	21
45–54	17
55+	15
Region	
Midwest	21
Northeast	15
South	43
West	21
Race/ethnicity	
White/Caucasian	62
Black/African American	17
Hispanic/Latino	12
Other	9
Employment status	
House wife/house husband	8
Permanent full-time employment	26
Permanent part-time employment	8
Unpaid employment (e.g., volunteer work)/ full-time care of family member	1
Retired	3
Self-employed/freelance	6
Student, in school or apprenticeship	6
Temporary, seasonal, or occasional work	2
Unable to work/disabled	5
Without work or currently not working, and looking for work	10
No answer	25
Education	
Grade school	1
Some high school	5
Graduated high school or GED	19
Some college—no degree	20
Graduated college—associate's degree	7
Graduated college—bachelor's degree	12
Postgraduate degree—MS, MA, MBA, MD, DVM, DDS, etc.	5
Technical school/vocational training	5
Doctorate—PhD	1
No answer	25

Uniform Formulary Beneficiary Advisory Panel (BAP)

Meeting Summary
September 25, 2019
Washington, D.C.

Present Panel Members

- Mr. Jon Ostrowski, Non Commissioned Officers Association, Chairperson
- Dr. Richard Bertin, Commissioned Officer Association (COA) of the United States Public Health Service, Inc.
- Ms. Theresa Buchanan, National Military Family Association
- Dr. Karen Dager, Health Net Federal Services
- Mr. John Du Teil, US Army Warrant Officers Association
- Mr. Charles Hostettler, AMSUS, The Society of Federal Health Professionals
- Dr. Jay Peloquin, Express Scripts, Inc.
- Dr. Lindsay Piirainen, USFHP Martin's Point Healthcare
- Dr. Michael Spatz, Humana
- Ms. Suzanne Walker, Military Officers Association of America

The meeting was held at Naval Heritage Center Theater, 701 Pennsylvania Ave., N.W., Washington D.C., and CAPT Edward Norton called the meeting to order at 9:00 A.M.

Agenda

- **Administrative Meeting (BAP members report no later than 8:30 AM)**
- **Sign-In**
- **Welcome and Opening Remarks**
- **Public Citizen Comments**
- **Therapeutic Class Reviews**

  Members of the DHA Pharmacy Operations Division (POD) Formulary Management Branch (FMB) will present relative clinical and cost-effective analyses along with the DoD Pharmacy & Therapeutics Committee (P&T) recommendations for the Uniform Formulary (UF) and any recommended Tier 4/Not Covered candidates.

  The P&T Committee made recommendations for the following drugs/drug classes during the August 2019 meeting:

- **Drug Class Reviews**

  - *High-Potency Topical Corticosteroids*
  - *Multiple Sclerosis: Interferons and Methyl Fumarate*

- **Newly Approved Drugs per 32 CFR 199.21(g)(5)**

  - *alpelisib (Piqray) – Oncological Agent for breast cancer*
  - *amifampridine (Ruzurgi) – Miscellaneous Neurological Agent for Lambert-Eaton myasthenic syndrome (LEMS)*
  - *amphetamine sulfate orally disintegrating IR tablet (Evekeo ODT) – Attention Deficit Hyperactivity Disorder (ADHD)*
  - *dolutegravir/lamivudine (Dovato) – Single-tablet regimen (STR) antiretroviral for Human Immunodeficiency Virus (HIV)*
  - *drospirenone (Slynd) – Progestogen-only contraceptive agent*
  - *erdafitinib (Balversa) – Oral Oncological Agent for urothelial cancer*
  - *galcanezumab-gnlm 100 mg injection (Emgality) – Migraine Agents: Calcitonin gene-related peptide (CGRP) inhibitors for cluster headache*
  - *halobetasol propionate 0.01%/tazarotene 0.045% (Duobrii) – Combination product for Plaque Psoriasis*
  - *immunoglobulin subcutaneous injection (Cutaquig) – Immunoglobulin for Immune Deficiency Disorders*
  - *mepolizumab injection (Nucala) – Miscellaneous Pulmonary I Agent for severe asthma and eosinophilic granulomatosis with polyangiitis (EGPA)*
  - *methylphenidate extended-release sprinkle capsules (Adhansia XR) – ADHD*
  - *methylphenidate extended-release sprinkle nighttime dosing capsules (Jornay PM) – ADHD*
  - *risankizumab-rzaa injection (Skyrizi) – Targeted Immunomodulatory Biologic (TIB) for Plaque Psoriasis*
  - *rosuvastatin sprinkle capsules (Ezallor Sprinkle) – Antilipidemics-I*
  - *solriamfetol (Sunosi) – Wakefulness Promoting Agent*
  - *tafamidis meglumine (Vyndaqel) – Miscellaneous Neurological Agents for cardiomyopathy associated with hereditary transthyretin-mediated amyloidosis (ATTR-CM)*
  - *triclabendazole (Egaten) – Antiinfectives: Anthelmintics for fascioliasis*

- **Utilization Management Issues**

  - ***Prior Authorization Criteria—New Criteria***

    - *Antibiotics: Tetracyclines – Doxycycline hyclate extended-release 80 mg – Oral tetracycline antibiotic for acne vulgaris or rosacea*
    - *Oral Oncologic Agents: alectinib (Alecensa), brigatinib (Alunbrig), ceritinib (Zykadia), and crizotinib (Xalkori)*

- *Vitamins: Prenatal – Prenatal multivitamin (Azesco)*
- *Cardiovascular Agents Miscellaneous: Droxidopa (Northera)*

➢ ***Prior Authorization Criteria—Updated Criteria***

- *Gastrointestinal-2 Agents: telotristat ethyl (Xermelo)*
- *Neurological Agents Miscellaneous: amifampridine (Firdapse)*
- *Parkinson's Agents: levodopa inhalation powder (Inbrija)*
- *ADHD – Wakefulness Promoting Agents: Wakefulness Promoting Agents: sodium oxybate (Xyrem)*
- *Corticosteroids – Immune Modulators: Atopic Dermatitis: dupilumab (Dupixent)*
- *Cystic Fibrosis Agents: tezacaftor/ivacaftor (Symdeko)*
- *Hematological agents: Platelets: avatrombopag (Doptelet)*
- *Immunosuppressives: belimumab (Benlysta)*
- *Oncological Agents: Acute Myelogenous Leukemia: ivosidenib (Tibsovo)*
- *Targeted Immunomodulatory Biologics (TIBs) – Non-Tumor Necrosis Factor (TNF) Inhibitors: apremilast (Otezla) and adalimumab (Humira)*
- *Weight Loss Agents: liraglutide 3 mg injection (Saxenda)*

➢ **Panel Discussions**

The Beneficiary Advisory Panel members will have the opportunity to ask questions to each of the presenters. Upon completion of the presentation and any questions, the Panel will discuss the recommendations and vote to accept or reject them. The Panel will provide comments on their vote as directed by the Panel Chairman.

Opening Remarks

CAPT Edward Norton introduced himself as the Alternate Designated Federal Officer (DFO) for the Uniform Formulary (UF) Beneficiary Advisory Panel (BAP). The Panel has convened to comment on the recommendations of the DoD Pharmacy and Therapeutics (P&T) Committee meeting, which occurred on August 7 – 8, 2019.

CAPT Norton indicated Title 10, United States, (U.S.C.) section 1074g, subsection b requires the Secretary of Defense to establish a DoD Uniform Formulary (UF) of the pharmaceutical agent and established the P&T committee to review the formulary on a periodic basis to make additional recommendations regarding the formulary as the committee determines necessary and appropriate.

In addition, 10 U.S.C. Section 1074g, subsection c, also requires the Secretary to establish a UF Beneficiary Advisory Panel (BAP) to review and comment on the development of the Uniform Formulary. The Panel includes members that represent non- governmental organizations and associations that represent the views and interests of a large number of eligible covered beneficiaries. The Panel's comments must be considered by the Director of the Defense Health Agency (DHA) before establishing the UF or implementing changes to the UF.

The Panel's meetings are conducted in accordance of the Federal Advisory Committee Act (FACA).

The duties of the Uniform Formulary Beneficiary Advisory Panel include the following:

- To review and comment on the recommendations of the P&T Committee concerning the establishment of the UF and subsequently recommending changes. Comments to the Director of the DHA regarding recommended formulary status, pre-authorizations and the effective dates for changing drugs from "formulary" to "non-formulary" status must be reviewed by the Director before making a final decision.

- To hold quarterly meetings in an open forum. The panel may not hold meetings except at the call or with the advance approval of the DFO and in consultation with the chairperson of the Panel.

- To prepare minutes of the proceedings and prepared comments of the Secretary or his designee regarding the Uniform Formulary or changes to the Formulary. The minutes will be available on the website, and comments will be prepared for the Director of DHA. As guidance to the Panel regarding this meeting, CAPT Norton said the role of the BAP is to comment on the UF recommendations made by the P&T Committee at their last meeting. While the department appreciates that the BAP may be interested in the drug class they selected for review, drugs recommended for the basic core formula (BCF) or specific pricing data, these items do not fall under the purview of the BAP.

- The P&T Committee met for approximately 16 hours conducting this review of the drug class recommendation presented today. Since this meeting is considerably shorter, the Panel will not receive the same extensive information as presented to the P&T Committee members. However, the BAP will receive an abbreviated version of each presentation and its discussion. The materials provided to the Panel are available on the TRICARE website. Detailed minutes of this meeting are being prepared. The BAP minutes, the DoD P&T Committee minutes, and the Director's decisions will be available on the TRICARE website in approximately four to six weeks.

The DFO provided ground rules for conducting the meeting:

- All discussions take place in an open public forum. There is to be no committee discussion outside the room, during breaks, or at lunch.

- Audience participation is limited to private citizens who signed up to address the Panel.

- Members of the Formulary Management Branch and P&T Committee are available to answer questions related to the BAP's deliberations. Should a misstatement be made, these individuals may interrupt to ensure the minutes accurately reflect relevant facts, regulations, or policy. When addressing the panel or responding to questions, please use the microphone.

CAPT Norton introduced the individual Panel members (see list above) and noted house-keeping considerations.

The public comments from Ironshore Pharmaceuticals were distributed to the Panel for consideration.

Chairman's Opening Remarks

Mr. Ostrowski welcomes all panel members and attendees. Dr. Spatz was thanked for attending the last 2 meetings and CAPT Norton congratulated on his forthcoming retirement.

DRUG CLASS REVIEW PRESENTATION

(POD Script – CDR HELLWIG)

GOOD MORNING. I am Commander Heather Hellwig, Chief of the Pharmacy and Therapeutics section of the DHA Pharmacy Operations Division. Joining me is doctor and Lieutenant Colonel Ronald Khoury, the Chief of the Formulary Management Branch of the DHA Pharmacy Operations Division, who will provide the physician perspective and comments on the recommendations made by the P&T Committee. Also joining us today is Commander Scott Raisor, a clinical pharmacist in the Formulary Management Branch. I would also like to recognize Mr. Bryan Wheeler, Deputy General Counsel.

The DoD Formulary Management Branch supports the DoD P&T Committee by conducting the relative clinical effectiveness analyses and relative cost-effectiveness analyses of the drugs and drug classes under review and consideration by the DoD P&T Committee for the Uniform Formulary (relative meaning in comparison to the other agents defined in the same class).

We are here to present an overview of the analyses presented to the P&T Committee. 32 Code of Federal Regulations (CFR) establishes procedures for inclusion or exclusion of pharmaceutical agents on the Uniform Formulary based upon both relative clinical effectiveness and relative cost-effectiveness.

The goal of this presentation is not to provide you with the same in-depth analyses presented to the DoD P&T Committee but a summary of the processes and analyses presented to the DoD P&T Committee. These include:

1) A brief overview of the relative clinical effectiveness analyses considered by the DoD P&T Committee. All reviews include but are not limited to the sources of information listed in 32 CFR 199.21 (e)(1) and (g)(5). All Tier 4/not covered candidates were reviewed in accordance with amended 32 CFR 199.21(e)(3) effective December 11, 2018. Also note that nonformulary medications are generally restricted to the mail order program according to amended section 199.21, revised paragraphs (h)(3)(i) and (ii), effective August 26, 2015.

2) A brief general overview of the relative cost-effectiveness analyses. This overview will be general in nature since we are unable to disclose the actual costs used in the economic models. This overview will include the factors used to evaluate the costs of the agents in relation to the safety, effectiveness, and clinical outcomes.

3) The DoD P&T Committee's Uniform Formulary recommendation is based upon the Committee's collective professional judgment when considering the analyses from both the relative clinical and relative cost-effectiveness evaluations.

   The Committee reviewed the following:

   a) The P&T Committee reviewed two Uniform Formulary Drug Classes:
      - the High-Potency Topical Corticosteroids class and
      - the Multiple Sclerosis – Interferons subclass and Methyl Fumarate subclass.

A summary table of the UF drug class recommendations and the numbers of affected utilizers are found on page 31 of the background document.

b) The P&T Committee also evaluated 17 newly approved drugs per 32 CFR 199.21(g)(5), which are currently in pending status and available under terms comparable to non-formulary drugs.

and

c) The Committee also discussed prior authorizations (PAs) in the utilization management section for **19** drugs in **14** drug classes.

- Antibiotics: Tetracyclines
- Oral Oncologic Agents
- Vitamins: Prenatal
- Cardiovascular Agents Miscellaneous
- Gastrointestinal-2 Agents
- Neurological Agents Miscellaneous
- Parkinson's Agents
- ADHD-Wakefulness Promoting Agents: Wakefulness Promoting Agents subclass
- Corticosteroids – Immune Modulators: Atopic Dermatitis subclass
- Cystic Fibrosis Agents
- Hematological Agents: Platelets subclass
- Immunosuppressives
- Targeted Immunomodulatory Biologics (TIBs)
- Weight Loss Agents

The DoD P&T Committee will make a recommendation as to the effective date of the agents being changed from the Uniform Formulary tier to the Nonformulary tier or Tier 4/Not Covered. Based on 32 CFR 199.21, such change will not be longer than 180 days from the final decision date but may be less.

I. UF CLASS REVIEWS—HIGH-POTENCY TOPICAL CORTICOSTEROIDS

CDR HELLWIG

P&T Comments

A. High-Potency Topical Corticosteroids

Background—The full Topical Corticosteroid class was previously reviewed in August 2013. The current review was limited to only the high-potency corticosteroids. The subclass is comprised of 9 parent drugs, amcinonide, fluocinonide, halcinonide, flurandrenolide, desoximetasone, betamethasone dipropionate, clobetasol propionate, halobetasol propionate, and diflorasone diacetate. These nine drugs are distributed across three Coopman structural classes (B, C, and D_1) and two Stoughton-Cornell potency groups (super high-potent and high-potent). Nine different potential vehicles are available: ointments, creams, lotions, solutions, foams, gels, sprays, shampoos, and tape. No one drug is available in all nine vehicles. Based on parent compound and vehicle, there are 39 total products in the subclass. Generic formulations are available for several of the products.

The clinical effectiveness review considered Coopman structural class, Stoughton-Cornell potency group, and vehicle, among other factors, when comparing the individual products, along with clinical effectiveness and safety.

The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) the following:

- There were no major changes to the previous conclusions from the 2013 review for the following:
- Issues of efficacy and safety within the Topical Corticosteroid class are considered class effects.
    - No particular agent within the same Stoughton-Cornell potency group and vehicle demonstrates a compelling advantage or disadvantage in either efficacy or safety compared to other agents in that same potency and vehicle group.
    - Topical corticosteroids within a potency group and vehicle are clinically interchangeable.
    - At least one product from each Coopman structural class is required on the formulary.
- Coopman Class C agents have the lowest cross-reactivity compared to products in the Coopman Class B and D_1 structural classes. Desoximetasone is the only Coopman C agent in the high-potency topical corticosteroid sub-class.
- Both super high-potent and high-potent agents are necessary on the formulary, as patients refractory to less potent (Stoughton-Cornell Group 2) agents may still respond to super-high potent (Stoughton-Cornell Group 1) agents. There are currently 21 super high-potent

and 18 high-potent products marketed, and there is no inherent additional clinical value to retaining all 39 products on the formulary.

- In addition to the parent structure and drug concentration, the type of vehicle also contributes to the potency classification of an individual topical corticosteroid. With regard to specific vehicle, the P&T Committee concluded the following:
  - Ointments and creams are individually unique vehicles and remain necessary options to include on the formulary. There are 9 ointments and 12 creams commercially available, and not all these products are required for MHS beneficiaries.
  - Lotions, solutions, foams, and gels have overlapping utility and are advantageous for treating the scalp and large body surface areas. Foams and solutions are the preferred vehicles for scalp use. Although hair-friendly products are necessary on the formulary, not all of the commercially available lotion, foams, and solutions are necessary for Military Health System (MHS) beneficiaries.
  - Sprays and tape have unique features, in that sprays offer patients the convenience of treating hard-to-reach body locations (e.g., the back) while the tape offers a physical barrier.
  - The primary advantage offered by gels, sprays, shampoos, and tape is patient convenience, and none are absolutely clinically necessary components of the benefit.
- With regard to efficacy, clinical trials conducted with the high-potency topical steroids are all of low quality. There is no robust phase III clinical trial evidence available. Clobetasol continues to be the high-potency topical corticosteroid with the largest amount of literature available.
- A comprehensive updated review of safety found no major differences from the conclusions reached in 2013, except for potential issues with inactive ingredients. Inactive ingredients, including propylene glycol, can cause allergic contact dermatitis. However, there are representative members within each Coopman class (B, C, and D_1) that do not contain propylene glycol.
- Professional treatment guidelines continue to support the use of high-potency topical corticosteroids across a wide array of dermatoses, with varying levels of evidence and recommendation strengths.
- Overall, the P&T Committee agreed that there were several candidates for Tier 4/not covered status, due to the clinical conclusions discussed above and the numerous representatives from each Coopman structural class, Stoughton-Cornell potency classification, and vehicle.

B. High-Potency Topical Corticosteroids—Relative Cost-Effectiveness Analysis and Conclusion

Cost-minimization analysis (CMA) and budget impact analysis (BIA) were performed to evaluate the High-Potency Topical Corticosteroids. For the cost analysis, branded high-

potency topical steroids without generic equivalents were evaluated in detail. The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) the following:

- CMA results for the subclass showed the following branded products were substantially less cost-effective than the remainder of the class: Bryhali lotion, Cordran tape, Impoyz cream, Ultravate lotion, and Lexette foam respectively.
- BIA was performed for the subclass to evaluate the potential impact of designating selected agents as formulary, NF, or Tier 4 on the UF. BIA results showed that the following designations demonstrated cost avoidance for the MHS:
  - Designating Ultravate cream & generic, Olux-E foam & generic, Cordran tape, and Topicort gel & generic as NF
  - Designating Impoyz cream, Apexicon-E cream & generic, Halog cream, Lexette foam & authorized generic, Clodan shampoo/cleanser kit, Bryhali lotion, Ultravate lotion, and Halog ointment as Tier 4

C. High-Potency Topical Corticosteroids—UF/Tier 4/Not Covered recommendation

The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent for all the members of the class, except for Cordran Tape: 14 for, 2 opposed, 0 abstained, 1 absent) the following formulary recommendations for the High-Potency Topical Corticosteroids as outlined below, based on clinical and cost-effectiveness.

When considering the High-Potency Topical Corticosteroid candidates for Tier 4/not covered status, the P&T Committee considered the information outlined in the interim rule, Section 702(b)(10) of the NDAA 2018 published on December 11, 2018, and found at: https://www.federalregister.gov/documents/2018/12/11/2018-26562/tricare-pharmacy-benefits-program-reforms. The interim rule allows for complete exclusion of drugs from TRICARE pharmacy benefit coverage when certain criteria are met. Tier 4 status will apply to all users of the recommended candidates.

- UF
  - betamethasone dipropionate 0.05% ointment
  - betamethasone/propylene glycol 0.05% ointment, cream, lotion, and gel
  - clobetasol propionate 0.05% ointment, cream, solution, lotion, shampoo, spray, gel, and foam
  - clobetasol propionate/emollient 0.05% cream
  - clobetasol propionate/emollient 0.05% emulsion foam
  - desoximetasone 0.25% ointment and cream
  - fluocinonide 0.05% ointment, cream, solution, and gel
  - fluocinonide/emollient base 0.05% cream
  - halobetasol propionate 0.05% ointment
  - *Note that all the agents recommended for UF status are currently on the formulary.*

- NF
  - amcinonide 0.1% ointment (Cyclocort, and generics)
  - clobetasol propionate/emollient 0.05% foam (Olux-E, generics) *(moves from UF to NF status)*
  - desoximetasone 0.05% gel (Topicort, generic) *(moves from UF to NF status)*
  - diflorasone diacetate 0.05% ointment (Psorcon, Apexicon, and generics)
  - diflorasone diacetate 0.05% cream (Psorcon, Apexicon, and generics
  - fluocinonide 0.1% cream (Vanos, and generics)
  - flurandrenolide 4 mcg/sq. cm tape (Cordran) *(moves from UF to NF status)*
  - halobetasol propionate 0.05% cream (Ultravate and generics *(moves from UF to NF status)*
- Tier 4/Not Covered
  - clobetasol propionate 0.025% cream (Impoyz)
  - clobetasol propionate 0.05% shampoo/cleanser (kit) (Clodan kit)
  - diflorasone diacetate/emollient 0.05% cream (Apexicon-E)
  - halcinonide 0.1% ointment (Halog)
  - halcinonide 0.1% cream (Halog)
  - halobetasol propionate 0.05% lotion (Ultravate)
  - halobetasol propionate 0.05% foam (Lexette & authorized) *(note that Lexette foam was previously recommended for Tier 4 status in February 2019, with implementation scheduled for August 28, 2019)*
  - halobetasol propionate 0.01% lotion (Bryhali)

  For all eight products recommended for Tier 4/Not Covered status, the P&T Committee concluded that Impoyz, Clodan kit, Apexicon-E, Halog ointment and cream, Ultravate, Lexette and authorized, and Bryhali provide very little to no additional clinical effectiveness relative to the other high-potency topical corticosteroids. Overall, the P&T Committee felt that that the needs of TRICARE beneficiaries can be met by the other high-potency topical steroids.

D. High-Potency Topical Corticosteroids—Manual Prior Authorization (PA) Criteria

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for amcinonide 0.1% and diflorasone diacetate 0.05% ointments, diflorasone diacetate 0.05% cream, clobetasol propionate/emollient 0.05% foam, desoximetasone 0.05% gel, and Cordran tape in all new and current users, due to the large number of clinically and cost-effective formulary alternatives available.

The PA criteria are as follows:

1. amcinonide 0.1% ointment and diflorasone diacetate 0.05% ointment

PA criteria apply to all new and current users of amcinonide 0.1% ointment and

diflorasone diacetate 0.05% ointment.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:
- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including clobetasol propionate 0.05% and fluocinonide 0.05% ointments. These agents do not require a PA.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to fluocinonide 0.05% AND desoximetasone 0.25% AND betamethasone dipropionate 0.05% ointments.
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

2. clobetasol propionate/emollient 0.05% foam

PA criteria apply to all new and current users of clobetasol propionate/emollient 0.05% foam.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:
- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including fluocinonide 0.05% solution and clobetasol propionate 0.05% solution. These agents do not require a PA.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to clobetasol propionate 0.05% solution, lotion, gel, AND foam
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

3. desoximetasone 0.05% gel

PA criteria apply to all new and current users of desoximetasone 0.05% gel.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:
- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including fluocinonide 0.05% solution and clobetasol propionate 0.05% solution. These agents do not require a PA.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to fluocinonide 0.05% solution AND gel
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

4. diflorasone diacetate 0.05% cream

PA criteria apply to all new and current users of diflorasone diacetate 0.05% cream.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:

- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including fluocinonide 0.05% and betamethasone/propylene glycol 0.05% creams. These agents do not require a PA.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to fluocinonide 0.05% AND betamethasone/propylene glycol (augmented) 0.05% AND desoximetasone 0.25% creams.
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

5. flurandrenolide 4 mcg/sq. cm (Cordran) tape

PA criteria apply to all new and current users of Cordran tape.

Manual PA Criteria: Coverage is approved if ALL of the following criteria are met:

- The prescription is written by a dermatologist or plastic surgeon
- The provider acknowledges that this agent has been identified as having cost-effective alternatives, including clobetasol propionate 0.05% ointment and fluocinonide 0.05% cream and solution. These agents do not require a PA.
- The provider acknowledges that barrier function can be accomplished by using an alternative agent (e.g., fluocinonide 0.05% cream) with an occlusive dressing. Please note occlusion increases transmission (i.e., potency); a lower potency agent should be used as an alternative to flurandrenolide tape if used with a barrier.
- The patient must have tried for at least 2 weeks and failed, have a contraindication to, or have had an adverse reaction to clobetasol propionate 0.05% ointment OR halobetasol propionate 0.05% ointment OR betamethasone dipropionate 0.05% ointment.
- The provider must describe why this agent is required as opposed to available alternatives.

PA expiration: 30 days
No PA renewals allowed; patients must fill out a new PA each time

E. High-Potency Topical Corticosteroids—UF/Tier 4/Not Covered and PA Implementation Plan

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) an effective date of 120 days from signing of the minutes in all points of service (POS), and that DHA send letters to beneficiaries who are affected by the Tier 4 decision and those affected by a change from UF to NF status.

F. Physician's Perspective

This subclass was reviewed due to the high degree of therapeutic interchangeability among products within the same potency sub-class and vehicle, and due to the large number of inexpensive generic products available.

Overall, 2/3 of the MHS utilization for the high potency steroids is for the cream and ointment formulations, and several of these formulations were recommended to stay on the Uniform formulary.

We did reach out to dermatologists for their input. Some of their comments were that having too many options can cause confusion and increase the risk of dosing errors; for example halobetasol is available in both a 0.05% and 0.01% formulation. Some of the providers mentioned that they only required clobetasol and fluocinonide on the formulary, (which are the two products with the highest utilization in the MHS), as long as there were different vehicles available. Others also commented that the number of products available on the formulary could be decreased, and recommended limiting the formulary to the most affordable agents.

For the formulary recommendation, determining what was needed was based on clinical reasons such as having a product from each Coopman class; including both super-high potent and high potent agents; and including a variety of vehicle formulations. The committee then assessed utilization patterns and cost,taking into account if large numbers of patients would be affected by a potential change from UF to NF. For the products recommended for UF status, they are all currently on the formulary, and represent 23 different products.

Out of the 8 products recommended for NF status, 4 are currently already designated NF. For the entire subclass, there were about 245,000 unique utilizers in the past year, and the formulary change from UF to NF for the 4 products that are currently UF will affect about 4,900 patients.

For the NF drugs, 6 products were recommended to have PAs, since there are several therapeutic alternatives which are cost effective. Although a "no grandfathering" scenario was recommended for all the PAs, it is very likely that by the time the PA is implemented, existing users would have completed their treatment course, due to the acute use of these products. Therefore the PA recommendations will are expected to effectively impact new users.

I wanted to make a few comments about Cordran tape.

- Cordran tape is currently on the UF, and in contrast to the other high potency steroids, the vast majority of the utilization is at the MTFs. It is intended for small areas that are difficult to treat, including fingertips, or to prevent the patient from scratching lesions. Cordran tape can be used for patients with keloid scars. There was a significant 1,600% price increase for the tape in 2017, and Cordran was considered for potential Tier 4/Not Covered status.

- A survey of our dermatology providers found that there were some mixed opinions on whether to move this product to Tier 4, but did recommend limiting use to dermatologists.

- The recommendation for Cordran tape was for NF status with a prior authorization. The two opposing votes for the Cordran formulary recommendation were because these P&T Committee members felt Tier 4 status was appropriate.

- The prior authorization is similar to the other topical steroid PAs, with the exception that Cordran tape must be prescribed by a dermatologist or plastic surgeon, and we do allow the provider to write in why the formulary alternatives are not acceptable, for example in the cases of patients with burns or keloids.

There are 8 products recommended for Tier 4 status; 6 of the products are currently designated as NF, one product (the Lexette foam brand) is already Tier 4 from the February 2019 meeting, and only one product (the Clodan shampoo kit) is currently UF. The Tier 4 recommendations will affect about 715 patients. However, when we looked at the total number of annual prescription fills, the majority of patients received about two fills yearly. The high potency topical steroids are not chronic medications, due to the risks associated with long term steroid use.

For the implementation period, the Committee did recommend 120 days after signing. We will send letters to the patients affected by the UF to NF changes and the Tier 4 recommendation. The patients affected by the Tier 4 change will get two letters – one at 60 days prior to implementation, and then at 30 days prior to implementation, if they are still on a Tier 4 drug. The patients affected by the PA recommendations won't receive letters, based on our review of the prescription utilization, and since the patient will likely have completed therapy by the implementation period.

G. Panel Comments

Mr. Hostettler mentioned that it was discussed in the March meeting that Tier 4 was to be judiciously used and 21% of the class is recommended for Tier 4. He is concerned that the Panel is setting a precedent regarding Tier 4 utilization. He also commented that the primary advantage of the available vehicle types (gels, sprays, shampoo, and tape) for this class was for patient convenience and questioned what value patient convenience is given.

CDR Hellwig responded that at least 1 of each vehicle type for this class was left on the formulary for patient convenience, including some deemed less necessary.

Mr. Hostettler asked if there are at least 2 uniform formulary products for each vehicle type as patients may not respond to the first prescription received.

Dr. Khoury had mentioned that this depends on the class, be it by Coopman Class or Stoughton Cornell Class, which is being referenced as some classes only have 1 vehicle type.

CDR Hellwig responded that tape only has 1 product. CDR Hellwig noted that prescribers were saying that they did not require all vehicle types and that some vehicle types fill the same niche such as gels and lotions.

Dr. Khoury noted that the prescribers are saying that all that is needed for treating most patients are 1 or 2 agents and that if the steroid is failing, it may be more related to the patient's disease not responding to the medication.

Mr. Hostettler commented that although some drugs had very little to no additional clinical effectiveness, there is some benefit to the patient.

Mr. Du Teil expressed his concern about more than 20% of the class moving to Tier 4. He asked why the products with "very little to no additional clinical effectiveness" were not moved to Tier 3, as opposed to Tier 4.

CDR Hellwig reiterated that some of the products are considered interchangeable and therefore provide little additional benefit over their counterparts. While there appears to be a higher percentage of Tier 4 agents than in the past, there is actually over 20 agents on the formulary which is more than most classes.

Mr. Hostettler expressed concern that there is no Tier 4 appeals process, potentially leaving physicians and patients with no options. The beneficiary would have options with an appeal process.

Dr. Khoury referenced the drug class PPIs which included designating agents Tier 4 in February. He stated that 2 out of 8 PPI agents were recommended for Tier 4 status, which is equal to 25% of the class, which is an even higher percentage than the current class in question. More important than the number of agents, is out of 245,000 unique utilizers, only 4000 of them are impacted by this Tier 4 recommendation (approximately1%). The impact this recommendation designating these agents Tier 4 on the beneficiary population is very low.

Mr. Hostettler responded that the numbers support the fact that the beneficiary impact is low. However, if you are one of the beneficiaries impacted, the recommendation could be significant. He also brought up that requiring a PA every 30 days for some of these agents would be difficult for prescriptions that come with multiple refills.

CDR Hellwig said that most patients don't get refills on this class of drugs. The mode (most common) amount of fills per prescription was 1 (average of 2 fills a year). However, there are patients with more complicated diseases that require more frequent use throughout the year.

Dr. Bertin stated that the beneficiary population he represents believes that Tier 4 is a very powerful and scary tool. Scary for the people who don't know much about drug cost issues and scary for those of us who do. He requested that formulary recommendations, especially Tier 4, be sensitive to the concerns of the beneficiaries and reiterated that Tier 4 should be used judiciously.

Dr. Bertin asked if the PA criteria was correct for clobetasol propionate/emollient 0.05% foam, where the beneficiary is required to try and fail each vehicle type (the solution, lotion, gel and foam) for 2 weeks. He also expressed concerns regarding the time it would take to complete each trial and go back to the doctor to get a new prescription. He also asked what if the patient condition did not require the use of a foam or one of the other products required by the trial.

CDR Hellwig concurred that this is correct and that there is no discernable clinical advantage of this foam type vs the other agent vehicles.

Dr. Piirainen expressed concern about the circumstance where a patient has had a PA approved already but needs a refill or additional medication for a larger area. They would have to reapply for a PA as a result of PA expirations being 30 days.

Dr. Peloquin asked if there are a lot of varying package sizes for these Non-Formulary medications as that may affect the required amounts for cases such as 2 weeks on 2 weeks off or larger required amounts.

CDR Hellwig, in response, said that the days' supply should correctly reflect the amount prescribed and is unsure if package size and quantity were considered when reviewing PA criteria. It was noted that there are no quantity limits on these products aside from tape, which is limited to 1 roll of tape. Prescribers can prescribe the necessary quantities per patient requirements.

Mr. Hostettler asked if there was discussion about extending the PA expiration past 30 days. He also stated that some patients require the medications for longer periods of time.

CDR Hellwig commented that she doesn't believe there was any discussion among the committee member for a longer PA expiration date.

Dr. Khoury mentioned that there would be concerns with using large amounts of high potency corticosteroids in a short period and in most cases an alternate course such as an oral course may be recommended past 2 weeks or for larger surface areas.

CDR Hellwig also reiterated that due to the large variety of formulary products, most patients will likely find an effective product.

Dr. Khoury noted that the PAs are monitored and audited. The PAs can be modified in the cases where clinical concerns are identified that were not previously known.

CDR Hellwig added that the pharmacy benefit group receives feedback from patients, including retail, about any difficulties they experience getting particular drugs.

Dr. Dager commented that there has been a lot of discussion regarding feedback on the PA. Has any feedback been received (complaints, other issues, etc.) received about Tier 4 drugs?

Dr. Khoury noted that the March 2019 Tier 4 recommendations were implemented on August 28th. We had yet to receive any relevant feedback that needed to be be shared with the BAP.

CDR Hellwig mentioned that a pathway was mapped out to address patient's questions and concerns regarding Tier 4.

Mr. Hostettler asked who beneficiaries can call if they have questions about Tier 4 medications.

Dr. Khoury responded that beneficiaries would most likely engage with the provider in the purchased care setting and MTF about Tier 4 products. If they had been prescribed an agent and were in need of switching, then they would be able to identify an alternative option. If it's through an MTF, that could occur through the MTF pharmacy. Additionally, patients can refer to their Pharmacy Benefits Manager (express scripts) regarding obtaining agents that are alternative to the Tier 4 designated product.

Mr. Hostettler asked about the process used to capture beneficiary Tier 4 complaints.

Mr. Ostrowski provided clarification by stating, there is no appeal process. Is there a process available for beneficiaries to comment and provide feedback? Can those comments be captured and shared with the Panel at a later date?

Mr. Hostettler asked for further clarification regarding the process for beneficiaries to provide feedback on PA and Tier 4 recommendations.

CAPT Norton noted that while beneficiaries cannot appeal a Tier 4 denial, beneficiaries can also write the Pharmacy Operations Division, Director of Defense Health Agency, or their congressman to file complaints and voice their concerns. As CDR Hellwig stated, the PA process/recommendations are evaluated and beneficiary feedback is taken into account as well as things such as new clinical information on the drug, changes in marketplace, feedback from providers, comments from physicians on the BAP, etc.

CDR Hellwig did mention that Tier 4 drugs will be re-evaluated again to ensure that their designation still makes sense given any new information/feedback.

There were no more questions or comments from the Panel. The chair called for a vote on the UF/Tier 4/Not Covered Recommendations, Manual PA Criteria, and UF and PA Implementation Plan for the High-Potency Topical Corticosteroids.

- **High-Potency Topical Corticosteroids – UF/Tier 4/Not Covered Recommendations**

  Concur: 9 Non-Concur: 1 Abstain: 0 Absent: 0

- **High-Potency Topical Corticosteroids – Manual PA Criteria**

  Concur: 9 Non-Concur: 1 Abstain: 0 Absent: 0

- **High-Potency Topical Corticosteroids – UF/Tier 4/Not Covered PA Implementation Plan**

  Concur: 9 Non-Concur: 1 Abstain: 0 Absent: 0

II. MULTIPLE SCLEROSIS – INTERFERONS AND METHYL FUMARATE

CDR RAISOR

P&T Comments

A. Multiple Sclerosis – Interferons and Methyl Fumarate—Relative Clinical Effectiveness Analysis and Conclusion

Background—The full Multiple Sclerosis (MS) drug class was previously evaluated for formulary status at the November 2014 P&T Committee meeting. However, this review focused on two subclasses, the Interferons and Methyl Fumarate. The other MS subclasses, including glatiramer, symptomatic agents, and oral miscellaneous drugs, were not reviewed and will maintain their current formulary status.

The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following for the MS drugs:

Background

- The interferons and dimethyl fumarate, along with glatiramer and the oral miscellaneous drugs, are all considered disease-modifying therapies (DMTs). DMTs are not prescribed for symptom improvement but for reducing relapses and new lesions on MRI.
- Professional treatment guidelines and MS organizations recommend availability of all DMTs without limitations and recommend choosing the appropriate MS therapy based on efficacy, safety, and individualized patient factors.

Interferons

- The five products in the subclass include the interferon beta-1b subcutaneous (SC) products (Betaseron and Extavia) and the interferon beta-1a products, Avonex intramuscular (IM), Rebif/Rebif Rebidose SC, and Plegridy IM.
- There were no significant changes from the November 2014 previous clinical conclusions which stated no one individual interferon is preferred over another in terms of efficacy or safety.
- Professional treatment guidelines from the American Academy of Neurology also do not give preference to one product over another.
- A 2017 network meta-analysis from the Institute for Clinical and Economic Review (ICER) stated the interferons are relatively similar in terms of efficacy for the relative risk of relapse rate and disability progression. Compared to placebo, the interferons have a 17%-36% reduction in the relative risk of relapse rate and a 19%-34% reduction in the relative risk of disability progression.
- The interferons have similar rates of serious adverse events and discontinuation due to adverse events. For the class, flulike symptoms are most common.
- The peginterferon beta-1a product Plegridy is similar to Avonex and Rebif, with the exception that it is a pegylated formulation. Plegridy may be associated with more serious adverse events than other interferons, but it shows a similar discontinuation rate with the other products.
- Interferons generally have fewer adverse events compared to other DMTs.
- Although Betaseron and Extavia utilized the same registration studies to gain FDA approval and contain the same active ingredient, the two products are not interchangeable at the pharmacy.
- There is a high degree of therapeutic interchangeability between the interferons.

Methyl Fumarate

- Dimethyl fumarate (Tecfidera) is an oral tablet and is currently the only product in the methyl fumarate subclass.
- There are no head-to-head trials comparing dimethyl fumarate and other DMTs.

- The 2017 ICER network meta-analysis showed that compared to placebo, treatment with dimethyl fumarate resulted in a 47% reduction in the relative risk of relapse rate and a 38% reduction in the relative risk of disability progression.
- Tecfidera has more serious adverse events and a greater discontinuation rate compared to the interferons.
- Tecfidera requires monitoring of the complete blood count and lymphocytes, due to the potential risk of developing progressive multifocal leukoencephalopathy (PML).
- At least two methyl fumarate products are pending FDA approval for late 2019 and mid-2020.

Overall Conclusion

- Patients with MS who are stable on an individual DMT should continue their current therapy unless the patient and provider decide a trial off therapy is warranted.
- In order to meet the needs of MHS beneficiaries, at least one interferon and one methyl fumarate product are required on the UF.
- The other DMT MS classes will remain on the UF.

B. Multiple Sclerosis – Interferons and Methyl Fumarate—Relative Cost-Effectiveness Analysis and Conclusion

The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

Interferon Subclass

- CMA results for the Interferon subclass showed that Extavia and Betaseron were the most cost effective products, followed by the interferon beta-1a products.
- BIA was performed for the Interferon subclass to evaluate the potential impact of designating selected agents as formulary, NF, or Tier 4 on the UF. BIA results showed that designating Rebif and Rebif Rebidose, Avonex IM, Betaseron, and Extavia as UF, and Plegridy as NF demonstrated cost avoidance for the Military Health System (MHS).

Methyl Fumarate Subclass

- BIA results for the Methyl Fumarate subclass showed that designating Tecfidera as UF demonstrated cost avoidance for the MHS.

C. Multiple Sclerosis – Interferons and Methyl Fumarate—UF Recommendation

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) the following for the Multiple Sclerosis agents, as outlined below, based on clinical and cost-effectiveness:

Interferons

- UF
  - interferon beta-1a IM (Avonex)
  - interferon beta-1a SC (Rebif, Rebif Rebidose)
  - interferon beta-1b SC (Betaseron)
  - interferon beta-1b (Extavia)

- NF
  - peginterferon beta-1a SC (Plegridy)

Methyl Fumarate

- UF
  - dimethyl fumarate (Tecfidera)
- NF
  - None

D. Multiple Sclerosis – Interferons and Methyl Fumarate—Manual PA Criteria

For dimethyl fumarate (Tecfidera), PA criteria have been in place since November 2013 to ensure appropriate safety monitoring. The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) updating the current manual PA criteria for dimethyl fumarate (Tecfidera) in new users to only allow use for the FDA-labeled indication of MS.

1. dimethyl fumarate (Tecfidera)
Changes from August 2019 are in BOLD.

Manual PA criteria apply to new users of Tecfidera.

Manual PA Criteria: Coverage approved for patients with:
- Documented diagnosis of relapsing forms of multiple sclerosis (MS).
- Complete blood count drawn within six months prior to initiation of therapy, due to risk of lymphopenia.
- Coverage is NOT provided for concomitant use with other disease-modifying drugs of MS

Non-FDA-approved uses are not approved.
PA does not expire.

E. Multiple Sclerosis – Interferons and Methyl Fumarate—UF and PA Implementation Plan

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) implementation effective upon signing of the minutes in all points of service (POS).

F. Physician's Perspective

The MS drugs have seen an overall reduction in the use of injectables in favor of oral therapies. We did not review the entire MS class, just the interferons and methyl fumarate subclasses.

For the UF recommendation, the unanimous decision was that every drug maintains its current formulary status, therefore there is no patient disruption. Since there were no copay changes, no letters are needed.

We will continue to keep the PA for Tecfidera due to the safety concerns of PML. The only change in the PA was explicitly stating that uses other than for MS are not allowed.

G. Panel Comments

Mr. Hostettler asked that if the discontinue rates for all interferons are similar, then why is there a NF recommendation for Plegridy.

CDR Raisor responded that it's based on cost effectiveness.

Mr. Hostettler asked if the new PA criteria for Tecfidera would affect current users.

CDR Raisor said that it would only apply to new users. This was identified as a typo in the Manual PA for Tecfidera.

There were no more questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, and UF and PA Implementation Plan for Multiple Sclerosis– Interferons and Methyl Fumarate

- **Multiple Sclerosis – Interferons and Methyl Fumarate – UF Recommendations**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

- **Multiple Sclerosis – Interferons and Methyl Fumarate – Manual PA Criteria**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

- **Multiple Sclerosis – Interferons and Methyl Fumarate – UF and PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

III. NEWLY APPROVED DRUGS PER 32 CFR 199.21(g)(5)

CDR HELLWIG

P&T Comments

A. Newly Approved Drugs per 32 CFR 199.21(g)(5)—Relative Clinical Effectiveness and Relative Cost-Effectiveness Conclusions

The P&T Committee agreed (group 1: 16 for, 0 opposed, 0 abstained, 1 absent; group 2: 17 for, 0 opposed, 0 abstained, 0 absent) with the relative clinical and cost-effectiveness analyses presented for the newly approved drugs reviewed according to 32 CFR 199.21(g)(5).

B. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF/Tier 4/Not Covered Recommendation

The P&T Committee recommended (group 1: 16 for, 0 opposed, 0 abstained, 1 absent; group 2: 17 for, 0 opposed, 0 abstained, 0 absent) the following:

- UF:
  - alpelisib (Piqray) – Oncological Agent for breast cancer
  - amifampridine (Ruzurgi) – Miscellaneous Neurological Agent for Lambert-Eaton myasthenic syndrome (LEMS)
  - amphetamine sulfate orally disintegrating IR tablet (Evekeo ODT) –Attention Deficit Hyperactivity Disorder (ADHD)
  - dolutegravir/lamivudine (Dovato) – Single-tablet regimen (STR) antiretroviral for Human Immunodeficiency Virus (HIV)
  - erdafitinib (Balversa) – Oral Oncological Agent for urothelial cancer
  - halobetasol propionate 0.01%/tazarotene 0.045% lotion (Duobrii) – Combination product for Plaque Psoriasis
  - immunoglobulin subcutaneous injection (Cutaquig) – Immunoglobulin for Immune Deficiency Disorders
  - mepolizumab injection (Nucala) – Miscellaneous Pulmonary I Agent for severe asthma and eosinophilic granulomatosis with polyangiitis (EGPA)
  - methylphenidate extended-release sprinkle capsules (Jornay PM) – ADHD

- tafamidis (Vyndaqel) – Miscellaneous Neurological Agents for cardiomyopathy associated with hereditary transthyretin-mediated amyloidosis (ATTR-CM)
- triclabendazole (Egaten) – Antiinfectives: Anthelmintics for fascioliasis

- NF:
  - drospirenone (Slynd) – Progestogen-only contraceptive agent
  - galcanezumab-gnlm 100 mg injection (Emgality) – Migraine Agents: Calcitonin gene-related peptide (CGRP) inhibitors for cluster headache. *Note that the Emgality 120 mg injection formulation for prevention of migraine headache remains on the UF.*
  - risankizumab-rzaa injection (Skyrizi) – Targeted Immunomodulatory Biologic (TIB) for Plaque Psoriasis
  - rosuvastatin sprinkle capsules (Ezallor Sprinkle) – Antilipidemics-I
  - solriamfetol (Sunosi) –Wakefulness Promoting Agent

- Tier 4 (Not Covered):
  - methylphenidate extended-release sprinkle capsules (Adhansia XR) – ADHD
    - Adhansia XR was recommended for Tier 4 status as it has very little to no additional clinical effectiveness relative to similar ADHD drugs; there is a significant safety risk due to its very long duration of action (particularly in children for insomnia and weight loss) relative to other ADHD drugs; and the needs of TRICARE beneficiaries are met by alternative agents.
      - Formulary alternatives to Adhansia XR include methylphenidate ER (Aptensio XR sprinkle cap and Quillivant XR suspension), for patients with swallowing difficulties; Concerta and generics; Ritalin LA and generics; Metadate CD and generics; dexmethylphenidate ER (Focalin XR and generics); and mixed amphetamine salts (Adderall XR and generics).

C. Newly Approved Drugs per 32 CFR 199.21(g)(5)—PA Criteria

The P&T Committee recommended (group 1: 16 for, 0 opposed, 0 abstained, 1 absent; group 2: 17 for, 0 opposed, 0 abstained, 0 absent) the following:

- ADHD: Applying manual PA criteria to new and current users of Jornay PM, requiring a trial of other clinically efficacious, safe, and cost-effective methylphenidate ER formulations with long durations of action first, including branded products targeted for patients with swallowing difficulties (i.e., Quillivant XR suspension or Aptensio XR sprinkle capsule).
- TIBs: Applying the same manual PA criteria in new users of Skyrizi that is currently in place for the other non-step-preferred TIBs. Patients must first try

Humira. Additionally for Skyrizi, a trial of both Stelara and Cosentyx is required if the patient cannot be treated with Humira.

- Migraine Agents: CGRP Inhibitors for Cluster Headache: Manual PA criteria apply to the CGRP Inhibitors that are approved for prevention of migraine headache, including Emgality 120 mg injection. PA criteria will apply to new users of Emgality 100 mg syringe for cluster headache, requiring a trial of traditional preventive therapies, including verapamil, topiramate, or lithium. Use of Emgality 100 mg will not be allowed for prevention of migraine headache.
- Applying manual PA criteria to new and current users of Sunosi and Nucala.
- Applying manual PA criteria to new users of Ruzurgi, Ezallor Sprinkle, Piqray, Balversa, Vyndaqel, and Evekeo ODT.

Full PA Criteria for the Newly Approved Drugs per 32 CFR 199.21(g)(5)

1. alpelisib (Piqray)

Manual PA is required for all new users of Piqray.

Manual PA Criteria: Piqray is approved if all criteria are met:

- Patient must be ≥ 18 years old.
- Patient is diagnosed with advanced or metastatic HR positive, HER2 negative breast cancer with PIK3CA mutation as confirmed by an FDA-approved test.
- Drug is prescribed by, or in consultation with, an oncologist/hematologist.
- Female patients are post-menopausal, or if pre-menopausal, they are receiving ovarian ablation/suppression.
- Female patients of reproductive potential will use effective contraception during therapy and for one week after the last dose.
- Patient has tried and failed, or is not a candidate for, adjuvant or neoadjuvant chemotherapy.
- Patient has had disease progression while on or after endocrine-based therapy.
- Patient will receive fulvestrant injection (Faslodex) therapy along with alpelisib (Piqray).
- Patient has no history of Stevens Johnson Syndrome, Erythema Multiforme, or Toxic Epidermal Necrolysis.
- Provider is aware and has informed patient of risk of serious, life-threatening skin reactions, including Stevens Johnson Syndrome; severe hyperglycemia; gastrointestinal toxicity, including severe diarrhea; kidney injury; lung injury including pneumonitis; pancreatitis; and severe hypersensitivity reactions.
- Provider is aware and has informed patient that safety has not been established in type 1 or uncontrolled type 2 diabetic patients.
- Male patients with female partners of reproductive potential should use condoms and effective contraception during therapy and for one week after last dose.

- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis:_____

Other non-FDA-approved uses are not approved.
Prior authorization does not expire.

2. amifampridine (Ruzurgi)

Manual PA is required for all new users of Ruzurgi.

Manual PA Criteria: Ruzurgi is approved if all criteria are met:
- Patient has Lambert-Eaton myasthenic syndrome (LEMS)

Non-FDA-approved uses other than LEMS in adults are not approved.
PA does not expire.

3. amphetamine sulfate orally disintegrating IR tablets (Evekeo ODT)

Manual PA is required for all new users of Evekeo ODT.

Manual PA Criteria: Evekeo ODT is approved if ALL criteria are met:
- Patient is 6-17 years of age with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) that has been appropriately documented in the medical record
- Patient has tried for at least two months and failed or has difficulty swallowing Adderall tabs (generic)
- Patient has tried for at least two months and failed or the patient has a contraindication to IR methylphenidate tablets or solution

Non-FDA-approved uses are not approved.
PA does not expire.

4. erdafitinib (Balversa)

Manual PA criteria apply to all new users of Balversa.

Manual PA Criteria: Erdafitinib (Balversa) is approved if all criteria are met:
- The patient is ≥ 18 years old
- Patient has locally advanced or metastatic urothelial carcinoma that has a susceptible FGFR3 or FGFR2 mutation confirmed with an FDA-approved test
- The patient has progressed during or following at least one line of prior platinum-containing chemotherapy (including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy)

- The drug is prescribed by or in consultation with an oncologist
- The patient will be evaluated by an ophthalmologist before starting treatment and every month for the first 4 months; then every 3 months thereafter
- The patient will be advised to seek emergent evaluation for new ocular symptoms
- The patient will be monitored for hyperphosphatemia. (Note that 33% of patients required a phosphate binder in the trial supporting FDA approval for erdafitinib)
- If the patient is female, she is not pregnant or planning to become pregnant.
- Female patients will not breastfeed.
- All patients (females AND males) of reproductive potential will use highly effective contraception during treatment and for 1 month after the last dose.

- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, the provider must list the diagnosis.

Other non-FDA-approved uses are not approved.
PA does not expire.

5. galcanezumab-gnlm 100 mg injection (Emgality)

Note that this PA applies to the Emgality 100 mg cluster headache formulation. The Emgality 120 mg migraine prophylaxis indication PA criteria is on a separate form.

Manual PA criteria apply to all new users of Emgality for episodic cluster headaches.

Manual PA Criteria: Emgality 100 mg at a dosage of 300 mg/month is approved if all criteria are met:

- Patient ≥ 18 years old and not pregnant
- The drug must be prescribed by or in consultation with a neurologist
- Patient has a diagnosis of episodic cluster headaches
- Patient has a contraindication to, intolerability to, or has failed an adequate trial of:
  - Verapamil, topiramate, or lithium
- Concurrent use with other CGRP inhibitors (e.g., Aimovig, Emgality 120 mg, Ajovy) is not allowed

Non-FDA-approved uses, including for migraine prophylaxis, chronic cluster headache, medication overuse headache, etc., are not approved.
PA expires after 6 months.

Renewal Criteria: Coverage will be approved indefinitely for continuation of therapy if there is a clinically appropriate reduction in weekly attacks (≥ 50% reduction in weekly cluster headache attack frequency) during an episode as reported by the patient.

6. mepolizumab injection (Nucala)

Manual PA is required for all new and current users of Nucala.

Manual PA Criteria: Nucala is approved if all criteria are met:

For eosinophilic asthma:

- The patient has a diagnosis of severe persistent eosinophilic asthma
- Patient must be ≥ 12 years old
- The drug is prescribed by an allergist, immunologist, or pulmonologist
- Patient has an eosinophilic phenotype asthma as defined as either
  - blood eosinophil count of > 150 cells/mcL within the past month while on oral corticosteroids OR
  - ≥ 300 cells/mcL within the past year
- The patient's asthma must be uncontrolled despite adherence to optimized medication therapy regimen, with uncontrolled asthma defined as
  - Hospitalization for asthma in the past year OR
  - Required course of oral corticosteroids twice in the past year OR
  - Daily high-dose inhaled corticosteroid (ICS) with inability to taper off the ICS
- The patient has tried and failed an adequate course (3 months) of at least two of the following while using a high-dose inhaled corticosteroid:
  - Inhaled long-acting beta agonist (LABA) (e.g., Serevent, Striverdi), long-acting muscarinic antagonist (LAMA) (e.g., Spiriva, Incruse), leukotriene receptor antagonist (e.g., Singulair, Accolate, Zyflo)

For eosinophilic granulomatosis with polyangiitis (EGPA):

- Patient must have diagnosis of EGPA
- The drug is prescribed by an allergist, immunologist, pulmonologist, rheumatologist, or hematologist
- Patient must be ≥ 18 years old
- The patient has had an adequate trial of at least 3 months of one of the following with an either an inadequate response to therapy, or significant side effects/toxicity or the patient has a contraindication to therapy with
  - Corticosteroids, cyclophosphamide, azathioprine, or methotrexate
- A quantity limit override for the 300 mg dose to allow three of the 100 mg syringes is approved for the EGPA indication only

Non-FDA-approved uses are not approved.
Prior authorization does not expire.

7. methylphenidate extended-release capsules (Jornay PM)

Manual PA is required for all new and current users of Jornay PM.

Manual PA Criteria: Jornay PM is approved if all criteria are met:

- Patient is 6 years and older with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) that has been appropriately documented in the medical record
- The patient must have tried for at least two months and failed Concerta (generic) or have difficulty swallowing pills
- The patient must have tried for at least two months and failed another long-acting methylphenidate (Methylphenidate ER/CD/LA, Quillivant XR, Aptensio XR)
- The patient must have tried for at least two months and failed or have a contraindication to Adderall XR (generic)
- The patient must have tried for at least two months an immediate release formulation methylphenidate product in conjunction with Concerta or another long-acting methylphenidate
- The provider must explain why the patient needs Jornay PM.

Non-FDA-approved uses are not approved.
PA does not expire.

8. risankizumab-rzaa injection (Skyrizi)

PA criteria apply to all new users of Skyrizi. The patient must have tried Humira, Stelara, and Cosentyx.

Manual PA Criteria: Skyrizi is approved if ALL criteria are met:

- The patient has a contraindication or has had an inadequate response to Humira, Cosentyx, AND Stelara OR
- The patient has had an adverse reaction to Humira, Cosentyx, AND Stelara that is not expected with the requested non-step-preferred TIB AND
- Patient is ≥ 18 years old
- The patient is diagnosed with moderate to severe plaque psoriasis and is a candidate for systemic therapy or phototherapy
- Patient has tried and had an inadequate response to non-biologic systemic therapy (e.g., methotrexate, aminosalicylates [e.g., sulfasalazine, mesalamine], corticosteroids, immunosuppressants [e.g., azathioprine])
- Coverage is NOT provided for concomitant use with other TIBs
- The patient has had a negative TB test result in past 12 months (or TB is adequately managed)

Non-FDA-approved uses are not approved.
PA does not expire.

9. rosuvastatin sprinkle capsules (Ezallor Sprinkle)

PA does not apply to patients 12 years of age and younger (age edit)

PA criteria apply to all new users of Ezallor Sprinkle older than 12 years of age.
Manual PA Criteria: Ezallor Sprinkle is approved if all criteria are met:

- Provider must explain why the patient requires rosuvastatin sprinkle capsules and cannot take simvastatin, atorvastatin, OR rosuvastatin tablets.

Non-FDA-approved uses are not approved.
PA does not expire.

10. solriamfetol (Sunosi)

Manual PA is required for all new and current users of Sunosi.

Manual PA Criteria: Sunosi is approved if all criteria are met:

- Patient must be ≥ 18 years old
- Sunosi is not approved for use in children, adolescents, or pregnant patients.
- Patient has a documented diagnosis of excessive daytime sleepiness associated with narcolepsy or a documented diagnosis of obstructive sleep apnea (OSA)
- For narcolepsy: Narcolepsy was diagnosed by polysomnogram or mean sleep latency time (MSLT) objective testing
- For narcolepsy: Other causes of sleepiness have been ruled out or treated including but not limited to obstructive sleep apnea
- For OSA: Patient's underlying airway obstruction has been treated with continuous positive airway pressure (CPAP) for at least 1 month prior to initiation, and the patient demonstrated adherence to therapy during this time
- For OSA: Patient will continue treatment for underlying airway obstruction (CPAP or similar) throughout duration of treatment
- Sunosi is prescribed by a neurologist, psychiatrist, or sleep medicine specialist
- The patient is not concurrently taking any of the following:
  - Central nervous system depressants, such as a narcotic analgesic (including tramadol), a benzodiazepine, or a sedative hypnotic
  - Monoamine oxidase inhibitor (MAOI) within the past 14 days
  - Modafinil, armodafinil, or stimulant-based therapy, such as amphetamine or methylphenidate
- The patient must have tried and failed and had an inadequate response to modafinil
- The patient must have tried and failed and had an inadequate response to armodafinil
- The patient must have tried and failed and had an inadequate response to stimulant-based therapy (amphetamine or methylphenidate)

- Patient and provider agree to monitor blood pressure and heart rate at baseline and periodically throughout treatment. If the patient has hypertension, the blood pressure is controlled.
- Patient does not have unstable cardiovascular disease, serious heart arrhythmias, or other serious heart problems

Non-FDA-approved uses are not approved (including but not limited to fibromyalgia, insomnia, excessive sleepiness not associated with narcolepsy, major depression, ADHD, or shift work disorder).

Prior authorization expires in 1 year. No renewal allowed. A new prescription will require a new PA to be submitted.

11. tafamidis meglumine (Vyndaqel)

Manual PA criteria apply to all new users of Vyndaqel.

Manual PA Criteria: Tafamidis (Vyndaqel) is approved if all criteria are met:
- The patient is ≥ 18 years old
- Patient has a diagnosis of wild type or hereditary transthyretin-mediated amyloidosis
- The drug is prescribed by or in consultation with a specialist who manages hereditary transthyretin amyloidosis (e.g., cardiologist, geneticist, neurologist)
- If the patient is female, she is not pregnant or planning to become pregnant
- Female patients will not breastfeed
- Female patients of reproductive potential will use highly effective contraception during treatment and for 1 month after the last dose

Non-FDA-approved uses (other than ATTR disease manifestations) are not approved.

PA does not expire.

D. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF and PA Implementation Plan

The P&T Committee recommended (group 1: 16 for, 0 opposed, 0 abstained, 1 absent; group 2: 17 for, 0 opposed, 0 abstained, 0 absent) the following:

- **New Drugs Recommended for UF or NF Status:** an effective date upon signing of the minutes in all points of service.

- **New Drugs Recommended for Tier 4 Status methylphenidate extended-release capsules (Adhansia XR):** 1) an effective date of the first Wednesday after a 120-day implementation period at all points of service, and 2) DHA send letters to beneficiaries who

are affected by the Tier 4/Not Covered recommendation at 30 days and 60 days prior to implementation.

E. Physician's Perspective

The Committee reviewed 17 new drugs, of which 11 were recommended for UF status, with 5 recommended for NF status, and 1 Tier 4/Not Covered candidate.

Prior authorization criteria will apply to 11 of the drugs. Several drugs were recommended for PAs since criteria already apply for the class, including the oncology drugs, the TIBs, and the migraine drugs. "No grandfathering," where both new and current users will be affected by the PA, is recommended for 3 of the drugs – the ADHD drug Jornay PM, the narcolepsy drug Sunosi, and the injectable asthma drug Nucala.

There were three ADHD drugs reviewed at the meeting, Jornay PM, Evekeo ODT, and Adhansia XR.

- Jornay PM was recommended for UF status, but with a PA. It has a delayed onset of action of about 6-8 hours, and is taken at night, so that the drug's onset of action will occur in the morning. However, it has a 14 hour duration of action, so adverse effects of insomnia and decreased appetite are a concern, especially for children. A PA was recommended because there are several cost-effective generic ADHD drugs available. The pediatrician member of the Committee recommended the PA require trials of two long-acting ADHD drugs and Adderall, plus an immediate release ADHD drug prior to the use of Jornay PM, due to the safety risks of the drug and lack of long-term data.

- Evekeo ODT was recommended for UF status, also with a PA. This drug contains 100% amphetamine which has a higher risk of adverse effects than the methylphenidate or mixed amphetamine salt products. It is only indicated for children, and several other ADHD products are available if a child has difficulty swallowing.

- Adhansia XR was recommended for Tier 4/Not covered status. This drug has a longer duration of action at 16 hours. The long duration has the risk of prolonging side effects, including lack of appetite and insomnia. The target group of patients most likely to benefit from this medication are children and adolescents ages 12-21 who need to do homework and other performance based activities (driving, extracurricular activities) into the evening hours. However there are several other methylphenidate products with durations of action of about 10-12 hours that would be appropriate for this target population.

F. Panel Comments

Mr. Hostettler asked how many beneficiaries are affected by Adhansia XR's Tier 4 recommendation.

CDR Hellwig stated that this is a new agent and currently there are only 3 patients utilizing the medication.

Mr. Du Teil asked if the duration of action of Adhansia XR had any bearing on the drug's designation of Tier 4 status or was there a cost consideration.

CDR Hellwig stated that there is very little data on this drug and so it is hard to determine whether the long duration of action (16 hours) will fulfill a niche patient requirement or whether it will introduce new side effects. Both duration of action and drug cost effectiveness were considered when determining Tier 4 status.
Mr. Hostettler asked for confirmation that the PA criteria for Emgality 100mg would only require a trial of one of: verapamil, topiramate, or lithium.

CDR Hellwig concurred.

Dr. Spatz stated that almost everything that had PA criteria, defined a duration of of treatment and inadequate response before moving on, with the exceptions of Skyrizi and Sunosi. He asked why "inadequate response" was not more specifically defined.

CDR Hellwig mentioned that Skyrizi is a long standing PA and that the wording was formatted to follow all other non-step preferred TIBs (Targeted Immunomodulatory Biologics). She said that the language used to determine inadequate response is looked at closer and that the intention is to prevent a physician from writing 2 prescriptions at the same time as well as having a patient from picking up a medication one day, only to try one only a few days after from a different provider. It was also mentioned that the language may have not been present on the PA criteria for Sunosi as a result of the amount of agents that must be tried first in addition to the PA expiration after 1 year. Following 1 year, the original PA criteria would again be required.

Dr. Bertin inquired about the last bulleted requirement under the PA criteria for Jornay where the provider would need to explain why the patient requires Jornay. He asked if this could explain away some of the other required criteria as it seems subjective. Can the provider provide the explanation or who makes the final decision?

CDR Hellwig explained that specific information is given to ESI for use in determining what criteria would be appropriate. Additionally, any write-in components for PA submissions are sent to pharmacist for professional judgement and review.

Mr. Hostettler pointed out that having to wait 8 months as a result of required PA criteria is a long time to wait to receive a drug that is FDA indicated for morning symptoms.

CDR Hellwig had stated that the FDA indication for Jornay PM is ADHD and has no language on approved use for morning symptoms.

Dr. Peloquin noted that some of the PA criteria are extensive and asked if PAs are being used to direct physicians on appropriate use.

CDR Hellwig responded that PAs are used to ensure the right patient is getting the drug. Safety information is included on PAs to ensure the safety of patients.

Dr. Khoury, referring to the FDA approval letters that are sent to manufacturers once a drug gains a new approval, often require up to 5 to 6 post marketing studies which are a combination of animal and, in some cases, pediatric studies that haven't been completed. These are intended to fully clarify the safety and effectiveness of the drugs. Further, some drugs receive accelerated approval without providing an overall survival benefit at the time of approval. Some drugs have failed to show an overall survival benefit, despite being approved for marketing. The number of new drugs available is overwhelming for the typical individual provider. In the past 3 years, the P&T committee has reviewed approximately 250 new drugs and I would suspect that most providers only use 5% to 10% on a regular basis. So, the PA criteria in these cases would provide additional patient safety measures for those providers that may not be fully informed of the data, efficacy, and safety of these new drugs. .

There were no more questions or comments from the Panel. The chair called for a vote on the UF/Tier 4/Not Covered Recommendation, PA Criteria, and UF and PA Implementation Plan for the Newly Approved Drugs.

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – UF/Tier 4/Not Covered Recommendations**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – Manual PA Criteria**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

- **Newly Approved Drugs per 32 CFR 199.21(g)(5) – UF and PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

IV. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA

CDR RAISOR

P&T Comments

A. New PA Criteria

New manual PA criteria were recommended by the P&T Committee due to a variety of reasons. The new manual PAs outlined below will apply to new users for the oncology drugs Alecensa, Alunbrig, Zykadia, and Xalkori and the orthostatic hypotension product Northera and to new and current users for the prescription multivitamin Azesco and the tetracycline product doxycycline hyclate ER 80 mg.

1. Antibiotics: Tetracyclines – Doxycycline hyclate extended-release 80 mg – Oral tetracycline antibiotic for acne vulgaris or rosacea

PA criteria were recommended for this new 80 mg ER doxycycline hyclate available from a single manufacturer. The P&T Committee reviewed the oral tetracycline class in February 2017 and agreed there is little evidence to support advantages of the newer doxycycline products over the traditional generic formulations in terms of salt (monohydrate versus hyclate), dosage form (tablet versus capsule versus scored tablets), or release mechanisms (IR versus ER versus DR). Cost-effective generic formulations of doxycycline hyclate (i.e., 50 mg and 100 mg immediate release) are available on the UF without a PA required.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new and current users of doxycycline hyclate ER 80 mg tablets.

Manual PA Criteria: Doxycycline hyclate extended-release 80 mg is approved if all criteria are met:

- This agent has been identified as having cost-effective alternatives. The provider must describe why this drug is required as opposed to available alternatives.

Non-FDA-approved uses are not approved.
PA does not expire.

2. Oral Oncologic Agents: alectinib (Alecensa), brigatinib (Alunbrig), ceritinib (Zykadia), and crizotinib (Xalkori)

PA criteria have not previously been required for the non-small cell lung cancer (NSCLC) drugs; however, PA is in place for several oncological drug classes. The P&T Committee reviewed four oral oncologic agents, Alecensa, Alunbrig, Zykadia, and Xalkori. PA criteria were recommended for these four products in new users in order to ensure prescribing in accordance with FDA-approved indications or National Comprehensive Cancer Network (NCCN) Guideline-endorsed off-label indications.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new users.

a) alectinib (Alecensa), brigatinib (Alunbrig), and ceritinib (Zykadia)

Manual PA Criteria: Alecensa, Alunbrig, or Zykadia is approved if all criteria are met:

- The patient has *metastatic* anaplastic lymphoma kinase (*ALK*)-positive NSCLC as detected by an FDA-approved test AND
- The drug is prescribed by or in consultation with a hematologist/oncologist OR
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, the provider must list the diagnosis.

Other non-FDA-approved uses are not approved.

Prior authorization does not expire.

b) crizotinib (Xalkori)

Manual PA Criteria: Xalkori is approved if all criteria are met:

- Patient has metastatic anaplastic lymphoma kinase (ALK)-positive NSCLC as detected by an FDA-approved test OR
- Patient has NSCLC with ROS1 rearrangement AND
- The drug is prescribed by or in consultation with a hematologist/oncologist OR
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, the provider must list the diagnosis.

Other non-FDA-approved uses are not approved

Prior authorization does not expire.

3. Vitamins: Prenatal – Prenatal multivitamin (Azesco)

Azesco is a prenatal multivitamin manufactured by a single manufacturer that requires a prescription prior to dispensing. The primary ingredients of Azesco are 13 mg of iron and 1 mg of folic acid. Prescription prenatal multivitamins are included in the TRICARE pharmacy benefit for women younger than age 45. This agent was identified as having numerous cost-effective alternatives (including Prenatal Vitamins Plus Low I, Prenatal Plus, Preplus, Prenatal, Prenatal Vitamins, Prenatal Multi+ DHA, Prenatal Vitamin + Low Iron, and Prenatal Plus DHA) that are available on the UF, where a PA is not required.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for new and current users of Azesco.

Manual PA Criteria: Azesco is approved if all criteria are met:

- This agent has been identified as having cost-effective alternatives. The provider must describe why this drug is required as opposed to available alternatives.

Non-FDA-approved uses are not approved.
PA does not expire.

4. Cardiovascular Agents Miscellaneous: Droxidopa (Northera)

Droxidopa (Northera) is an alpha/beta agonist approved in February 2014 for neurogenic orthostatic hypotension (NOH). The product labeling for Northera contains a black box warning that it may cause or exacerbate supine hypertension. A consensus statement from the American Autonomic Society and the National Parkinson Foundation for NOH was published in 2017 and recommends treatments including midodrine, fludrocortisone, and pyridostigmine, in addition to droxidopa. No one pharmacologic treatment is preferred over another in the guidelines. PA criteria were recommended for Northera to ensure appropriate use of clinically and cost-effective alternative therapies for neurogenic orthostatic hypotension first.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) manual PA criteria for droxidopa in new users.

Manual PA Criteria: Northera is approved if all criteria are met:
- Patient is ≥ 18 years of age
- Patient has been diagnosed with symptomatic Neurogenic Orthostatic Hypotension (NOH) due to primary autonomic failure (Parkinson's disease [PD], multiple system atrophy [MSA], and pure autonomic failure [PAF]), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy
- The drug is prescribed by or in consultation with a cardiologist or a neurologist
- The patient has tried two other medications (e.g., fludrocortisone, pyridostigmine, or midodrine) and failed to respond to therapy
- Patient has initiated non-pharmacological measures including but not limited to elevation of the head of the bed, orthostatic compression garments, increased salt intake, and appropriate physical training

Non-FDA-approved uses are not approved.
PA does not expire.

B. New PA Criteria—PA Implementation

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) new PAs for Alecensa, Alunbrig, Zykadia, Xalkori, Azesco, Northera, and doxycycline hyclate ER 80 mg become effective 90 days after the signing of the minutes. DHA will send letters to beneficiaries affected by the new PA requirements for Azesco and doxycycline hyclate extended-release 80 mg if applicable, as new and current users will be subject to the PA.

C. Physician's Perspective

There were drugs from four classes where new PA criteria were recommended.

Doxycycline 80 mg: This product is for a new 80 mg dosage strength by one manufacturer that is not cost effective compared to the most commonly dispensed 50 mg and 100 mg strengths. There is already step therapy in the tetracycline class, so the PA criteria reflect what is already in place for the non-step preferred products. We currently don't have any utilization of this drug.

NSCLC drugs (Alecensa, Alunbrig, Zykadia, Xalkori): This is part of our ongoing process of reviewing the oncology drugs to determine which ones do not have PAs in place. These drugs are all approved for non-small cell lung cancer, and PA was recommended to ensure the appropriate patients receive the drugs, based on FDA indications. These new PA's allow off-label uses that are included in the NCCN guidelines be considered as part of the PA review, before having the provider file an appeal.

Azesco: This product is a prescription prenatal vitamin that is over 12,000 times more expensive than the other prescription prenatal vitamins. Legend prenatal vitamins are part of the TRICARE pharmacy benefit, so having the PA is the most appropriate option to ensure this product is not used in the DoD. Currently as of Sept 18, 2019 we haven't had any utilization in DOD.

Droxidopa (Northera): This drug has not previously been reviewed by the P&T Committee, since it has been on the market since 2014. The recommended PA criteria are in alignment with what is recommended in the professional treatment guidelines for neurogenic orthostatic hypotension. There is only limited evidence for this drug, and it is marginally effective with a risk of adverse events. The PA criteria recommended here are similar to what other health plans have and will apply to new users only.

D. Panel Comments

Mr. Hostettler asked if the PA criteria for Doxycycline Hyclate and Azesco meant that it would be difficult to get these products approved.

Dr. Khoury responded saying that those are the current PA criteria and if there are concerns that we haven't captured, they will be captured in comments/feedback from providers.

Mr. Hostettler also noted that Azesco (Prenatal Vitamin) seemed like a Tier 4 candidate.

Dr. Khoury responded it is unusual because it requires a prescription and it is a vitamin not a drug. Otherwise, it would be considered potentially for not covered status.

Mr. Hostettler asked for confirmation that Droxidopa PA criteria is for new users only.

CDR Raisor concurred.

Dr. Bertin asked about pharmacist review of Tetracycline and Azesco and whether they are being told to deny PA at that level.

Dr. Khoury responded the language is not telling the physician that the PA request will be denied. The PAs, with that language, are specifically meant to ensure the pharmacist has a discretion if the patient has a legitimate reason to request the drug not captured in the form.

Dr. Pirrainen, referencing the oncology agents, asked if PA review would have to be in consultation with an Oncologist or Hemotologist, in the case where a provider were prescribing off label.

CDR Raisor stated that it was the intent of the committee was to have it in consultation with or written by a specialist.

There were no more questions or comments from the Panel. The chair called for a vote on the New Manual PA Criteria, and the PA Implementation Plan for the New Manual PA Criteria.

- **New Manual PA Criteria**

  Concur: 9 Non-Concur: 1 Abstain: 0 Absent: 0

- **New Manual PA Criteria – PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

V. UTILIZATION MANAGEMENT—UPDATED MANUAL PA CRITERIA

CDR RAISOR

P&T Comments

A. Updated PA Criteria

Updates to the step therapy and manual PA criteria for several drugs were recommended by the P&T Committee due to a variety of reasons, including expanded FDA indications, pediatric uses, clinical trial data, or to be consistent with existing PAs for the drug class. The updated manual PAs outlined below will apply to new users.

The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) updates to the manual PA criteria for Xyrem, Dupixent, Symdeko, Doptelet, Benlysta, Tibsovo, Otezla, Humira, Xermelo, Firdapse, and Inbrija.

The updates are as follows:

Updated Criteria for reasons other than new FDA indications

1. **Gastrointestinal-2 Agents: telotristat ethyl (Xermelo)** – Manual PA criteria for Xermelo were first recommended in May 2017. Manual PA criteria for Xermelo were updated to reflect the TELECAST trial, which allowed for use in carcinoid syndrome diarrhea in persons having less than 4 bowel movements per day with or without concurrent somatostatin analog therapy.

2. **Neurological Agents Miscellaneous: amifampridine (Firdapse)** – Manual PA criteria for Firdapse for treating LEMS were first recommended in May 2019. Ruzurgi is another amifampridine formulation (see section VI B on page 14). Although the package labeling for Ruzurgi states it is approved for pediatric patients, the clinical trial used to gain FDA approval was conducted in adult patients with a mean age of 52 years, and the maximal dosing is higher with Ruzurgi than Firdapse (100 mg vs. 80 mg, respectively). Ruzurgi is cost-effective compared to Firdapse. Manual PA criteria for Firdapse were updated to require a trial of the cost-effective amifampridine agent Ruzurgi first in new patients.

3. **Parkinson's Agents: levodopa inhalation powder (Inbrija)** – Manual PA criteria for Inbrija were first recommended in May 2019. Manual PA criteria were updated to remove the 1-year expiration date and renewal criteria, as the other Parkinson's drugs have PAs that do not expire.

New FDA-Approved Indications or Age Ranges

1. **ADHD-Wakefulness Promoting Agents: Wakefulness Promoting Agents: sodium oxybate (Xyrem)** – Manual PA criteria were updated to reflect a new FDA-approved indication for use in children ≥ 7 years of age for the treatment of cataplexy in patients with narcolepsy.

2. **Corticosteroids – Immune Modulators: Atopic Dermatitis: dupilumab (Dupixent)** – Manual PA criteria were updated for the new indication for add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.

3. **Cystic Fibrosis Agents: tezacaftor/ivacaftor (Symdeko)** – Manual PA criteria were updated to reflect a new indication for treatment of patients ≥ 6 years of age in the treatment of cystic fibrosis.

4. **Hematological agents: Platelets: avatrombopag (Doptelet)** – Manual PA criteria were updated to reflect a new indication for thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment.

5. **Immunosuppressives: belimumab (Benlysta)** – Manual PA criteria were updated to reflect a new indication for the treatment of patients as young as 5 years of age with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy.

6. **Oncological Agents: Acute Myelogenous Leukemia: ivosidenib (Tibsovo)** – Manual PA criteria were updated to reflect a new indication for the treatment of adult patients with newly diagnosed acute myelogenous leukemia (AML) who are aged 75 years or older who have comorbidities that preclude use of intensive induction chemotherapy.

7. **Targeted Immunomodulatory Biologics (TIBs) – Non-Tumor Necrosis Factor (TNF) Inhibitors: apremilast (Otezla)** – Manual PA criteria were updated to reflect a new indication for treatment of adult patients with oral ulcers associated with Behçet's disease. Note that for Behçet's disease, a trial of adalimumab (Humira) is not required first.

8. **Targeted Immunomodulatory Biologics (TIBs) – Tumor Necrosis Factor (TNF) Inhibitors: adalimumab (Humira)** – Manual PA criteria for Humira were updated to allow for off-label use in pediatric patients for plaque psoriasis. In the European Union, Humira is approved in the pediatric population for plaque psoriasis, and data exists to support its use in this age group. Note that pediatric patients are not required to use the DoD's step-preferred Humira first for plaque psoriasis given that it is currently off-label in the United States.

B. Updated PA Criteria—Implementation Plan

The P&T Committee recommended (15 for, 0 opposed, 0 abstained, 2 absent) updates to the current PA criteria for Firdapse, Xermelo, Inbrija, Xyrem, Symdeko, Benlysta, Otezla, Tibsovo, Dupixent, Doptelet, and Humira in new users become effective 30 days after the signing of the minutes.

C. Weight Loss Agents: liraglutide 3 mg (Saxenda)—Updated PA Criteria

The P&T Committee was briefed on trends in the current utilization and spend for the weight loss agents, which were reviewed in November 2017. Generic phentermine is the most utilized weight loss agent, while liraglutide 3 mg injection (Saxenda) is the second most utilized weight loss agent, but ranks first in total cost per patient. A review of Saxenda claims data found that the majority of patients did not meet the criteria for a trial of other branded weight loss drugs first. The P&T Committee recommended updating the manual PA criteria for liraglutide 3 mg (Saxenda) to streamline the PA form and more closely reflect the original intent of the November 2017 P&T Committee meeting.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) updating the manual PA criteria for new and current users of Saxenda who do not have a

diagnosis of diabetes. Previous trials of other weight loss drugs must be documented prior to use of Saxenda.

D. Weight Loss Agents: liraglutide 3 mg (Saxenda)—Implementation Plan

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) an effective date 60 days after the signing of the minutes in all points of service.

E. Physician's Perspective

The majority of the PA updates made at this meeting were very straightforward, and do represent that the Committee continually monitors the drugs that we have PAs on and provides updates when needed.

Firdapse - Earlier in this meeting another amifampridine product, Ruzurgi was presented as a newly approved drug, and given UF status with a PA required. Ruzurgi and Firdapse contain the same active ingredient. The recommendation for the Firdapse PA update is to require a trial of Ruzurgi first. Ruzugri actually allows more flexibility, since the package insert provides instructions for making a suspension for small children and also for patients with feeding tubes. Although Ruzurgi is only approved for children aged 6 to 17 years, the clinical trial was conducted in adults, and providers are willing to use this drug in adults. This fact is supported by a review of MHS utilization for Ruzurgi which shows that there are six patients on the drug, and 4 of these 6 patients are over the age of 18 years. The PA update will only apply to new users. Currently we have 8 patients on Firdapse.

Weight loss drugs – Saxenda: When we reviewed the medication profiles of the MHS patients taking Saxenda, we found that they did not satisfy the PA criteria recommended back in November 2017 requiring a trial of the other branded weight loss drugs first. Therefore the recommendation is that patients currently on Saxenda will be required to go through the PA again, but only if they do not have a diagnosis of diabetes. Our data pull can show patients who have an ICD-10 code for diabetes. Therefore the "no grandfathering" will only apply to patients without diabetes; this will affect about 786 patients. We are not affecting patients receiving Saxenda who have a diagnosis of diabetes, which is about 295 patients. We will send letters to the patients without a diabetes diagnosis, informing them of the PA requirements.

F. Panel Comments

Mr. Hostettler asked for confirmation that the new manual PA criteria for Tibsovo was meant to say 75 and above.

CDR Raisor concurred saying at least 75.

Mr. Hostettler, in regards to weight loss agents' updated PA criteria, asked how many agents patients have to go through if they have diabetes.

Dr. Khoury responded that patients would need to try and fail or have a contraindication to 4 agents.

There were no more questions or comments from the Panel. The chair called for a vote on the Updated Manual PA Criteria and PA Implementation Plan for the drugs referenced and the Weight Loss Agents.

- **Updated Manual PA Criteria**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

- **Updated PA Criteria – PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

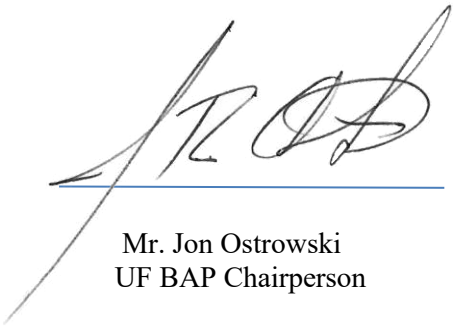
- **Weight Loss Agents - Updated Manual PA Criteria**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

- **Weight Loss Agents - PA Implementation Plan**

  Concur: 10 Non-Concur: 0 Abstain: 0 Absent: 0

Meeting Adjourned



Mr. Jon Ostrowski
UF BAP Chairperson

Appendix I **09/25/2019 BAP Meeting**

Informational Item—SUMMARY OF RECOMMENDATIONS AND BENEFICIARY IMPACT August 2019

Table of Implementation Status of UF Recommendations/Decisions Summary

DoD PEC Drug Class	UF Drugs	NF Drugs	Tier 4/Not Covered Drugs	Implement Date	Notes and Unique Users Affected
High-Potency Topical Corticosteroids	*Note that all are currently UF* ▪ betamethasone dipropionate 0.05% ointment ▪ betamethasone/propylene glycol 0.05% ointment, cream, lotion, gel ▪ clobetasol propionate 0.05% ointment, cream, solution, lotion, shampoo, spray, gel, foam ▪ clobetasol propionate/emollient 0.05% cream ▪ clobetasol propionate/emollient 0.05% emulsion foam ▪ desoximetasone 0.25% ointment, cream ▪ fluocinonide 0.05% ointment, cream, solution, gel ▪ fluocinonide/emollient base 0.05% cream ▪ halobetasol propionate 0.05% ointment	▪ amcinonide 0.1% ointment (Cyclocort, generics) ▪ clobetasol propionate/emollient 0.05% foam (Olux-E, generics) *moves from UF to NF* ▪ desoximetasone 0.05% gel (Topicort, generic) *moves from UF to NF* ▪ diflorasone diacetate 0.05% ointment, cream (Psorcon, Apexicon, generics) ▪ fluocinonide 0.1% cream (Vanos, generics) ▪ flurandrenolide 4 mcg/sq. cm (Cordran) tape *moves from UF to NF* ▪ halobetasol propionate 0.05% cream (Ultravate, generics) *moves from UF to NF*	▪ clobetasol propionate 0.025% cream (Impoyz) ▪ clobetasol propionate 0.05% shampoo/cleanser (kit) (Clodan kit) ▪ diflorasone diacetate/emollient 0.05% cream (Apexicon-E) ▪ halcinonide 0.1% ointment (Halog) ▪ halcinonide 0.1% cream (Halog) ▪ halobetasol propionate 0.05% lotion (Ultravate) ▪ halobetasol propionate 0.05% foam (Lexette & authorized generic) ▪ halobetasol propionate 0.01% lotion (Bryhali)	Pending signing of the minutes / 120 days	▪ Manual PA criteria applies to all new and current users for the following products: ▪ amcinonide 0.1% ointment ▪ diflorasone diacetate 0.05% ointment ▪ diflorasone diacetate 0.05% cream ▪ clobetasol propionate/emollient 0.05% foam ▪ desoximetasone 0.05% gel ▪ flurandrenolide 4 mcg/sq. cm (Cordran) tape ▪ Note the Lexette foam was previously recommended for Tier 4 status at the February 2019 meeting, which was implemented on August 28, 2019. <u>Unique Users Affected (Tier 4 candidates)</u> Mail – 195 MTF – 18 Retail – 502 Total – 715 (UF to NF changes) Mail – 1,061 MTF – 1,318 Retail – 2,533 Total – 4,912

DoD PEC Drug Class	UF Drugs	NF Drugs	Tier 4/Not Covered Drugs	Implement Date	Notes and Unique Users Affected
Multiple Sclerosis: Interferons and Methyl Fumarate	**Interferons** ▪ Interferon beta-1a (Avonex) ▪ Interferon beta-1a (Rebif, Rebif Rebidose) ▪ Interferon beta-1b (Betaseron) ▪ Interferon beta-1b (Extavia) **Methyl Fumarate** ▪ dimethyl fumarate (Tecfidera)	**Interferons** peginterferon beta-1a (Plegridy)	▪ None	Upon signing of the minutes	▪ The MS subclasses of Glatiramer, symptomatic agents, and Oral Miscellaneous were not reviewed ▪ Updated manual PA criteria for all users of dimethyl fumarate (Tecfidera); off-label uses are not allowed Unique Users Affected – Not applicable, no change to formulary status.

Drugs with Prior Authorization Criteria—Unique Utilizers Affected

Drug	MTF	Mail Order	Retail	Total
Weight Loss Agents – liraglutide 3 mg injection (Saxenda)	45	177	575	786
Vitamins: Prenatal – Prenatal multivitamin (Azesco)	0	0	0	0
Antibiotics: Tetracyclines – Doxycycline hyclate extended-release 80 mg	0	0	0	0

Appendix II **09/25/2019 BAP Meeting**

Brief Listing of Acronyms Used in this Summary

Abbreviated terms are spelled out in full in this summary; when they are first used, the acronym is listed in parentheses immediately following the term. All of the terms commonly used as acronyms in the Panel discussions are listed below for easy reference. The term "Pan" in this summary refers to the "Uniform Formulary Beneficiary Panel," the group who's meeting in the subject of this report.

- ADHD – Attention Deficit Hyperactivity Disorder
- AIDS – Acquired Immune Deficiency Syndrome
- ALL – Acute Lymphoblastic Leukemia
- AML – Acute Myeloid Leukemia
- BIA – Budget Impact Analysis
- CFR – Code of Federal Regulations
- CMA – Cost Minimization Analysis
- DHA – Defense Health Agency
- DMARDs – Disease Modifying Anti-Rheumatic Drugs
- DoD- Department of Defense
- ER – Extended Release
- FDA – Food & Drug Administration
- G – Grams
- GI-2 – Gastrointestinal-2
- GLP1RA – Glucagon-Like Peptide-1 Agonists
- HAE – Hereditary Angiodema
- HD – Extended Release
- HER2 – Human Epidermal Growth Factor Receptor
- HFA – Hydrofluoroalkane
- HIV – Human Immunodeficiency Virus
- ICS/LABAs – Inhaled Corticosteroids/Long-Acting Beta Agonists
- INSTI – Integrase Strand Transfer Inhibitors
- JIA – Juvenile Idiopathic Arthritis
- MAOI – Monamine Oxidase Inhibitors
- MHS – Military Health Systems
- mL- milliliter
- MTF – Military Treatment Facility
- NDAA – National Defense Authorization Act
- NDC – National Drug Codes
- NF – Non-Formulary
- NKI – Neurokinin
- NNRT1 – Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
- NPH – Neutral Protamine Hagedorn
- OIC – Opioid-Induced Constipation

- PA- Prior Authorization
- PAMORAs – Peripherally-Acting MU Opioid Receptor Agonists
- PEG – Percutaneous Endoscopic Gastronomy
- P&T – Pharmacy & Therapeutics
- pJLA – Plyarticular Juvenile Idiopathic Arthritis
- PPIs – Proton Pump Inhibitors
- PrEP – Pre-Exposure Prohylaxis
- SGLT2 – Sodium Glucose Co-Transporter
- SQ – Subcutaneously
- SU – Sulfoylurea
- TIBs – Targeted Immunomodulatory Biologics
- TNF – Anti-Tumor Necrosis Factor
- TRICARE – Healthcare Network
- UF – Uniform Formulary
- VMAT2 – Vesicular Monoamine Transporter 2
- XR – Extended Release

Private Citizen Comments

Ironshore Pharmaceuticals and Development, Inc.
a subsidiary of Highland Therapeutics

TO: Colonel Paul J. Hoerner, USAF
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101

FROM: Ironshore Pharmaceuticals Inc.

DATE: September 18, 2019

RE: JORNAY PM™ (methylphenidate HCl Extended-Release Capsules)
Prior Authorization Criteria

Dear Colonel Hoerner,

On behalf of Ironshore Pharmaceuticals, the manufacturer of JORNAY PM™ (methylphenidate HCl Extended-Release Capsules), I appreciate the opportunity to comment on the Prior Authorization Criteria recommended by the Pharmacy & Therapeutics Committee in its August 8th Recommendations to the Uniform Formulary Beneficiary Advisory Panel (BAP). The recommended criteria are as follows:

- Patient is 6 years and older with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) that has been appropriately documented in the medical record
- The patient must have tried for at least two months and failed Concerta (generic) or have difficulty swallowing pills
- The patient must have tried for at least two months and failed another long-acting methylphenidate (Methylphenidate ER/CD/LA, Quillivant XR, Aptensio XR)
- The patient must have tried for at least two months and failed or have a contraindication to Adderall XR (generic)
- Must have tried for at least two months an immediate release formulation methylphenidate product in conjunction with Concerta or another long-acting methylphenidate
- Please explain why the patient needs Jornay PM.

This recommendation requires patients to have tried and failed on four different Uniform Formulary products/regimens for at least 2 months each prior to JORNAY PM being approved for use for the patient. We respectfully request that the criteria be modified to give the clinicians more latitude in determining the timeline for assessing efficacy in their patients. While we understand that JORNAY PM typically would not be used first-line or even second-line, we request the Committee consider revising the criteria to appropriate age and diagnosis plus failure on no more than two stimulants available within the ADHD Category.

Clinical Considerations: Early morning functioning is a significant unmet need in many patients affected by ADHD, and JORNAY PM is the only ADHD stimulant medication with FDA-approved labeling demonstrating early morning symptom control (see attached publications). This is important both for patients who have challenges with the morning routine and those who start school very early in the morning and are unable to take traditional ADHD medication early enough for it to have full effect at the beginning of the school day. Children in single parent military households – where spouses have been deployed – may benefit greatly from this early morning symptom control. JORNAY PM was developed using a novel drug delivery technology that incorporates a delayed-release layer that limits release of the drug overnight, and an extended-release layer which provides a

long, slow release of drug throughout the day. This unique evening dosing provides efficacy from the time of awakening without sacrificing efficacy later in the afternoon and evening.

Thus, in our view it is unduly burdensome to require children to try and fail on four different medications/medication combinations (with differing potential side effects) over the course of 8 months before being able to try JORNAY PM. First, each medication failure has real consequences for these children; they may suffer from significant side effects, have trouble at school, and/or fall behind in classwork because they aren't able to concentrate. Further, during this trial period, they may well continue to have problems maintaining positive peer and family relationships. In addition, this 4-step process creates an unnecessary burden for families. Each medication change typically requires two doctor's visits – one to get the medication and then a 30-day follow-up – that's 8 appointments before they can get JORNAY PM. Often it is difficult to schedule doctor appointments after school or on weekends, so each visit may mean missed school for children who may already struggle academically. Moreover, the impact of an 8-month period on the life of a child should not be discounted – that is almost an entire school year where a child may struggle socially, emotionally, and academically.

To best serve DoD Tricare beneficiaries, we ask that DoD consider taking steps to simplify the number of step edits to no more than two, which still allows for trial of the first-line agent but limits the number of trials, so that access (and patient success) does not become unachievable or is unduly delayed.

Cost Considerations: We understand the need to contain costs associated with prescription drugs, and for this reason we offered a significant additional discount beyond the Federal Ceiling Price to the Tricare Retail Pharmacy Program per a Uniform Formulary Additional Discount Program (UF ADP) offer. While we fully intended to submit a BPA offer of additional discount, we did not submit this offer based on our understanding at the time that we could not do so prior to execution of an FSS Interim Agreement with the Department of Veterans Affairs (VA). Once our FSS Interim Agreement is in place (and we are currently working with VA to facilitate its award) we intend to offer an additional FSS discount to DoD per a BPA.

Thank you for your time and consideration,

L Eugtins

Lewis Warrington, MD
Vice President, Medical Affairs

W Scott Evangelista

W. Scott Evangelista
President, Ironshore Pharmaceuticals

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JORNAY PM™ safely and effectively. See full prescribing information for JORNAY PM.

JORNAY PM (methylphenidate hydrochloride) extended-release capsules, for oral use, CII
Initial U.S. Approval: 1955

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

INDICATIONS AND USAGE

JORNAY PM is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. (1)

DOSAGE AND ADMINISTRATION

- JORNAY PM should be taken only in the evening. (2.2)
- Recommended starting dose for patients 6 years and above is 20 mg daily in the evening. (2.2)
- Adjust the timing of administration between 6:30 p.m. and 9:30 p.m. to optimize the tolerability and the efficacy the next morning and throughout the day.
- Dosage may be increased weekly in increments of 20 mg per day up to a maximum daily dose of 100 mg. (2.2)
- Patients are advised to take JORNAY PM consistently either with food or without food. (2.2)
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce. (2.2)
- To avoid substitution errors and overdosage, do not substitute for other methylphenidate products on a milligram-per-milligram basis. (2.3)

DOSAGE FORMS AND STRENGTHS

- Extended-Release Capsules: 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg. JORNAY PM exhibits both delayed-release and extended-release properties. (3, 11)

CONTRAINDICATIONS

- Known hypersensitivity to methylphenidate or product components. (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI) or use of an MAOI within the preceding 14 days. (4)

WARNINGS AND PRECAUTIONS

- *Serious Cardiovascular Reactions:* Sudden death has been reported in association with CNS stimulants at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions:* Use of CNS stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to JORNAY PM use. (5.4)
- *Priapism:* Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* CNS stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth:* Monitor height and weight at appropriate intervals in pediatric patients. (5.7)

ADVERSE REACTIONS

Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions for pediatric patients and adults are: appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.

Additional adverse reactions (≥5% and twice the rate of placebo) in pediatric patients 6 to 12 years treated with JORNAY PM: headache, psychomotor hyperactivity, and mood swings. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ironshore Pharmaceuticals Inc. at 1-877-938-4766 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including JORNAY PM™, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), (9.3)]*.

1 INDICATIONS AND USAGE

JORNAY PM is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating pediatric patients and adults with CNS stimulants, including JORNAY PM, assess for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse, dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate for the need for JORNAY PM use *[see Boxed Warning, Warnings and Precautions (5.1) and Drug Abuse and Dependence (9)]*.

2.2 General Dosing Information

JORNAY PM is given orally once daily in the evening. JORNAY PM should not be taken in the morning.

The recommended starting dose of JORNAY PM for patients 6 years and older is 20 mg once daily in the evening. The dose may be titrated weekly in increments of 20 mg. Daily doses above 100 mg have not been studied and are not recommended.

Initiate dosing at 8:00 p.m. Adjust the timing of administration between 6:30 p.m. and 9:30 p.m. to optimize the tolerability and efficacy the next morning and throughout the day. In clinical trials of patients aged 6 to 12 years, the most common dosing time (>70% of patients) was 8:00 p.m., with an allowed range between 6:30 p.m. and 9:30 p.m. Following determination of the optimal administration time, advise patients to maintain a consistent dosing time.

Patients who miss their dose of JORNAY PM at the regularly scheduled time should take it as soon as they remember that same evening. If a patient remembers the missed dose the following morning, they should skip the missed dose and wait until their next scheduled evening administration.

Advise patients to take JORNAY PM consistently, either with food or without food.

JORNAY PM may be taken whole, or the capsule may be opened, and the entire contents sprinkled onto applesauce. If the patient is using the sprinkled administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken at the same time.

Pharmacological treatment of ADHD may be needed for extended periods. Periodically re-evaluate the long-term use of JORNAY PM and adjust dosage as needed.

2.3 Switching from Other Methylphenidate Products

If switching from other methylphenidate products, discontinue that treatment, and titrate with JORNAY PM using the titration schedule described above.

Do not substitute JORNAY PM for other methylphenidate products on a milligram-per-milligram basis because these products have different pharmacokinetic profiles from JORNAY PM and may have different methylphenidate base composition *[see Description (11) and Clinical Pharmacology (12.3)]*.

2.4 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or, if necessary, discontinue the drug. JORNAY PM should be periodically discontinued to assess the child's condition. If improvement is not observed after appropriate dosage adjustment over a one-month period, discontinue drug.

3 DOSAGE FORMS AND STRENGTHS

JORNAY PM (methylphenidate hydrochloride) extended-release capsules exhibit both delayed-release and extended-release properties and are available in the following dose strengths:

- 20 mg capsules with ivory opaque body and light green opaque cap;
- 40 mg capsules with ivory opaque body and blue-green opaque cap;
- 60 mg capsules with white opaque body and powder blue opaque cap;
- 80 mg capsules with white opaque body and light blue opaque cap; and
- 100 mg capsules with white opaque body and dark blue opaque cap.

All capsules are imprinted with the dose in black on the body and "IRONSHORE" in black on the cap, except for the 100 mg capsule, on which "IRONSHORE" is imprinted in white.

4 CONTRAINDICATIONS

JORNAY PM is contraindicated in patients:

- With a history of hypersensitivity to methylphenidate or other components of JORNAY PM. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products *[see Adverse Reactions (6)]*.

- Receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of a monoamine oxidase inhibitor, because of the risk of hypertensive crisis *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk for medication abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Drug Abuse and Dependence (9.2, 9.3)]*.

5.2 Serious Cardiovascular Reactions

Sudden death, stroke, and myocardial infarction have been reported in adults treated with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious cardiac problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia,

coronary artery disease, and other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with JORNAY PM.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants may cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such occur, consider discontinuing JORNAY PM. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared with 0 in placebo-treated patients.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric patients and adults. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

CNS stimulants, including JORNAY PM, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Long-term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or nonmedication-treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in

height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including JORNAY PM. Patients not growing or gaining height or weight as expected may need to have their treatment interrupted.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Drug Dependence *[see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*
- Hypersensitivity to methylphenidate or other components of the JORNAY PM *[see Contraindications (4)]*
- Hypertensive crisis when used concomitantly with monoamine oxidase inhibitors *[see Contraindications (4) and Drug Interactions (7.1)]*
- Serious Cardiovascular Reactions *[see Warnings and Precautions (5.2)]*
- Blood Pressure and Heart Rate Increases *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Priapism *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (5.6)]*
- Long-term Suppression of Growth *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD

Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia.

Clinical Trials Experience with JORNAY PM in Pediatric Patients (6 to 12 years) with ADHD

The safety of JORNAY PM was evaluated in 280 patients (6 to 12 years of age) who participated in two controlled clinical studies of patients with ADHD *[see Clinical Studies (14)]*.

Study 1, conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week open-label dose-optimization phase in which all patients received JORNAY PM (n=125; mean dose 50 mg), followed by a 1-week, double-blind controlled phase in which patients were randomized to continue JORNAY PM (n=65) or switch to placebo (n=54). During the open-label JORNAY PM treatment phase, adverse reactions reported in > 5% of patients included: any insomnia (41%), decreased appetite (27%), affect lability (22%), headache (19%), upper respiratory tract infection (17%), upper abdominal pain (9%), nausea or vomiting (9%), increased diastolic blood pressure (8%), tachycardia (7%), and irritability (6%). Three patients discontinued treatment because of adverse reactions of affect lability, panic attacks, and agitation and aggression. Because of the trial design (6-week open-label active treatment phase followed by a 1-week, randomized, double-blind, placebo-controlled withdrawal), the adverse reaction rates described in the double-blind phase are lower than expected

in clinical practice. No difference occurred in the incidence of adverse reactions between JORNAY PM and placebo during the 1-week, double-blind, placebo-controlled treatment phase.

Study 2 was a 3-week, placebo-controlled study of JORNAY PM (n=81; mean dose 52mg) in pediatric patients 6 to 12 years.

Most Common Adverse Reactions (incidence of ≥ 5% and at a rate at least twice placebo): any insomnia, decreased appetite, headache, vomiting, nausea, psychomotor hyperactivity, and affect lability or mood swings.

One patient in the JORNAY PM group discontinued from the study due to mood swings.

Table 1 provides the incidence of adverse reactions reported in Study 2 (incidence of 2% or more and at least twice placebo) among pediatric patients 6 to 12 years in a 3-week clinical trial.

Table 1: Adverse Reactions Occurring in ≥2% of JORNAY PM-treated Pediatric Patients and Greater than Placebo in a 3-Week ADHD Study (Study 2)

Body Organ System	Adverse Reaction	JORNAY PM (N=81)	Placebo (N=80)
Psychiatric disorders	Any insomnia	33%	9%
	Initial insomnia	14%	5%
	Middle insomnia	11%	4%
	Terminal insomnia	11%	1%
	Insomnia, not specified	4%	1%
	Affect lability/ Mood swings	6%	1%
Metabolism and nutrition disorders	Decreased appetite	19%	4%
Nervous system disorders	Headache	10%	5%
	Psychomotor hyperactivity	5%	1%
Cardiovascular	Blood pressure diastolic increased	7%	4%
Gastrointestinal disorders	Vomiting	9%	0%
	Nausea	6%	0%
Infections and infestations	Nasopharyngitis	3%	1%
	Pharyngitis streptococcal	3%	0%
Injury, poisoning and procedural complications	Contusion	3%	0%
Musculoskeletal and connective tissue disorders	Back pain	3%	0%
Skin and subcutaneous tissue disorders	Rash	2%	0%

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably

estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole

Eye Disorders: Diplopia, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Hyperpyrexia

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus, Rashes, Eruptions, and Exanthemas

Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal, Severe hepatic injury

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis

Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Libido changes, Mania

Urogential System: Priapism

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

7 DRUG INTERACTIONS

7.1 MAO Inhibitors

Do not administer JORNAY PM concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAO inhibitors and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to JORNAY PM during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.

Risk Summary

Published studies and postmarketing reports on methylphenidate use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes *[see Data]*. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 2 and 9 times the maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m^2 basis, respectively. However, spina bifida was observed in rabbits at a dose 31 times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre-and post-

natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 3.5 times the MRHD given to adolescents *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

CNS stimulant medications, such as JORNAY PM, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Human Data

A limited number of pregnancies have been reported in published observational studies and postmarketing reports describing methylphenidate use during pregnancy. Due to the small number of methylphenidate-exposed pregnancies with known outcomes, these data cannot definitely establish or exclude any drug-associated risk during pregnancy. Methodological limitations of these observational studies include small sample size, concomitant use of other medications, lack of detail regarding dose and duration of exposure to methylphenidate and nongeneralizability of the enrolled populations.

Animal Data

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 31 times the maximum recommended human dose (MRHD) of 100 mg/day given to adolescents on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (9 times the MRHD given to adolescents on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (6 times the MRHD given to adolescents on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD given to adolescents on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JORNAY PM and any potential adverse effects on the breastfed infant from JORNAY PM or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of JORNAY PM in pediatric patients less than 6 years have not been established.

The safety and effectiveness of JORNAY PM have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical studies in pediatric patients 6 to 12 years, pharmacokinetic data in adults, and safety information from other methylphenidate-containing products *[see Clinical Studies (14) and see Clinical Pharmacology (12.3)*].

The long-term efficacy of methylphenidate in pediatric patients has not been established.

Long-Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including JORNAY PM. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.7)]*.

Juvenile Animal Toxicity Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 2.5 times the maximum recommended human dose (MRHD) of 100 mg/day given to children on a mg/m^2 basis.

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal Day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with ≥ 50 mg/kg/day (approximately ≥ 2.5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis), and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (5 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (0.25 times the MRHD of 100 mg/day given to children on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

JORNAY PM has not been studied in patients older than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

JORNAY PM contains methylphenidate, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including JORNAY PM, other methylphenidate-containing products, and amphetamines, have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration, which can result in overdose and death *[see Overdosage (10)]*.

To reduce the abuse of CNS stimulants including JORNAY PM, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on

proper storage and disposal of CNS stimulants *[see How Supplied/Storage and Handling (16)]*, monitor for signs of abuse while on therapy, and re-evaluate the need for JORNAY PM use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants including JORNAY PM.

Dependence

Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants, including JORNAY PM. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include: dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

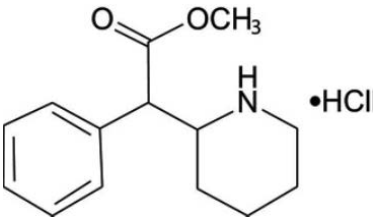
10.2 Management of Overdose

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdosage with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosages. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

11 DESCRIPTION

JORNAY PM contains methylphenidate hydrochloride, a central nervous system (CNS) stimulant.

Methylphenidate hydrochloride is a white, odorless crystalline powder. Its aqueous solutions are acidic. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. The chemical name of methylphenidate hydrochloride is *d,l* (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its molecular formula is $C_{14}H_{19}NO_2$•HCl and the molecular weight is 269.77. Its structural formula is



The molecular formula of the free base is $C_{14}H_{19}NO_2$ and its molecular weight is 233.31.

JORNAY PM extended-release capsules contain beads with two functional film coatings (outer delayed-release and inner extended-release) surrounding a drug core coated with methylphenidate hydrochloride. The outer, delayed-release coating delays the initial release of methylphenidate while the inner extended-release coating controls the release throughout the day. JORNAY PM is available as extended-release capsules for oral use in five strengths. Each capsule contains 20 mg, 40 mg, 60 mg, 80 mg, or 100 mg of methylphenidate hydrochloride, which is equivalent to 17.4 mg, 34.8 mg, 52.2 mg, 69.6 mg, or 87.0 mg of methylphenidate free base, respectively.

JORNAY PM capsules also contain the following inactive ingredients: dibutyl sebacate, diglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer Type B, microcrystalline cellulose, monoglycerides, polysorbate 80, and talc. The capsule shell of 20 and 40 mg strength capsules is made of FD&C Blue #1, hypromellose, titanium dioxide, yellow iron oxide, and black ink for the imprint. The capsule shell of 60 and 80 mg strength capsules is made of FD&C Blue #1, hypromellose, titanium dioxide, and black ink for the imprint. The capsules shell of 100 mg strength capsule is made of black iron oxide, FD&C Blue #1, hypromellose, red iron oxide, titanium dioxide, and black ink, and white ink for the imprint.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant. The exact mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprising the *d*- and *l*-isomers. The *d*-isomer is more pharmacologically active than the *l*-isomer. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

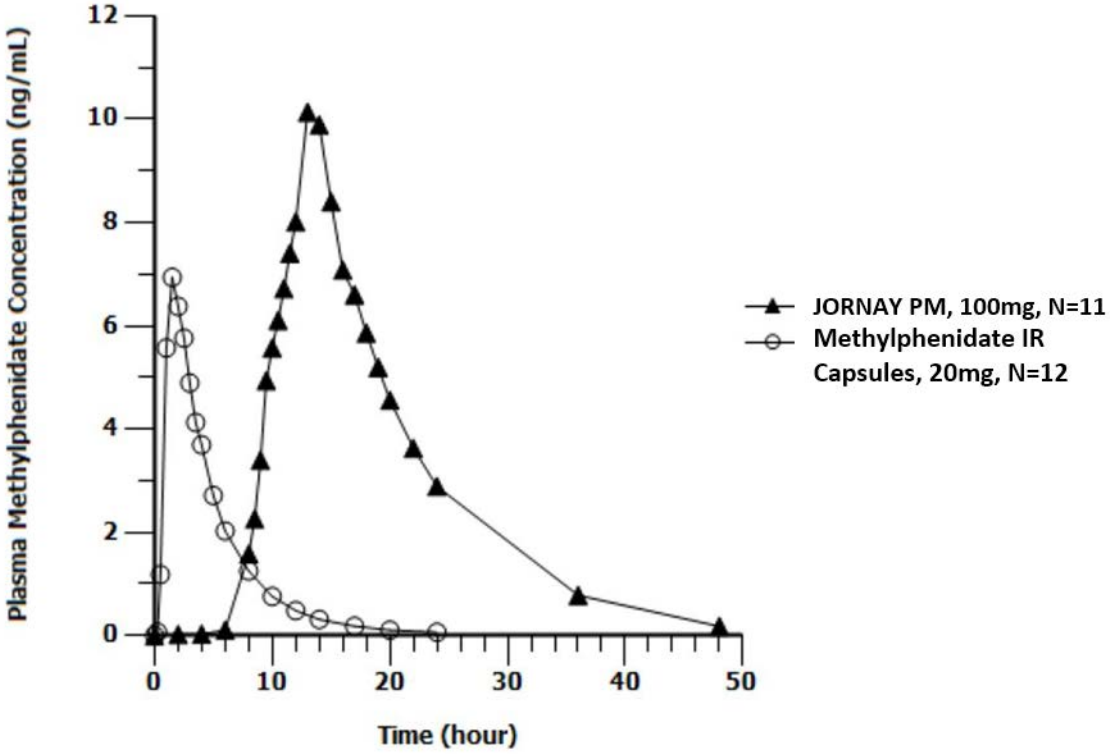
12.3 Pharmacokinetics

The pharmacokinetics of methylphenidate was dose-proportional between 20 mg and 100 mg dose level.

Absorption

The pharmacokinetics of methylphenidate after a single, 100 mg oral dose of JORNAY PM administered in the evening at 9 pm were studied in healthy adults. The initial absorption of methylphenidate into plasma is delayed such that no more than 5% of total drug is available within the first 10 hours after dosing. After the lag period, the absorption of methylphenidate occurs in a single peak with a median T_{max} 14.0 hours, followed by a gradual decline throughout the rest of the day.

Figure 1: Arithmetic Mean Plasma Methylphenidate Concentrations following a Single, Oral, 100 mg Dose of JORNAY PM (Methylphenidate Hydrochloride Extended-Release Capsule) or Methylphenidate Immediate-Release Oral Product Administered in a Crossover Manner to Healthy Adult Subjects



The relative bioavailability of JORNAY PM (given once a day) compared to the same daily dose of a methylphenidate immediate-release oral product (given 3 times a day) in adults is 73.9%.

Food Effects

Compared to the fasted state, JORNAY PM taken with a high-fat meal at night exhibited similar mean $AUC_{0-\infty}$, a 14% lower mean C_{max}, and a median T_{max} extended by approximately 2.5 hours. After JORNAY PM was taken at night, a morning meal had no effect on the pharmacokinetics of methylphenidate.

The pharmacokinetic parameters were similar when JORNAY PM was taken as a whole capsule or when sprinkled on applesauce.

Elimination

The apparent half-life of methylphenidate in adults following oral administration of JORNAY PM was approximately 5.9 hours.

Metabolism

In humans, methylphenidate is metabolized primarily by de-esterification to α-phenyl-piperidine acetic acid (PPAA). The metabolite has little pharmacologic activity.

Excretion

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Alcohol Effect:

In vitro testing showed that approximately 97% of methylphenidate was released from JORNAY PM capsules in 2 hours in the presence of 40% alcohol. The increase in methylphenidate release rate was not observed in the presence of 5 to 20% alcohol. No *in vivo* studies have been conducted to assess the effect of alcohol on drug exposure.

Specific populations:

Pediatric Patients

The pharmacokinetics of methylphenidate after a single, 54 mg oral dose of JORNAY PM administered in the evening at 9 pm were studied in two separate studies in adults and in children and adolescent patients with ADHD between 8 and 17 years of age. The plasma methylphenidate concentration curves were qualitatively similar in healthy adult volunteers, children 8 to 12 years, and adolescents with ADHD. Body weight dose normalized AUC and C_{max} were similar in children, adolescents, and adults. However, there were differences in mean PK parameters between children, adolescents, and adults; children were exposed to higher levels of methylphenidate when provided the same dose of JORNAY PM (C_{max}: children = 11.6 ng/mL, adolescents = 7.2 ng/mL, adults = 6.0 ng/mL; AUC_t: children = 206 ng·hr/mL, adolescents = 106 ng·hr/mL, adults = 83.4 ng·hr/mL).

Patients with Renal Impairment:

There is no experience with the use of JORNAY PM in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of JORNAY PM.

Patients with Hepatic Impairment

There is no experience with the use of JORNAY PM in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 1.5 times the maximum recommended human dose (MRHD) of 100 mg/day given to children on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 2 times the MRHD (children) on a mg/m^2 basis.

In a 24-week carcinogenicity study in the transgenic mouse strain $p53^{+/-}$, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis:

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility:

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 6-times the maximum recommended human dose of 100 mg/day given to adolescents on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of JORNAY PM was established in two clinical studies of JORNAY PM in pediatric patients 6 to 12 years of age (N = 278) who met DSM-5 criteria for ADHD inattentive, hyperactive-impulsive, or combined inattentive/hyperactive-impulsive subtypes.

Study 1 (NCT#02493777), conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week, open-label, dose-optimization phase in which all patients (n = 117) received JORNAY PM (once each evening; flexible dosing from 20 mg to 100 mg), followed by a 1-week, double-blind, placebo-controlled withdrawal phase in which patients were randomized to continue JORNAY PM (n=64; mean dose 67 mg) or switch to placebo (n=53). After 1 week of double-blind treatment, patients were evaluated in an analog classroom over a 12-hour period using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. Possible scores range from 0 (normal/ no impairment) to 78 (maximal impairment). The primary efficacy endpoint was the model-adjusted average of all post-dose SKAMP combined scores measured during the 12-hour analog testing period from 8:00 a.m. to 8:00 p.m. The secondary efficacy measure was the morning subscale of the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R AM), to measure manifestations of ADHD in the early morning. This clinician-rated scale is based on parent interview using three questions and assesses manifestations of ADHD during the early morning period. Possible scores range from 0 (no ADHD manifestations) to 9 (severe ADHD manifestations).

The primary efficacy endpoint, the model-adjusted average of all post-dose SKAMP combined scores measured during the 12-hour analog testing period, was statistically significantly better (lower) for JORNAY PM compared with placebo (Table 2). JORNAY PM showed improvement over placebo at time points (9 and 10 a.m., and 12, 2, 4, 6 and 7 p.m.) on the next day after the evening dosing. Figure 2 shows the LS mean and standard error of SKAMP combined scores at each of the individual time points from 8:00 a.m. to 8:00 p.m. The secondary efficacy endpoint, the PREMB-R AM, was also statistically significantly better (lower) for JORNAY PM versus placebo.

Study 2 (NCT#02520388) was a 3-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in pediatric patients, 6 to 12 years of age. Patients were randomized to an evening dose of 40, 60, or 80 mg JORNAY PM (n=81) or placebo (n=80). The primary efficacy measure was the ADHD Rating Scale (ADHD-RS-IV) Total Score, measuring severity of manifestations throughout the day. Possible scores range from 0 (no ADHD manifestations) to 54 (severe symptoms of both ADHD subtypes). Normative scores range 18 to 29 in ADHD. The secondary efficacy measure was the Before School Functioning Questionnaire (BSFQ), a clinician-rated 20-item questionnaire assessing ADHD manifestations on a severity scale of 0 to 3. BSFQ is intended to assess early morning before school activities from the time the child awakens and some behaviors not specific to early morning. Possible scores range from 0 (no difficulty) to 60 (severe difficulty).

After 3 weeks of treatment, the ADHD-RS-IV total scores were statistically significantly better (lower) for JORNAY PM than placebo (Table 2). The secondary efficacy endpoint, the BSFQ, was also statistically significantly better (lower) for JORNAY PM versus placebo.

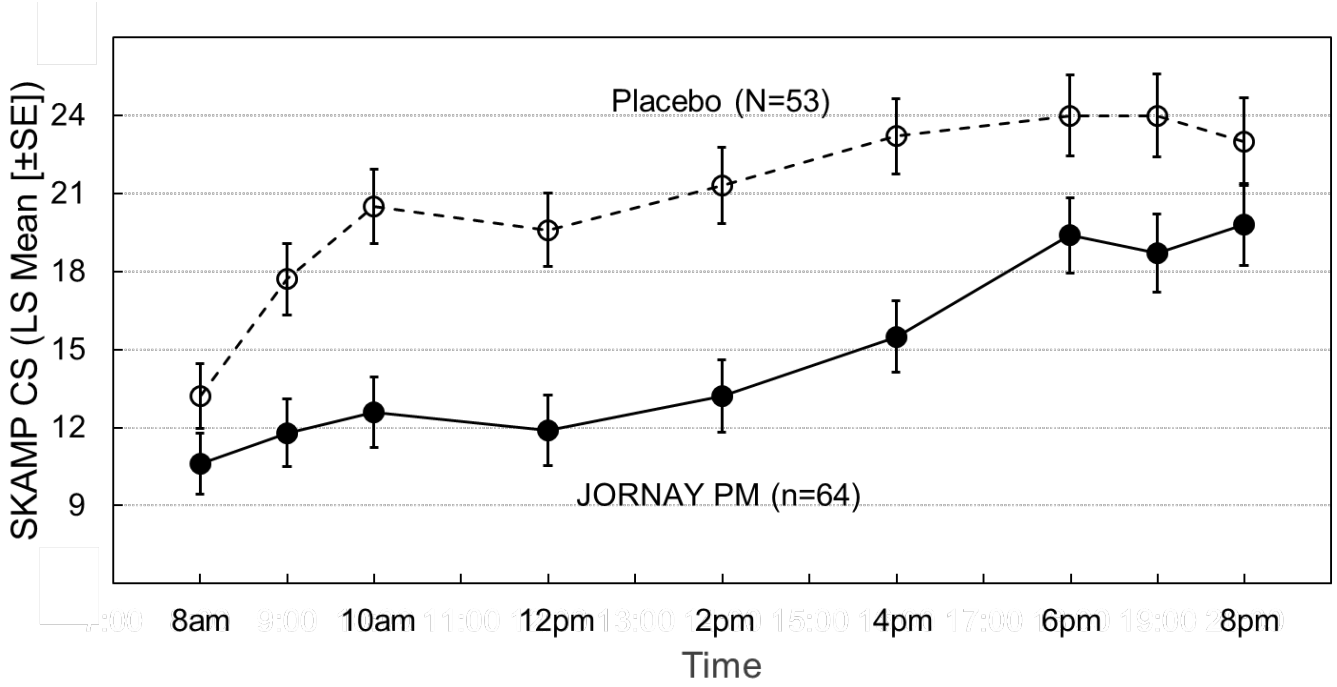
Table 2 summarizes the primary endpoint results for Study 1 and Study 2.

Table 2: Summary of Primary Efficacy Results in Pediatric Patients (6 – 12 years) with ADHD (Studies 1 and 2)

Study Number.	**Measure** (Primary Endpoint)	Treatment Group (#ITT Subjects)	Mean Baseline Score (SD)	LS Mean (SE)	Placebo-subtracted Difference (95% CI)
Study 1	**SKAMP CS Average**	JORNAY PM (64)	NA	14.8 (1.17)	-5.9 (-9.1, -2.7)
		Placebo (53)	NA	20.7 (1.22)	
Study 2	**ADHD-RS-IV**	JORNAY PM (81)	43.1 (7.33)	24.1 (1.50)	-7.0 (-11.4, -2.7)
		Placebo (80)	43.5 (6.84)	31.2 (1.60)	

ITT: Intent-to-treat. SE: Standard Error. SD: Standard Deviation. CI: Confidence Interval. NA: Not Available.
CS: Combined Score (sum of items 1-13)

Figure 2: Study 1—LS Mean SKAMP Combined Score on Day after Final Treatment, as Measured in an Analogue Classroom, N=117



LS = Least Squares; CS = Combined Score (sum of items 1-13); N= Sample Size; SE = Standard Error

16 HOW SUPPLIED/STORAGE AND HANDLING

JORNAY PM (methylphenidate hydrochloride) extended-release capsules are available as follows:

20 mg Capsules – ivory opaque body and light green opaque cap (imprinted with “20 mg” in black on the body and “IRONSHORE” in black on the cap)
Bottles of 100.....……NDC 71376-201-03
40 mg Capsules – ivory opaque body and blue-green opaque cap (imprinted with “40 mg” in black on the body and “IRONSHORE” in black on the cap)

Bottles of 100.....……NDC 71376-202-03
60 mg Capsules – white opaque body and powder blue opaque cap (imprinted with “60 mg” in black on the body and “IRONSHORE” in black on the cap)
Bottles of 100.....……NDC 71376-203-03
80 mg Capsules – white opaque body and light blue opaque cap (imprinted with “80 mg” in black on the body and “IRONSHORE” in black on the cap)
Bottles of 100.....…… NDC 71376-204-03
100 mg Capsules – white opaque body and dark blue opaque cap (imprinted with “100 mg” in black on the body and “IRONSHORE” in white on the cap)
Bottles of 100.....……NDC 71376-205-03

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Protect from humidity.

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired JORNAY PM by a medicine take-back program or by an authorized collector registered with the Drug Enforcement Administration. If no take-back program or authorized collector is available, mix JORNAY PM with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard JORNAY PM in the household trash.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/Potential for Abuse and Dependence

Advise patients that JORNAY PM is a federally controlled substance, and it can be abused or lead to dependence *[see Drug Abuse and Dependence (9.1, 9.2, 9.3)]*. Instruct patients that they should not give JORNAY PM to anyone else. Advise patients to store JORNAY PM in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired JORNAY PM through a medicine take-back program if available *[Warnings and Precautions (5.1), Abuse and Dependence (9.2, 9.3), How Supplied/Storage and Handling (16)]*.

Dosage and Administration Instructions

Advise patients that JORNAY PM is taken once daily in the evening. Advise patients that JORNAY PM should not be taken in the morning. It should be taken consistently, either with food or without food, and patients should establish a routine pattern of administration time.

For patients who take JORNAY PM sprinkled over applesauce, the contents of the entire capsule should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. When initiating treatment with JORNAY PM, provide dosage escalation and administration instructions *[see Dosage and Administration (2)]*.

Advise patients that if they forget to take JORNAY PM at their regularly scheduled time, they may take it as soon as they remember that same evening. If a patient remembers the following morning that they forgot to take their JORNAY PM dose the evening before, advise the patient to wait until their next scheduled evening administration.

Serious Cardiovascular Risks

Advise patients that there is a potential for serious cardiovascular risks including sudden death, myocardial infarction, stroke, and hypertension with JORNAY PM use. Instruct patients to contact a healthcare provider

immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Blood Pressure and Heart Rate Increases

Advise patients that JORNAY PM can cause elevations in blood pressure and heart rate *[see Warnings and Precautions (5.3)]*.

Psychiatric Risks

Advise patients that JORNAY PM, at recommended doses, can cause psychotic or manic symptoms, even in patients without a prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Priapism

Advise patients, caregivers, and family members of the possibility of painful or prolonged penile erections (priapism). Instruct the patient to seek immediate medical attention in the event of priapism *[see Warnings and Precautions (5.5)]*.

Circulation Problems in Fingers and Toes [peripheral vasculopathy, including Raynaud's phenomenon]

- Instruct patients about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change from pale, to blue, to red.
- Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.
- Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking JORNAY PM.
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Suppression of Growth

Advise patients, caregivers, and family members that JORNAY PM can cause slowing of growth and weight loss *[see Warnings and Precautions (5.7)]*.

Alcohol Effect

Advise patients to avoid alcohol, while taking JORNAY PM. Consumption of alcohol while taking JORNAY PM may result in a more rapid release of the dose of methylphenidate *[see Clinical Pharmacology (12.3)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to JORNAY PM during pregnancy *[see Use in Specific Populations (8.1)]*.

Packaged by:
Patheon Puerto Rico, Inc.
Manatí, Puerto Rico, 00674 USA

Manufactured for:
Ironshore Pharmaceuticals, Inc.
Cherry Hill, NJ, 08002 USA

MEDICATION GUIDE
JORNAY PM (JOR-nay)
(methylphenidate hydrochloride)
extended-release capsules, CII

What is the most important information I should know about JORNAY PM?

JORNAY PM can cause serious side effects, including:

- **Abuse and dependence.** JORNAY PM contains methylphenidate. JORNAY PM, other methylphenidate containing products, and amphetamines, have a high chance for abuse and can cause physical and psychological dependence. Your healthcare provider should check you or your child for signs of abuse and dependence before and during treatment with JORNAY PM.
  - Tell your healthcare provider if you or your child has ever abused or been dependent on alcohol, prescription medicines, or street drugs.
  - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **Heart-related problems, including:**
  - sudden death, stroke, and heart attack in adults
  - sudden death in children who have heart problems or heart defects
  - increased blood pressure and heart rate

  Your healthcare provider should check you or your child carefully for heart problems before starting JORNAY PM. Tell your healthcare provider if you or your child has any heart problems, heart defects, or high blood pressure.

  Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with JORNAY PM.

  Call your healthcare provider right away or go to the nearest hospital emergency room right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with JORNAY PM.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior and thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

  Tell your healthcare provider about any mental problems you or your child has, or about a family history of suicide, bipolar illness, or depression.

  Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with JORNAY PM, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What is JORNAY PM?

JORNAY PM is a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in people 6 years of age and older. JORNAY PM may help increase attention and decrease impulsiveness and hyperactivity in people 6 years of age and older with ADHD.

It is not known if JORNAY PM is safe and effective in children under 6 years of age.

JORNAY PM is a federally controlled substance (CII) because it contains methylphenidate that can be a target for people who abuse prescription medicines or street drugs. Keep JORNAY PM in a safe place to protect it from theft. Never give your JORNAY PM to anyone else, because it may cause death or harm them. Selling or giving away JORNAY PM may harm others, and is against the law.

Who should not take JORNAY PM?

Do not take JORNAY PM if you or your child is:

- allergic to methylphenidate hydrochloride, or any of the ingredients in JORNAY PM. See the end of this Medication Guide for a complete list of ingredients in JORNAY PM.
- taking or has taken within the last 14 days, a medicine used to treat depression called a monoamine oxidase inhibitor (MAOI).

Before taking JORNAY PM, tell your or your child's healthcare provider about all medical conditions, including if you or your child:

- have heart problems, heart defects, or high blood pressure

- have mental problems including psychosis, mania, bipolar illness, or depression, or have a family history of suicide, bipolar illness, or depression
- have circulation problems in fingers or toes
- are pregnant or plan to become pregnant. It is not known whether JORNAY PM will harm your unborn baby.
  - There is a pregnancy registry for females who are exposed to JORNAY PM during pregnancy. The purpose of the registry is to collect information about the health of females exposed to JORNAY PM and their baby. If you or your child becomes pregnant during treatment with JORNAY PM, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants. You can register by calling 1-866-961-2388.
- are breastfeeding or plan to breastfeed. JORNAY PM passes into breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with JORNAY PM.

Tell your healthcare provider about all of the medicines that you or your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

JORNAY PM and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted during treatment with JORNAY PM.

Your healthcare provider will decide whether JORNAY PM can be taken with other medicines.

Especially tell your healthcare provider if you or your child takes medicine to treat depression, including MAOIs.

Know the medicines that you or your child takes. Keep a list of the medicines with you to show your healthcare provider and pharmacist when you or your child get a new medicine.

Do not start any new medicine during treatment with JORNAY PM without talking to your or your child's healthcare provider first.

How should JORNAY PM be taken?

- Take JORNAY PM exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose and timing of the JORNAY PM dose if needed.
- **Take JORNAY PM by mouth 1 time each day in the evening between 6:30 p.m. and 9:30 p.m.**
- Take JORNAY PM at the same time each evening. JORNAY PM **should not** be taken in the morning.
- JORNAY PM can be taken with or without food, but take it the same way each time.
- JORNAY PM capsules may be swallowed whole, or if JORNAY PM capsules cannot be swallowed whole, the capsules may be opened and sprinkled onto applesauce. Make sure to sprinkle all the JORNAY PM onto the applesauce. The JORNAY PM dose should not be divided.
  - swallow **all** the applesauce and medicine mixture right away
  - **do not** chew the applesauce and medicine mixture
  - **do not** store the applesauce and medicine mixture
- Your healthcare provider may sometimes stop JORNAY PM treatment for a while to check for ADHD symptoms.
- If a dose of JORNAY PM is missed, it should be taken as soon as you remember the same evening. If you do not remember until the next morning you should not take the dose. Wait until that evening to take the next scheduled dose. **A missed dose should not be taken in the morning.**
- If you or your child takes too much JORNAY PM, call your healthcare provider or go to the nearest hospital emergency room right away.

What should be avoided during treatment with JORNAY PM?

- Avoid drinking alcohol during treatment with JORNAY PM. This may cause a faster release of the JORNAY PM medicine.

What are possible side effects of JORNAY PM?

JORNAY PM can cause serious side effects, including:

- See **"What is the most important information I should know about JORNAY PM?"**
- **Painful and prolonged erections (priapism).** Priapism has happened in males who take products that contain methylphenidate. If you or your child develops priapism, get medical help right away.
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon). Signs and symptoms may include:**
  - fingers or toes may feel numb, cool, or painful
  - fingers or toes may change color from pale, to blue, to red

Tell your healthcare provider if you or your child has numbness, pain, skin color change, or sensitivity to temperature in the fingers or toes.

Call your healthcare provider right away if you or your child has any signs of unexplained wounds appearing on fingers or toes during treatment with JORNAY PM.

- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with JORNAY PM. JORNAY PM treatment may be stopped if your child is not gaining weight or height.

The most common side effects of methylphenidate products in children, adolescents, and adults with ADHD include:

- decreased appetite
- trouble sleeping
- nausea
- vomiting
- indigestion
- stomach pain
- weight loss
- anxiety
- dizziness
- irritability
- mood swings (affect liability)
- increased heart rate
- increased blood pressure

The most common side effects of JORNAY PM, in children age 6 to 12 with ADHD include:

- trouble sleeping
- decreased appetite
- restlessness (psychomotor hyperactivity)
- headache
- nausea
- mood swings
- vomiting

These are not all the possible side effects of JORNAY PM.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JORNAY PM?

- Store JORNAY PM at room temperature between 68°F to 77°F (20°C to 25°C).
- Store JORNAY PM in a safe place, like a locked cabinet. Protect from humidity.
- Dispose of remaining, unused, or expired JORNAY PM by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix JORNAY PM with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away JORNAY PM in the household trash.

Keep JORNAY PM and all medicines out of the reach of children.

General information about the safe and effective use of JORNAY PM.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use JORNAY PM for a condition for which it was not prescribed. Do not give JORNAY PM to other people, even if they have the same symptoms. It may harm them, and it is against the law.

You can ask your doctor or pharmacist for information about JORNAY PM that is written for healthcare professionals.

What are the ingredients in JORNAY PM?

Active Ingredient: methylphenidate hydrochloride

Inactive Ingredients: dibutyl sebacate, diglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer Type B, microcrystalline cellulose, monoglycerides, polysorbate 80, and talc.

The capsule shell of 20 and 40 mg strength capsules contains FD&C Blue #1, hypromellose, titanium dioxide, yellow iron oxide, and black ink for the imprint. The capsule shell of 60 and 80 mg strength capsules contains FD&C Blue #1, hypromellose, titanium dioxide, and black ink for the imprint. The capsules shell of 100 mg strength capsule contains black iron oxide, FD&C Blue#1, hypromellose, red iron oxide, titanium dioxide, black ink, and white ink for the imprint.

Manufactured for Ironshore Pharmaceuticals, Inc.:

For more information about JORNAY PM go to www.jornaypm.com or call 1-877-938-4766.

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Early Morning Functioning in Stimulant-Treated Children and Adolescents with Attention-Deficit/Hyperactivity Disorder, and its Impact on Caregivers

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Abstract

Objective: The purpose of this study was to examine the temporal occurrence and severity of inadequate attention-deficit/hyperactivity disorder (ADHD) symptom control throughout the day, and, more specifically, the frequency and severity of associated functional impairments and their apparent emotional impact on parents and caregivers during the early morning routine before school, in children and adolescents with ADHD currently treated with stable doses of stimulant medications.
Methods: Information was obtained from 201 primary caregivers of children and adolescents with ADHD using a self-administered, on-line quantitative research survey.
Results: Inadequately controlled ADHD symptoms were rated as most severe during the evening homework time and the early morning routine. The majority of caregivers reported early morning ADHD symptoms and impairment of early morning functioning (EMF) as moderate to severe. Caregiver reactions to their child's early morning ADHD symptoms and unwanted behaviors included feeling overwhelmed, exhausted, and constantly stressed.
Conclusions: Control of EMF impairments from inadequately controlled ADHD symptoms is a significant unmet need in children and adolescents with ADHD treated with stable morning doses of stimulant medications. Current orally administered stimulant treatment options have not addressed this challenge.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is among the most common childhood psychiatric conditions (Pliszka and AACAP Work Group on Quality Issues 2007) with an estimated prevalence range of 5.9–7.1% in children and adolescents (Willcutt 2012). According to the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. (DSM-V), the essential diagnostic feature of ADHD is a persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning or development (American Psychiatric Association 2013). In order to meet the diagnostic criteria for ADHD, there must be clear evidence of interference with, or the reduced quality of, social, academic, or occupational functioning attributable to the symptoms (American Psychiatric Association 2013). A host of studies have associated ADHD in children and adolescents with significant behavioral consequences including psychopathology, school and occupational failure, family and peer difficulties, emotional problems, and low self-esteem (Shaw et al. 2012). Additionally, ADHD has also been shown to have negative effects on families as a whole, such as disturbed interpersonal relationships, less perceived family cohesiveness and greater conflict, depression in parents, and higher incidences of divorce and separation (Wymbs et al. 2008; Chang et al. 2013; Gau and Chang 2013). Accordingly, the American Academy of Child and Adolescent Psychiatry Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder recommends that a well-thought-out and comprehensive treatment plan for patients with ADHD should consist of psychopharmacologic and/or behavior therapy (Pliszka and AACAP Work Group on Quality Issues 2007).

Behavioral symptoms in children with ADHD have been shown to fluctuate across the day (Antrop et al. 2005). Stimulant-based medications such as methylphenidate (MPH) and amphetamines (AMP) have been the cornerstone of ADHD pharmacotherapy for several decades (Pliszka and AACAP Work Group on Quality Issues 2007), and their temporal effects on behavioral symptoms in children and adolescents have been assessed at different times throughout the day. The earliest temporal assessments of stimulant treatment effect focused on adequate control of ADHD symptoms in school. In the last decade, the temporal effects of stimulant medications in controlling ADHD symptoms have evolved in parallel with the evolution of numerous long-acting, extended-

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release (ER) stimulant medications; to include both in-school and after-school symptom control.

Although it is known that many home-based difficulties for children and adolescents with ADHD occur before the school day begins (Whalen et al. 2006) and that the time from awakening to arrival at school may represent up to 20% of the day (~ 2–3 hours) for children and adolescents with ADHD and their families (Wilens et al. 2010), little is known about the specific nature of early morning functioning (EMF) impairments in stimulant-treated children and adolescents with ADHD or the impact of these impairments on caregivers.

Recent interest has now begun to focus on the issue of inadequately controlled ADHD symptoms that occur during the early morning hours before the school day begins and to date, three pharmacotherapy-based efficacy studies have addressed the effects of different MPH formulations on EMF in children and adolescents with ADHD (Sangal et al. 2006; Wilens et al. 2010; Döpfner et al. 2011). The earliest of the published studies was a randomized, double-blind, crossover trial designed to assess the effects of three-times-daily administration of immediate-release (IR) MPH (before 8:00 a.m., at or near noon, and between 4:00 and 5:00 p.m.) versus twice daily atomoxetine on sleep parameters in 85 children and adolescents ages 6–14 with ADHD (Sangal et al. 2006). The 13 item Daily Parent Rating of Evening and Morning Behavior (DPREMB) scale was among the study's secondary outcome measures and included caregiver ratings of core ADHD symptoms and behavioral problems typically experienced by children with ADHD in the early morning (4 items) and late afternoon/evening (9 items) (Michelson et al. 2002). The results of the study pertaining to improvements in EMF demonstrated that atomoxetine was shown to have significant beneficial treatment effects on two of the four EMF items as compared to the thrice-daily IR MPH regimen. The mean changes from baseline on the DPREMB for the morning subscale score were −1.18 for atomoxetine and −0.41 for IR MPH, which was statistically significant favoring atomoxetine ($p < 0.001$). When looking specifically at the treatment effect for the IR-MPH group on the DPREMB (morning) parent-rated questions, ''How difficult was it to get your child out of bed this morning?'', ''How much difficulty did your child have getting ready this morning?'', ''How much was your child arguing or struggling excessively this morning?'', and ''How irritable and quick was your child to lose his or her temper this morning?'', the mean change scores compared with baseline values ranged from 0.03 (worsening) to −0.22 (minor improvement). In summary, oral administration of IR-MPH before 8:00 a.m. did not demonstrate statistically significant improvements in early morning ADHD symptoms and behaviors in children and adolescents when compared with baseline values (Sangal et al. 2006).

The second study (Döpfner et al. 2011), was a non-interventional, non-controlled, multicenter, prospective, observational, postmarketing surveillance study, which assessed the efficacy of a once-daily modified-release MPH formulation in 822 children and adolescents with ADHD ages 6–17 years. Although the time of dosing was not specified, most once-daily ADHD medications are administered in the morning immediately after awakening or at breakfast time. As a secondary measure, this study used the parent version of the Day Profile of ADHD Symptoms (DAYAS-P) questionnaire, a new rating scale that assesses the daily profile of ADHD externalizing symptoms from early morning until bedtime (Breuer et al. 2011). Data from the DAYAS-P questionnaire indicated that treatment resulted in statistically significant improvement ($p < 0.001$) in the total score for morning/before-school symptoms and behavioral problems from visit 1 (1.37 ± 0.77) to visit 3 (1.02 ± 0.72), and for the ADHD symptom score for the morning before school from visit 1 (1.38 ± 0.71) to visit 3 (1.02 ± 0.78), although the Cohen's d for effect size for both ratings was rather low (0.51 and 0.47, respectively) (Döpfner et al. 2011).

Only one randomized, placebo-controlled study has focused exclusively on inadequately controlled ADHD symptoms and associated EMF impairments in children ages 6–12 years with ADHD by examining the efficacy of a transdermal MPH formulation (MTS) administered once-daily between 6:00 and 7:00 a.m. (Wilens et al. 2010). The study's primary outcome measures include the ADHD-Rating Scale (ADHD-RS) and ADHD-AM-RS (for the time period 6:00–9:00 a.m. only). This study also included a new clinician-rated and completed 20 item questionnaire (the Before-School Functioning Questionnaire [BSFQ]) as a secondary outcome measure. The questionnaire was generated from commonly reported areas of dysfunction in the early morning (6:00–9:00 a.m.), before-school activities associated with ADHD symptomatology, such as breakfast, hygiene, time awareness, and getting to school. The psychometric properties of the BSFQ have recently been validated by Faraone et al. (2015). Results of the study demonstrated significant reductions with MTS compared to placebo for the ADHD-RS total score ($p < 0.001$), ADHD-AM-RS ($p = 0.003$), and BSFQ total score ($p = 0.001$). Of the 20 before-school items that comprised the BSFQ, only three did not show statistically significant differences ($p < 0.05$) between the transdermal MPH- and placebo-treated groups (''Did your child have difficulty with: being quiet; awaiting his/her turn; and getting to school?''). There was a 69% reduction in the subjects' total score for transdermal MPH versus a 23% reduction for transdermal placebo. The items that had the largest difference in favor of transdermal MPH versus placebo included listening, following directions, attention, distraction, and hygiene ($p < 0.01$) (Wilens et al. 2010).

When viewed collectively, the results from the two aforementioned pharmacologic studies with orally administered MPH suggesting that the acute treatment has benefits for inadequately controlled early morning ADHD symptoms and associated behaviors are inconclusive. These mixed results also suggest the need for further research on EMF impairments in stimulant-treated children and adolescents with ADHD. Further, these three studies appear to suggest a need for a more formalized assessment of EMF, as well as a need for further exploration regarding the mechanisms by which pharmacotherapies may improve some aspects of early morning ADHD symptoms and functioning, as opposed to others.

In addition to pharmacotherapeutic efficacy studies, one large, on-line, parent-completed questionnaire survey study conducted in Europe was designed to examine the impact of ADHD on their children's/adolescent's everyday activities, general behavior, and family relationships, and to assess the effect of stimulant medications on the behaviors of their children and adolescents with ADHD during times of day when parents have the closest contact with their children and adolescents, such as the early morning (Coghill et al. 2008). Survey results demonstrated that a significantly higher percentage of children and adolescents ages 6–18 years with ADHD receiving stimulant medication experienced impaired functioning during their morning routine (from 7:00 to 8:00 a.m.; waking up, getting ready for school) compared with unmedicated children and adolescents with ADHD (55% vs. 36%, respectively; $p < 0.05$). Additionally, parents reported that children and adolescents with ADHD receiving 12 hour stimulant medications experienced greater levels of functional impairments during the morning routine than those receiving 6–8 hour stimulant medications. Coghill et al. noted a possible limitation of the study in that traditionally in

Europe, the most severely symptomatic and impaired ADHD children and adolescents are the ones who are treated with stimulant medications (in general) and further, that longer acting stimulant medications (12 hour) are often reserved for the most severely ill patients whereas the 6–8 hour medications are typically utilized for less severely ill ADHD patients. Therefore, this stratification of ADHD patient symptom severity assignment to stimulant treatment and use of modified-release formulations specifically for the most highly symptomatic patients, may account for the apparent diminished benefit of stimulant treatment on early morning ADHD symptoms reported by the authors. Importantly, this large quantitative research survey study clearly detected evidence of early morning ADHD symptomatology and related EMF impairments in children and adolescents treated with stimulant medications. In aggregate, the survey's EMF findings add further evidence to pharmacologic studies in suggesting that morning administration of oral stimulant medications may not provide meaningful clinical control of early morning ADHD symptoms, so as to improve functioning during the school-age child's early morning routines (Coghill et al. 2008).

In summary, a review of the current ADHD clinical literature would suggest that despite recent formulation advances in oral stimulant medications designed to provide increasingly longer duration of treatment benefit throughout the day, very little is known about the specific prevalence, frequency, and severity of inadequately controlled ADHD symptoms and related EMF impairments that likely occur during the early morning routine in stimulant-treated children and adolescents.

The objectives of this parent self-report-based, quantitative research survey were to determine the temporal occurrence and severity of inadequately controlled ADHD symptoms throughout the day in children and adolescents with ADHD who are currently treated with stable doses of stimulant medications. More importantly, the survey allowed for a quantitative exploration of the temporal occurrence, frequency, and severity of inadequately controlled ADHD symptoms specifically related to the early morning hours of the day, before school; as well as detailed descriptions of related functional impairments, unwanted behaviors and their apparent emotional impact on parents and caregivers.

Methods

Survey development and description

This self-administered, anonymous, on-line quantitative research survey was conducted between December 31, 2012 and January 24, 2013. An on-line, primary caregiver-completed questionnaire was designed with input from experts in the field of child and adolescent psychiatry to determine from parent self-reports if inadequately controlled ADHD symptoms exist in children and adolescents with ADHD who are currently treated with stable doses of stimulant medications. Second, parents were asked to define these inadequately controlled ADHD symptoms, if present, with respect to their temporal occurrence and severity. Of particular interest were the detailed responses of those parents who identify the ''Early Morning Routine,'' defined in the survey as ''from the moment the child/adolescent awakens to the time they leave for school'' and including activities such as getting out of bed, getting dressed, brushing teeth, sitting down for breakfast, having breakfast, and getting ready to leave the household, as a problematic time period for the inadequate control of ADHD symptoms. Caregivers who identified inadequately controlled ADHD symptoms during the Early Morning Routine (Likert severity rating > 2) were asked to continue the survey by answering a series of multiple choice and open-ended questions. This portion of the survey allowed respondents to provide detailed descriptions of related functional mpairments and unwanted behaviors that manifest from these inadequately controlled ADHD symptoms. Additionally, it allowed for assessment of their ADHD symptom severity and frequency of early morning ADHD symptom occurrence across the weekdays when school was in session.

The survey contained 32 primary questions and 30 subquestions for a total of 62 questions. On average, the time taken for primary caregivers of children/adolescents with ADHD to complete the survey was 20 minutes.

This study was sponsored by Ironshore Pharmaceuticals & Development, Inc. and conducted by Repass & Partners, an experienced market research firm. The survey did not contain any option for any of the 18 standard types of protected health information (PHI) data to be collected. Surveys were completed voluntarily and anonymously. Caregiver respondents were blinded as to the research sponsor, and the survey was conducted in accordance with and adherence to The Marketing Research Association's (MRA) Code of Marketing Research Standards (Marketing Research Organization 2013).

Sampling strategy

Parent/primary caregiver research respondents were derived from nationally representative consumer research panels consisting of both presumed or known households of children and adolescents with ADHD ($n = 10{,}750$). To ensure that 200 surveys were completed, an additional invitation was sent to households with unknown child/adolescent-ADHD diagnostic status ($n = 142{,}999$). Primary caregivers who volunteered to participate in the survey first completed a screening questionnaire to ensure that the following requisite inclusion criteria were met prior to beginning the general survey: 1) Must be the parent (≥65% of completed surveys) or primary caregiver for a child/adolescent 6–17 years of age diagnosed with ADHD and 2) that child or adolescent's primary ADHD medication must be a stimulant medication and 3) the dosage of the stimulant medication must have been stable for at least 3 months prior to taking the survey. Caregivers who were employed by a physician, a hospital, a pharmaceutical manufacturer, or a pharmacy or marketing research firm were not eligible to participate.

Eligible respondents were subsequently screened to assess for the presence of inadequately controlled ADHD symptoms at any time throughout the day. If inadequately controlled ADHD symptoms were present, the caregiver was asked to identify in which of the following temporal periods of the day did the symptoms manifest and at what severity level (Likert scale 1–10): 1) The Early Morning Routine, 2) During the School Day, 3) Afternoon Homework Time, 4) Dinner Time, 5) Evening Homework Time, and 6) Bedtime.

Results

A total of 2013 caregivers volunteered to participate in the survey and 290 (14.0%) met the requisite screening criteria and entered into the formal survey; 280 respondents (97.0%) identified at least one temporal period of the day when their child's/adolescent's ADHD symptoms were inadequately controlled and 264 caregivers (91.0%) specifically identified the Early Morning Routine as a time period when inadequately controlled ADHD

symptoms manifested with at least mild severity (Likert scale ≥ 2). A total of 201 caregivers completed the entire survey, including the specific details for how the Early Morning Routine was impacted by these inadequately controlled ADHD symptoms; therefore, this is the number that was used for the majority of the analyses.

Adult respondent and child/adolescent patient demographic information is presented in Tables 1 and 2, respectively. Among respondents, 45.3% (91/201) were between the ages of 36 and 45, 33.3% (67/201) had completed college, 25.9% (52/201) reported earning $50,000–75,000 per year, and 72.6% (146/201) reported being the mother of a child/adolescent with ADHD. Almost half (46.3%, 93/201) reported that there were two children/adolescents living in the household, and 50.1% (236/471) reported that the age of all children/adolescents living in the household was between 6 and 12 years and that 55.0% (259/471) of all the children/adolescents living in the household were male. The majority (87.1%, 175/201) reported that only one child/adolescent in the household was receiving stimulant treatment for ADHD. As for the child/adolescent patients reported on by caregivers in completed surveys, 71.1% (143/201) were male, 59.7% (120/201) were 6–12 years of age, and the mean age was 11.3 years. The majority had been diagnosed with the combined subtype of ADHD (78.6%, 158/201) and smaller numbers were diagnosed with the inattentive (12.9%, 26/201) and hyperactive-impulsive (8.5%, 17/201) subtypes. Two thirds (67.0%, 135/201) of the children and adolescents reported on by their caregivers had been diagnosed with one or more of nine comorbidities examined. The most frequently diagnosed comorbid conditions for these children and adolescents with ADHD were learning disability (37.8%, 76/201), anxiety (31.3%, 63/201), and oppositional defiant disorder (ODD) (24.4%, 49/201). Subgroup analyses of caregiver respondent ratings indicated that early morning ADHD symptom scores were higher for Medicaid patients than for those with commercial insurance, for children (6–12) than for adolescents (13–17), for children diagnosed with comorbid ODD than for those without, and for children taking a supplemental ADHD medication in addition to their primary stimulant medication than for those who were not.

Table 1. Adult Respondent Demographic Information

	n *(%)*
Age of respondent (years)	
18–25	1/201 (0.5)
26–35	62/201 (30.8)
36–45	91/201 (45.3)
46–55	40/201 (19.9)
56–65	7/201 (3.5)
Education level of respondent	
High school	31/201 (15.4)
Trade/Technical school	12/201 (6.0)
Some college	63/201 (31.3)
College graduate	67/201 (33.3)
Masters/Advanced degree	28/201 (13.9)
Income level of respondent	
< $30,000	35/201 (17.4)
$30,000–$49,999	45/201 (22.4)
$50,000–$74,999	52/201 (25.9)
$75,000–$99,999	32/201 (15.9)
$100,000–$124,999	17/201 (8.5)
≥ $125,000	19/201 (9.5)
Refused to answer/Did not know	1/201 (0.5)
Respondent relationship to child/adolescent with ADHD	
Mother	146/201 (72.6)
Father	36/201 (17.9)
Other	19/201 (9.5)
Total number of children/adolescents in the household	
1	45/201 (22.4)
2	93/201 (46.3)
3	32/201 (15.9)
4	19/201 (9.5)
≥ 5	12/201 (6.0)
Age of all children/adolescents in the household (years)	
< 6	74/471 (15.7)
6–12	236/471 (50.1)
13–17	161/471 (34.2)
Gender of all children/adolescents in the household	
Male	259/471 (55.0)
Female	212/471 (45.0)
Number of children/adolescents in the household taking ADHD medication	
1	175/201 (87.1)
2	24/201 (11.9)
3	2/201 (1.0)

ADHD, attention-deficit/hyperactivity disorder.

MPH HCl ER was the most frequently reported primary ADHD medication (30.3%, 61/201), and 59.7% (120/201) of these children/adolescents with ADHD were not receiving any supplemental ADHD medications. Of those who did receive supplemental ADHD medications, AMP and dextroamphetamine mixed salts, IR (9.0%, 18/201), MPH HCl IR (7.0%, 14/201), and MPH HCl ER (7.0%, 14/201) were the most frequently used. Almost one third of subjects were reported to have been taking their primary ADHD medication for 6–12 months (30.8%, 62/201), and an equal number had been receiving their primary ADHD medication for > 2 years. Approximately two thirds of the patients (67.2%, 135/201) received their primary ADHD medication once daily and 65.7% (132/201) were taking their primary stimulant medication 7 days a week during the school year for ADHD symptom management. Most (33.3%, 103/309) of the patients were administered this medication at 7 a.m., whereas 6 p.m. to midnight and 8 a.m. were the second and third most common administration times of day, respectively (16.5%, 51/309 and 13.9%, 43/309). For those patients receiving supplemental medication, most (23.4%, 26/111) were administered with this medication between 6 p.m. and midnight. Regarding frequency of follow-up with the physician charged with treating patients with ADHD, most (87/201, 43.3%) were followed up more than three times per year.

When asked to rate the overall severity of treated patient ADHD symptoms on a 10 point scale where 1 indicated no ADHD symptoms and 10 indicated significant ADHD symptoms, respondents reported an average score of 5.45 (Fig. 1). Symptoms of ADHD were regarded as most severe during the Early Morning Routine (6.45) and Evening Homework (6.46) times of day. The average level of overall functional impairment caused by ADHD symptoms during the Early Morning Routine time of day was rated by respondents as 6.09 on a 10 point scale, where 1 indicated mild impairment and 10 indicated severe impairment (Fig. 2). More specifically, 59.7% (120/201) of caregivers reported overall ADHD symptoms throughout the day as moderate to severe (ADHD symptom score 5–10) and concordantly, 75.6% (152/201) of parents reported impairment of EMF as moderate to severe (Early Morning Impairment of Functioning score 5–10).

Almost three quarters of respondents reported that easy distractibility (74.1%, 149/201) and failure to listen (72.6%, 146/201)

Table 2. Child/Adolescent Patient Demographic Information

	n (%)
Gender	
Male	143/201 (71.1)
Female	58/201 (28.9)
Age	
6–12	120/201 (59.7)
13–17	81/120 (40.3)
ADHD subtype	
Hyperactive/impulsive	17/201 (8.5)
Inattentive	26/201 (12.9)
Combined	158/201 (78.6)
Primary ADHD medication	
Methylphenidate HCl, ER	61/201 (30.3)
Amphetamine, dextroamphetamine mixed salts, ER	51/201 (25.4)
Methylphenidate HCl, IR	25/201 (12.4)
Lisdexamfetamine dimesylate	25/201 (12.4)
Dexmethylphenidate HCl, IR, and ER	18/201 (9.0)
Amphetamine, dextroamphetamine mixed salts, IR	18/201 (9.0)
Methylphenidate transdermal	3/201 (1.5)
Supplemental ADHD medication	
Methylphenidate HCl, ER	14/201 (7.0)
Amphetamine, dextroamphetamine mixed salts, ER	13/201 (6.5)
Dexmethylphenidate HCl, IR, and ER	4/201 (2.0)
Lisdexamfetamine dimesylate	2/201 (1.0)
Amphetamine, dextroamphetamine mixed salts, IR	18/201 (9.0)
Methylphenidate HCl, IR	14/201 (7.0)
Guanfacine HCl, ER	7/201 (3.5)
Atomoxetine HCl	4/201 (2.0)
Methylphenidate transdermal	1/201 (0.5)
Other	4/201 (2.0)
None	120/201 (59.7)
Length of time taking primary ADHD medication	
3–6 months	25/201 (12.4)
6–12 months	62/201 (30.8)
1–2 years	52/201 (25.9)
>2 years	62/201 (30.8)
Number of times per day taking primary medication	
Once	135/201 (67.2)
Twice	49/201 (24.4)
Three or more	17/201 (8.5)
Time of day taking primary medication ($n=201$ responses with multiple times)	
Midnight–5 a.m.	10/309 (3.2)
6 a.m.	37/309 (12.0)
7 a.m.	103/309 (33.3)
8 a.m.	43/309 (13.9)
9 a.m.–noon	28/309 (9.1)
1–5 p.m.	37/309 (12.0)
6 p.m.–midnight	51/309 (16.5)
Time of day taking supplemental medication ($n=81$ responses with multiple times)	
Midnight–5 a.m.	8/111 (7.2)
6 a.m.	7/111 (6.3)
7 a.m.	24/111 (21.6)
8 a.m.	13/111 (11.7)
9 a.m.–noon	17/111 (15.3)
1–5 p.m.	16/111 (14.4)
6 p.m.–midnight	26/111 (23.4)
Days per week taking ADHD medication during the school year	
7	132/201 (65.7)
6	10/201 (5.0)
5	50/201 (24.9)
4	4/201 (2.0)
1–3	5/201 (2.5)
Frequency of routine follow-up with ADHD physician	
Less than once a year	11/201 (5.5)
Once a year	23/201 (11.4)
Twice a year	44/201 (21.9)
Three times a year	36/201 (17.9)
More than three times a year	87/201 (43.3)

ADHD, Attention-deficit/hyperactivity disorder; ER, extended-release; IR, immediate-release.

were the ADHD symptoms that appeared most frequently during Early Morning Routine time of day (Fig. 3). When asked about unwanted behaviors that appeared frequently during the Early Morning Routine time of day, roughly half of the respondents reported that being impulsive/acting without thinking (49.3%, 99/201) and failure to finish things (48.8%, 98/201) were the most frequent (Fig. 4). Respondents reported that they often felt overwhelmed and exhausted (40.8%, 82/201) as a result of patient ADHD symptoms during the Early Morning Routine time of day, and a higher percentage reported sometimes feeling constantly stressed (46.8%, 94/201), raising their voices more than they wanted to (43.8%, 88/201), feeling inadequate as a caregiver (43.8%, 88/201), and punishing his/her child/adolescent more and praising the child/adolescent less (43.8%, 88/201; Fig. 5). Approximately one third (34.3%, 69/201) of respondents reported that the challenges of the Early Morning Routine, associated with their child's/adolescent's inadequately controlled ADHD symptoms, had a somewhat negative effect on their relationship with the patient and 7.5% (15/201) stated that it had a very negative effect on their relationship with the patient. However, some parents stated that it had a very positive impact (10%, 20/201), somewhat positive impact (21.4%, 43/201), or no impact (26.9%, 54/201) on their overall relationship with the patient. When asked about their satisfaction with their child's/adolescent's current ADHD medication in providing meaningful symptom relief during the Early Morning

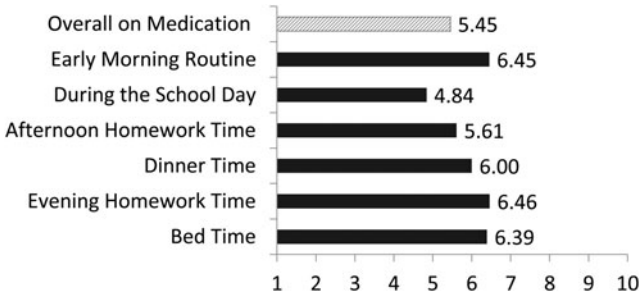

FIG. 1. Attention-deficit/hyperactivity disorder (ADHD) symptom severity, overall and times of day, using a scale of 1–10 where 1 means no ADHD symptoms and 10 means significant ADHD symptoms.

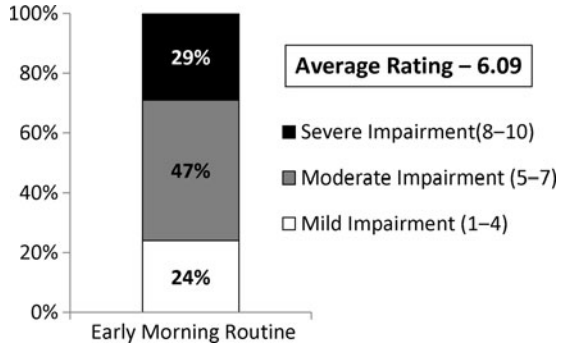

FIG. 2. Overall impairment of functioning from attention-deficit/hyperactivity disorder symptoms during the Early Morning Routine, using a scale of 1–10 where 1 means ''Mild Impairment'' and 10 means ''Severe Impairment.'' The average rating of impairment was 6.09.

Routine time of day, most (38.8%, 78/201) reported that they were only somewhat satisfied, 10.9% (22/201) were not very satisfied, 3.0% (6/201) were not at all satisfied, 35.8% (72/201) were very satisfied, and 11.4% (23/201) were extremely satisfied. A majority of respondents (79.1%, 159/201) reported discussing patient EMF impairments with the patient's physician, and almost half (48.3%, 97/201) reported that they had previously woken up early in order to administer ADHD medication to their child/adolescent in an attempt to help mitigate early morning ADHD symptoms.

Discussion

The temporal occurrence of inadequately controlled ADHD symptoms, specifically during the Early Morning Routine, has only recently received attention in clinical trials involving stimulant medications. Inadequately controlled early morning ADHD symptoms in stimulant-treated children and adolescents can be attributed to the delayed onset of clinically meaningful symptom control afforded by oral stimulant medications that are dosed subsequent to awakening.

To our knowledge, this is the first quantitative research survey directly assessing parent/caregiver perceptions of: 1) The relative prevalence and severity of inadequately controlled early morning ADHD symptoms, 2) their impact on early morning behaviors and EMF, and 3) their apparent emotional impact on the parent and 4) on the parent–child relationship. As such, this research survey produced several important quantitative findings. First, survey data indicated that caregivers regarded the Early Morning Routine as a period frequently associated with moderate to severe ADHD-symptom-related functional impairments in children and adolescents with ADHD, despite morning administration of stable doses of stimulant medications. Second, caregivers reported a host of negative emotional feelings as a result of their child's inadequately controlled early morning ADHD symptoms. Third, approximately one third of caregivers reported that their child's ADHD symptom-related functional impairments during the Early Morning Routine contributed to a somewhat negative relationship with their child. Interestingly, caregivers overwhelmingly acknowledged that they had discussed EMF impairments with the child or adolescent's treating physician, and more than half expressed room for improvement regarding satisfaction with the current medication regimen during this time of day.

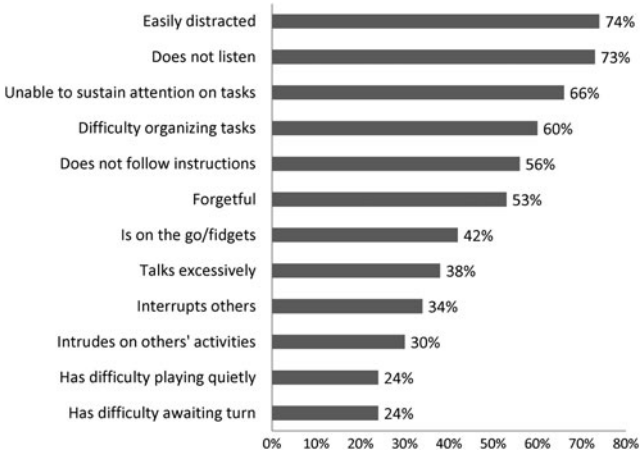

FIG. 3. Attention-deficit/hyperactivity disorder symptoms appearing frequently during the Early Morning Routine.

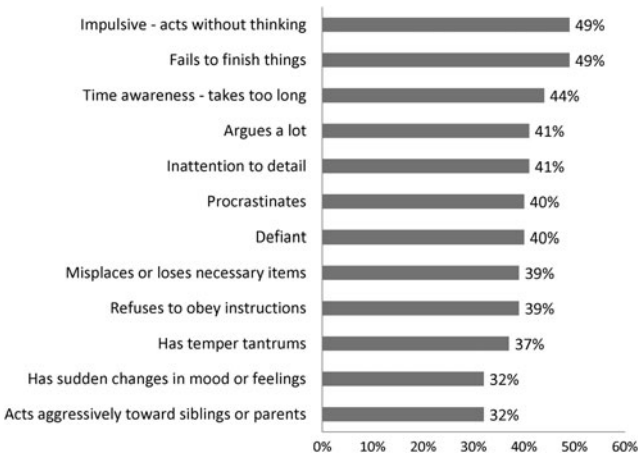

FIG. 4. Unwanted behaviors appearing frequently during the Early Morning Routine.

Limitations

The current study had several limitations. Survey instruments such as the one developed for the current study may lack some of the specificity of formally validated ADHD assessment tools used to assess symptom severity and functional impact. Furthermore, the surveys were completed through the anonymity of the Internet, were not subject to immediate assessment, and could not offer the opportunity for clarification provided by questionnaires administered during one-on-one research interviews. Survey data are collected in real world circumstances and unlike clinical trials, cannot be fully controlled. The study also did not include an untreated ADHD control group to serve as a comparator, which could have provided some additional insight regarding EMF impairments in children and adolescents with ADHD who were not treated with stimulant medications. It should be noted, however, that parental/primary caregiver surveys can be an important tool for evaluating the impact of EMF impairments on children and adolescents with ADHD and their caregivers in ''real-world'' settings, and that such information is difficult to obtain from clinical trials. Additionally, the detailed survey data reported in this study represent an important addition to the sparse clinical literature regarding EMF impairments in children and adolescents with ADHD treated with a stimulant medication, as well as the potential impact of impaired EMF on the parent–child relationship.

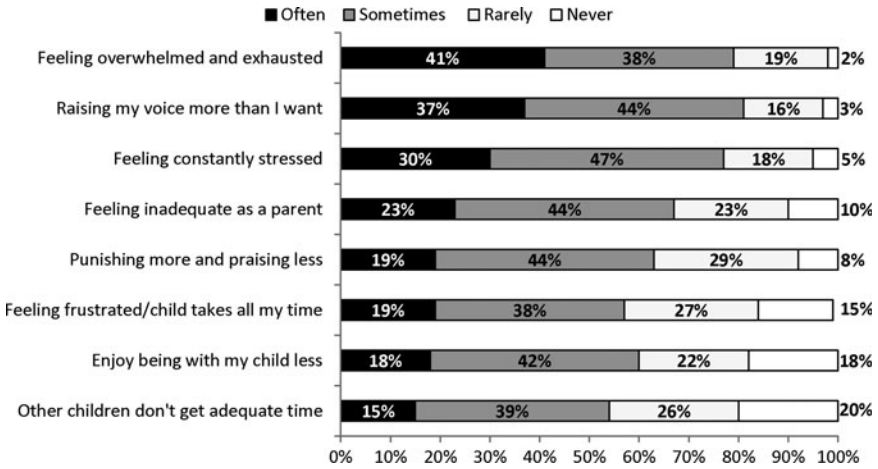

FIG. 5. Caregiver reactions to attention-deficit/hyperactivity disorder symptoms during the Early Morning Routine.

Conclusions

The issue of ADHD symptom control in the early morning time period is a meaningful issue to parents and caregivers, as almost half (48.3%) of caregivers indicated they had woken up early to administer their child's ADHD medication, and 79.1% of caregivers had previously discussed their child's early morning functional impairments with their doctor. The results from this quantitative research survey study strongly suggest that despite early morning administration of stable doses of existing formulations of stimulant medications, parents/primary caregivers of children and adolescents with ADHD report a high prevalence of inadequately controlled, early morning ADHD symptoms, and the severity of these early morning symptoms and related functional impairments are moderate to severe for a majority of their children. Importantly, they also noted that oftentimes their relationship with their child or adolescent with ADHD was negatively affected by these inadequately managed ADHD symptoms. These results further suggest that pharmacologic management of EMF impairments caused by ADHD symptoms remains a significant unmet need in children and adolescents with ADHD following the morning administration of stimulant medications. Finally, formulation research to explore development of additional stimulant-based treatment options for children and adolescents with ADHD should most likely include a focus on drug delivery mechanisms designed to provide clinically meaningful control of early morning ADHD symptoms and commensurate improvements in overall functioning during the early morning routines of school-age children. Finally, we concur with the observations of Faraone et al. (2015) that, given the clinical and practical impact of ADHD on morning symptoms and functioning, a scale specifically developed and validated to measure morning behaviors impaired by the symptoms of ADHD should be used in future trials of ADHD medications for youth.

Clinical Significance

Despite improvements in drug delivery systems for ADHD medications, EMF remains an issue in many children and adolescents with ADHD (Whalen et al. 2006). Current stimulant formulations cannot offer meaningful control of ADHD symptoms for at least 1 hour following oral ingestion (Swanson et al. 2003). This study confirms that the early morning routine continues to be a problematic time of the day for children and adolescents with ADHD treated with stimulant medication and their families.

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Disclosures

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Original Research

Early Morning Functional Impairments in Stimulant-Treated Children with Attention-Deficit/Hyperactivity Disorder Versus Controls: Impact on the Family

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Abstract

Objective: Children with attention-deficit/hyperactivity disorder (ADHD) frequently manifest early morning functional (EMF) impairments before school. We conducted a quantitative research survey to assess the impact of these EMF impairments on the family unit (caregiver, spouse/partner, and siblings).

Study Design: We developed an online survey questionnaire to collect data from 300 primary caregivers of children with ADHD and 50 primary caregivers of children who did not have ADHD.

Results: Although the ADHD children we surveyed were currently treated with stable doses of stimulants as their primary ADHD medication for at least 3 months, their parents reported high levels of EMF impairments in the child, which had a substantial negative effect on the emotional well-being of parents, on parents' functioning during the early morning routine, and on the level of conflict with siblings. The impact of EMF impairments on family functioning was mediated by the severity of the index child's impairments.

Conclusions: EMF impairments exert a pervasive and significantly negative emotional and functional burden on not only the primary caregiver but also on the spouse/partner and siblings. This work suggests that adequate ADHD symptom control during the early morning period may be an unmet need for school-age children with ADHD being treated with stimulants. More work is needed to confirm this finding and determine the degree to which symptom control at other times of day is also an unmet need.

Keywords: ADHD, morning, family, siblings, parents, functioning

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common, persistent, and impairing psychiatric disorder affecting many children aged 3–17 years worldwide (Faraone et al. 2015a). Although much is known about how ADHD impacts patients and their families (Faraone et al. 2015a), little is known about the effects of ADHD during particular times of the day, especially on early morning functioning (EMF).

The EMF of children with ADHD, especially on school days, deserves special attention for several reasons. Between waking and arriving at school, children must appropriately sequence and complete a series of complex behaviors (e.g., dressing, eating, self-hygiene/brushing teeth, and gathering school books) in the context of other family members who may also be engaged in the same or similar goal-directed activities. Completing these behaviors requires time management, working memory, and self-regulation skills as well as social skills and cooperation that are frequently impaired by ADHD symptoms (Whalen et al. 2006). When children fail to efficiently complete their morning routine, it puts them at risk for being late to school and forgetting to take homework and other materials to school. These issues may lead to academic and social difficulties.

Inadequate control of ADHD symptoms during the early morning routine before school can also be significantly disruptive

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to siblings and parents who must also be prepared and depart the home for their own scheduled activities in a timely manner.

A study by Barkley and Cunningham (1979) showed that ADHD impaired early morning organization, self-care, preparation for the school day, and transportation to school. Whalen et al. (2006) showed that children's ADHD symptoms led to less effective parenting behaviors, especially before school. Sallee (2015) surveyed 201 primary caregivers of youth with ADHD treated with stable doses of stimulant medication. Despite being maintained on stimulant medications, 75% of the caregivers rated their child's early morning routine before school as a period associated with moderate-to-severe symptoms of the disorder and related functional impairments. Many caregivers also experienced negative emotions related to their child's early morning impairments. The caregivers experienced stress while getting their child ready for school as well. About half said that these symptoms and impairments were harmful to the parent–child relationship. The authors concluded that early morning ADHD symptoms and EMF impairments were inadequately controlled for many youth with ADHD treated with stable morning doses of stimulant medications.

Given that EMF impairments may produce downstream adverse impacts on the entire day for the affected child as well as other family members, several studies assessed the efficacy of ADHD treatments for EMF impairments. Two placebo-controlled clinical trials assessed EMF impairments using the Before-School Functioning Questionnaire (BSFQ), which has documented reliability, internal homogeneity, and concurrent validity (Faraone et al. 2015b). Wilens et al. (2013) randomized ADHD youth to receive either continued stimulant treatment plus guanfacine extended release (GXR) in the morning (GXR AM) or evening (GXR PM), or continued stimulant treatment plus placebo. Parent-rated BSFQ scores indicated that EMF impairments improved with both GXR AM and PM. A crossover study of ADHD youth compared the methylphenidate transdermal system (MTS) with a placebo transdermal system (PTS) (Wilens et al. 2010). Compared to the PTS, MTS significantly reduced the investigator-rated BSFQ total score, but not the child self-rated BSFQ total score. The Daily Parent Rating of Evening and Morning Behavior (DPREMB) (Faraone et al. 2015a) was used by Michelson et al. (2002) in a double-blind study of atomoxetine treatment. Atomoxetine was not better than placebo for improving four early morning behaviors reported by parents. In contrast, two studies using a revised version of the same scale (DPREMB-R) reported greater improvements in EMF for atomoxetine versus placebo in randomized controlled clinical trials (Sutton et al. 2003; Kelsey et al. 2004), and two trials showed that, compared with stimulant treatment, atomoxetine was more effective for treating EMF impairments (Sangal et al. 2006; Whalen, et al. 2010).

The few data available on EMF and ADHD suggest that it is a considerable source of impairment for children with ADHD as well as stress within their families, and current pharmacotherapies show variable efficacy. However, no prior study has assessed EMF impairments and its effects on both the stimulant-treated child with ADHD and their family using a controlled study. Such a study of stimulant-treated children is needed to determine if EMF impairments are an unmet need for the pharmacotherapy of ADHD. We did not include children treated with nonstimulants due to cost considerations and the fact that only a small minority of ADHD youth are treated with nonstimulants as their primary ADHD medication.

To fill this gap in the literature, we conducted a survey of primary caregivers of children with and without ADHD. We had several goals: (1) to assess the nature and severity of EMF impairments associated with stimulant-treated ADHD and (2) to assess the prevalence, frequency, and impact of EMF impairments on the caregiver, spouse/partner, and siblings of stimulant-treated ADHD children and adolescents. We hypothesized that compared with families not having children with ADHD, those having children with ADHD, who expressed at least mild ADHD symptoms in the morning, would, despite being treated with stimulants, show higher levels of EMF impairments and these impairments would have deleterious effects on the family. We also tested the hypothesis that the impact on the family would be mediated by the severity of the EMF impairments.

Methods

Survey participants were 300 caregivers of children diagnosed with ADHD and 50 caregivers of children not diagnosed with ADHD. Potential survey participants were drawn from the Lightspeed GMI US Panel ($N = 1{,}269{,}000$). The Lightspeed GMI panel is constructed so that its consented panel members are generally representative of the U.S. population in terms of age, gender, income, ethnicity, geography, employment, and educational levels in the household (see Appendix). GMI collects a wide range of valuable consumer information about habits, characteristics, behaviors, and medical conditions that aid in survey targeting. To improve survey productivity, our panel sample for parents of ADHD children was initially drawn from the subset of GMI US panel members who had previously identified that they had a child with ADHD aged 6–17 years (targeted sample, $n = 17{,}130$). Once that subset was exhausted, survey invitations were sent to the subset of GMI US panelists with children aged 6–17 years ($n = 253{,}800$). Lightspeed GMI also provided the survey programming and online hosting for the project.

As an incentive for participation, those who completed the survey were awarded points as participation incentives. The number of points awarded is based on a proprietary formula that factors in survey length and difficulty of recruiting. A longer survey has a higher point value incentive than a shorter one. A survey with a difficult-to-recruit audience awards more points than an easier-to-recruit survey. After accumulating points, members are able to redeem them for items within Lightspeed GMI's rewards catalog. Examples of items panel members can redeem points for include the following: PayPal and Amazon e-certificates, gift cards, vouchers, cash, electronics, and home and personal care products.

Inclusion in the ADHD group required four criteria: (1) being self-identified as the primary caregiver of an ADHD child aged 6 to 17 years; (2) the child with ADHD was taking stimulant medication as his or her primary ADHD medication; (3) he or she was taking a stable dose of their primary stimulant medication for 3 months or more; and (4) the caregiver rated that the severity of the child's ADHD symptoms throughout the entire day and during the early morning routine, as two or more on a scale of 1 (no symptoms) to 10 (significant symptoms). We selected ADHD children showing at least mild evidence of ADHD in the morning because our goal was to determine if the expression of ADHD symptoms in the morning was associated with impairments in stimulant-treated children.

The study was conducted in April of 2016. Caregiver respondents were blinded as to the research sponsor. The survey was conducted in accordance with and adherence to the Marketing Research Association Code of Standards. Potential respondents were invited to participate through an email message. The survey invitation did not specifically refer to ADHD or/and EMF; so it did

not bias participation toward families struggling with this domain of problems. The exact wording of the invitation was, ''Today we are conducting a marketing research study concerning healthcare for your family. Your opinions are important to us. Please continue with the survey.'' The survey, which was administered as an online questionnaire, required about 20 minutes for completion. It did not contain any option for any of the 18 standard types of PHI data to be collected and thus did not require IRB approval. Surveys were completed voluntarily and anonymously.

For the ADHD families, if there was more than one child with ADHD in the household, respondents were instructed to select the ADHD child who had the most severe ADHD symptoms. For the non-ADHD sample, respondents were instructed to select the child whose birthday was next. We refer to these selected children as the ''index'' children. The questions asked to caregivers of ADHD and non-ADHD youth were slightly different. For example, regarding concerns for safety, the former were asked the following question: ''How often do your child's inadequately controlled ADHD symptoms during the early morning routine (before school) cause you concern for their safety and well-being in the home?'' and the latter were asked the following question: ''How often does your child's behavior during the early morning routine (before school) cause you concern for their safety and well-being in the home?''

We compared ADHD and non-ADHD families using logistic regression with ADHD status as the outcome and the demographic and family impact measures as independent variables. We first tested for demographic differences and included significant demographic predictors as covariates in all models. Because the family impact measures are conceptual outcomes, a more standard approach would have been to use these outcomes as dependent variables. However, doing so creates analytic problems due to the extreme nonnormality of the data and the strong assumptions we would need to analyze ordinal data. Logistic regression requires minimal assumptions and provides a valid method of establishing the statistical significance of the association.

To test the hypothesis that the impact on the families of ADHD youth was mediated by the severity of the EMF impairments, we included the severity of EMF impairments in the index child as a covariate in models testing for the association of ADHD family status and family impact. Our measure of severity was the answer to the following question: ''On a scale from 1 to 10, where 1 means ''Mildly Impaired'' and 10 means ''Very Severely Impaired'', how severe is that child's functional impairment (or difficulty to function) during the early morning routine?.''

Results

The families with and without ADHD children did not differ in age of the index child (11.6 vs. 11.9; $z = 0.5$, $p = 0.6$), or relationship of the caregiver to the child ($X^2[3] = 1.6$, $p = 0.7$). The index children in the ADHD group were more likely to be male (68% vs. 44%; $z = 3.2$, $p = 0.001$). Thus, all the following analyses are statistically corrected for sex of the index child. Forty-six percent of the ADHD youth were taking an amphetamine formulation and 54% were taking a methylphenidate formulation. Twenty-seven percent had been taking their medication for 3 to 6 months; 21% for 6 months to a year; 21% for one to 2 years; and 31% for more than 2 years.

EMF impairments among ADHD children

Overall, 77% of caregivers rated the severity of EMF impairment in their child with ADHD as moderate-to-severe (severity rating of 5–10 on a 10-point severity scale). On the same severity scale from 1 to 10, where 1 means ''Mildly Impaired'' and 10 means ''Very Severely Impaired,'' ADHD children were rated as having higher mean levels of EMF impairment compared with controls (6.2 vs. 1.5; $z = 6.7$, $p < 0.001$). This shows that ADHD children who express some ADHD symptoms in the morning are at risk for EMF impairments. Consistent with this, the median number of school days each week that the child had EMF impairments was greater for youth with ADHD (4 days per week vs. 1 day per week; $z = 5.8$, $p < 0.001$).

We asked parents about 10 maladaptive behaviors occurring during the EMF period. Seven of these impairments were significantly more common among youth with ADHD compared with those without ADHD, and only 2% of youth with ADHD demonstrated none of these frequent maladaptive behaviors compared with 52% of non-ADHD youth (Fig. 1). Seventy-eight percent of the parents of ADHD youth had discussed the issue of EMF impairments with their doctor.

We asked the parents of the children with ADHD if they, or another adult in the household, ever woke their child with ADHD up earlier than their normal waking time to administer ADHD medication and then let them go back to sleep, so that the medication could provide more effective ADHD symptom control in the early morning. Fifty-seven percent indicated that they had used this strategy a median of 4 days per week during the school year. Seventy-eight percent of those who used this strategy indicated that its impact was either very positive or somewhat positive.

Impact of EMF impairments on parents and siblings

As shown in Figure 2, the child's EMF impairments had a substantial and statistically significant negative impact on the emotional well-being of the caregivers of youth with ADHD. In response to EMF impairments, the caregivers of youth with ADHD were significantly more likely than caregivers of non-ADHD youth to report raising their voice more often, and feeling overwhelmed and exhausted, constantly stressed, inadequate as a parent, frustrated their child with ADHD consumed all their time, and guilty they were neglecting their other children.

Compared with caregivers of youth without ADHD, the caregivers of youth having ADHD were more likely to report that EMF impairments led to more stress from sibling conflict, greater disruption of the child's breakfast, greater disruption of the caregiver's morning routine, and a greater likelihood of being late for their own morning activities (all p's < 0.001). We found similar results when assessing the effects of the child's EMF impairments on the spouses/partners of the caregivers. During the early morning period, the caregivers of youth with ADHD reported significantly more conflict with their spouses/partners, more disruption of their spouse's/partner's early morning routine, and that the child's EMF impairments kept the spouses/partners from being on time (all p's < 0.01).

Parents were asked how often EMF impairments caused them concern for the index child's safety and well-being inside and outside the home. The same question was also asked if such ADHD-related EMF of the index child also affected the safety and well-being of the siblings. As Figure 3 shows, concerns about index child and sibling safety were significantly and substantially higher among the parents of children with ADHD (all p's < 0.001).

We also assessed the impact of the index child's EMF on the morning routines of their siblings. Compared with the parents not having an ADHD child, those with an ADHD child were more

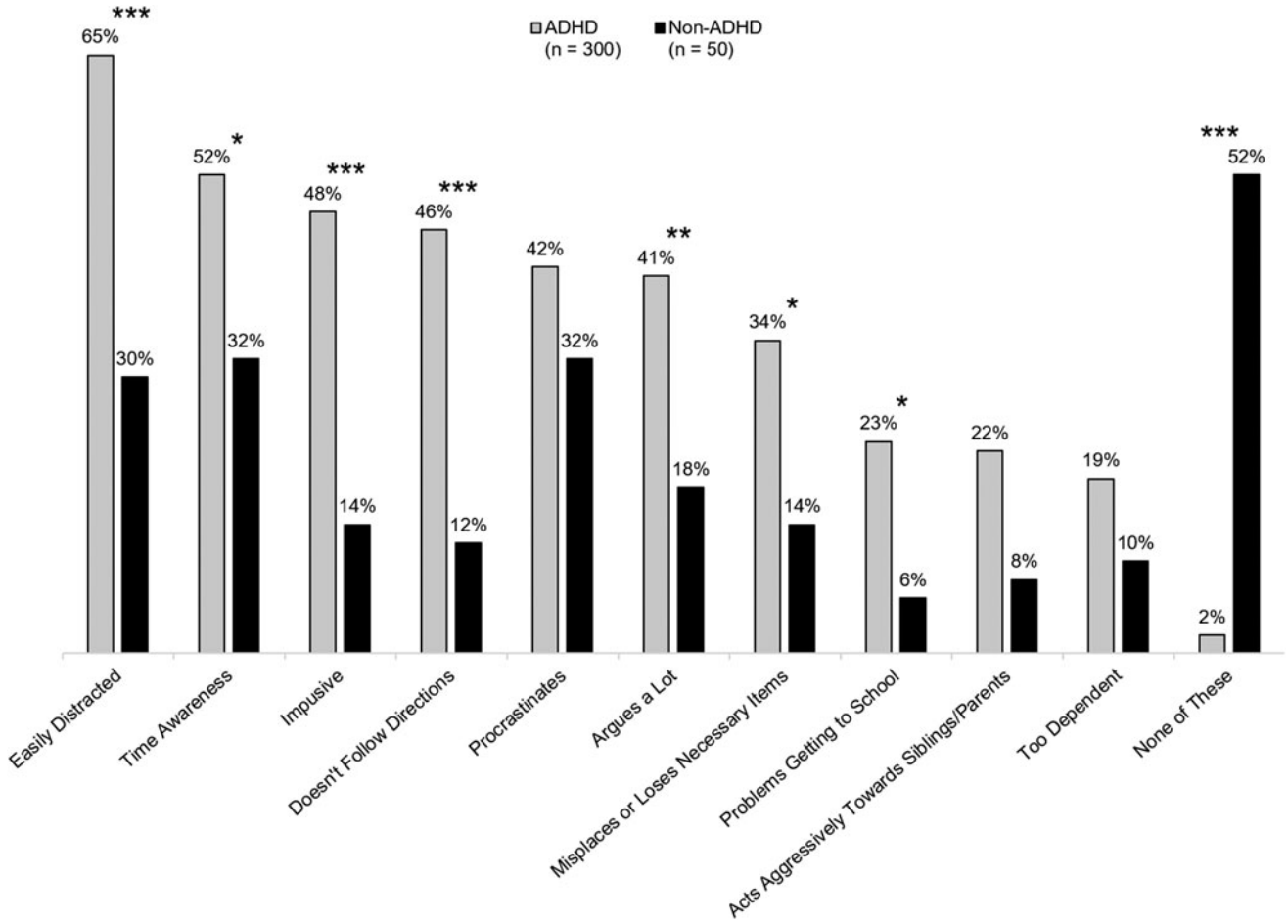

FIG. 1. ADHD child's maladaptive behaviors and EMF impairments occurring ''frequently.'' Caregivers were given a list of EMF behaviors and asked to indicate which ones occurred ''frequently.'' $*p<0.05$, $**p<0.01$, and $***p<0.001$ vs. non-ADHD. ADHD, attention-deficit/hyperactivity disorder; EMF, early morning functioning.

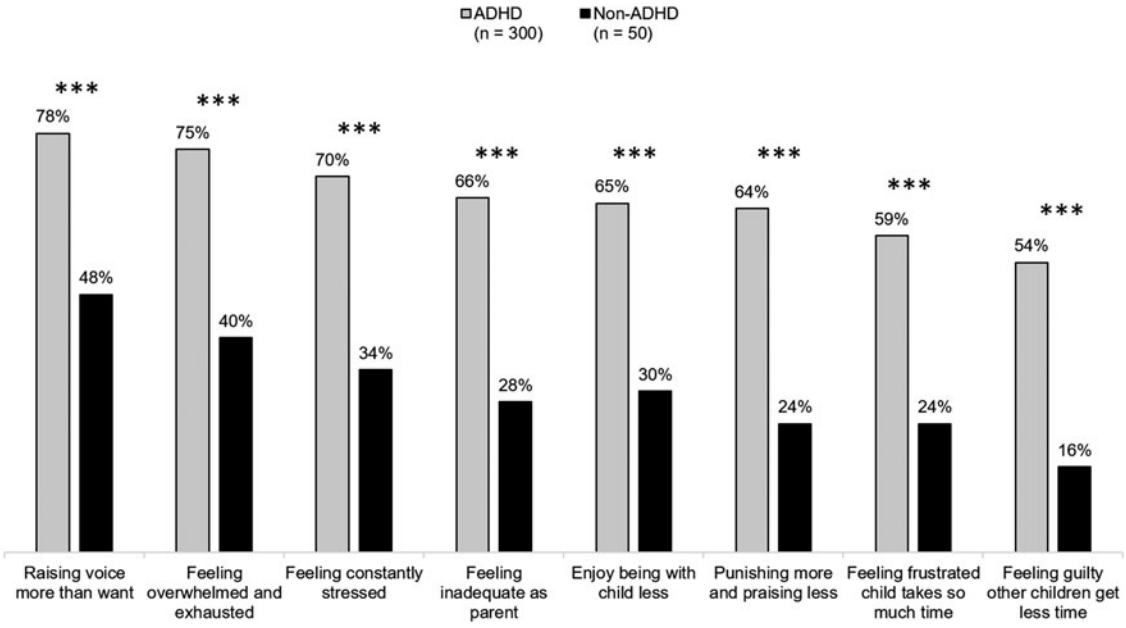

FIG. 2. Parent feelings toward their child's impaired EMF occurring ''sometimes'' or ''often.'' Caregivers rated behaviors on a four-point scale: ''never occurs,'' ''rarely occurs,'' ''sometimes occurs,'' and ''often occurs.'' $***p<0.001$ vs. non-ADHD. ADHD, attention-deficit/hyperactivity disorder; EMF, early morning functioning.

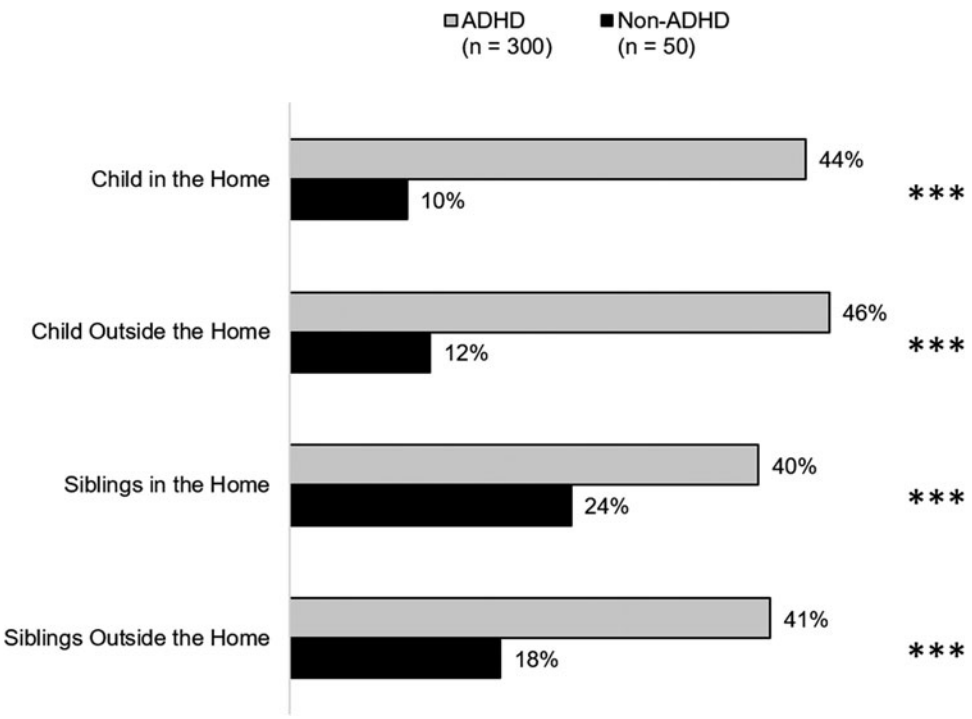

FIG. 3. Parent concern about their child's/sibling's safety occurring ''often'' or ''very often.'' Caregivers rated behaviors on a five-point scale: ''never,'' ''rarely,'' ''sometimes,'' ''often,'' and ''very often.'' ***$p < 0.001$ vs. non-ADHD. Note: 258 ADHD families had siblings and 34 non-ADHD families had siblings. ADHD, attention-deficit/hyperactivity disorder.

likely to report significant or very significant disruptions of the siblings' morning routines (42% vs. 18%, $p < 0.001$), disruptions causing siblings to be late ($p < 0.001$), disruption of the family breakfast ($p < 0.001$), and conflict with siblings ($p < 0.05$). Fifty-two percent of parents with ADHD children reported that sibling complaints about the index child's EMF impairments or disruption of the sibling's morning routine occurred often or very often compared with 18% of control families ($p < 0.001$).

Mediation of impact on family by severity of EMF impairments in the child

We added the severity of the EMF impairments in the index child as a covariate in all the models testing for the association of ADHD family status and family impact. For all these models except one, the association between ADHD family status and impact on the family lost significance when EMF impairment was a covariate (all p's > 0.05). The exception was the model testing for the impact on parental stress due to conflicts among siblings in the early morning ($p = 0.04$). To determine if the severity of EMF impairments associated with ADHD was predictive of impact on the family, we conducted regression analyses limited to the ADHD families that predicted the family impact variables from the severity of the ADHD child's EMF impairments. We found significant correlations between the EMF impairment severity of the ADHD child and all the family impact variables (all p's < 0.001; correlations ranging from 0.44 to 0.68).

Discussion

Although the ADHD children we surveyed had been treated with stimulant medications as their primary ADHD medication for at least 3 months, they still had elevated levels of EMF impairments compared with controls. This shows that ADHD children who express some ADHD symptoms in the morning are at risk for EMF impairments. These impairments diminished the emotional well-being of parents, interfered with the parental early morning routine, and increased the level of conflict among siblings and between caregiver and their spouse/partner. These findings confirm the survey findings reported by Sallee (2015), who also studied stimulant-treated youth with ADHD.

The impact of EMF impairments on the family was substantial. The parents in ADHD families were highly likely to report feeling adverse emotions, more conflict with spouses/partners, and greater disruption of the parental morning routine. The EMF impairments of ADHD children were also associated with higher levels of conflict with siblings and disruption of their morning routines. These findings are consistent with prior work indicating that families of patients with ADHD experience elevated levels of distress that impact family functioning (Whalen et al. 2006). Of particular concern, almost half of the parents of youth with ADHD expressed concern about the safety of their child and that of their other children due to the EMF impairments related to the child with ADHD. This finding is especially notable for clinicians given that children with ADHD are at significantly higher risk for a variety of types of accidents (Swensen et al. 2004) and the injury rates from accidents are reduced by medication treatment (Dalsgaard et al. 2015).

Consistent with our hypothesis, mediation analyses showed that the differences in family functioning between the families with and without ADHD were mediated (or could be accounted for) by the severity of EMF impairments in the index child. This finding, to some extent, reflects that nature of the questions about family impact, which asked about the effect of EMF impairments on family functioning (see Supplementary Data; Supplementary Data are available online at www.liebertpub.com/cap). Thus, the mediation analyses confirm that parents were responding as requested, that is,

they were reporting problems in the family caused by the EMF impairments of the index child. These findings show that the adverse family functioning results were not simply due to the presence of ADHD in the child, but were, in fact, associated with the index child's EMF impairments. As further support for this idea, within the ADHD families, we found significant correlations between the EMF impairment severity of the ADHD child and all the family impact variables.

Our conclusions are tempered by several methodological limitations. We used an online survey to collect data rather than in person, structured interviews. The use of the former may have decreased the sensitivity of our assessments. It is, however, unlikely that the use of online methodology would have created spurious findings. Our survey had not previously been tested for either reliability or validity. Low reliability and validity would have added noise to the analyses and made it difficult to find statistical significance. Thus, negative findings should be interpreted with caution. In contrast, low reliability and validity would not explain the pattern of significant differences we found across many measures. Our design does not allow us to conclude if EMF impairments were due to delayed onset of stimulant effects or to underdosing or overall partial response.

We did not confirm the parental reports of their children's ADHD diagnoses and only collected EMF data from one parent. That means that some findings could be accounted for by method variance, that is, the parents may not have been able to discriminate EMF problems from global impairment and safety concerns. Without behavioral data or multiple respondents, we cannot with certainty separate child dysfunction from parental concern. Thus, using multiple respondents would have been ideal. Despite these concerns, single respondent surveys have a strong precedent for survey research, for example, it has been used by the Center for Disease Control (Visser et al. 2014). Moreover, using one parent to provide information about the psychiatric and functional status of children has a strong precedent in prior literature.

Because we only recruited families having children with ADHD who were stimulant treated, our findings may not generalize to families that have children with ADHD who are untreated or who are treated through other modalities. Like other surveys, our data are restricted to parent retrospective reports, not observations of actual behaviors. To most accurately assess the effects of ADHD on EMF impairments, the best design would be to include behavioral samples at early morning and at other times of the day and to evaluate whether our findings are specific to EMF or are, perhaps, simply a reflection of functional impairments throughout the day. Although the panel from which respondents were selected was representative of the U.S. population, given the low response rate, it is possible that our sample is biased in unknown ways. Thus, we cannot be sure to which populations our results will generalize. Our population cannot be biased, however, with regard to EMF because the email used to recruit respondents did not indicate a specific interest in ADHD children and adolescents with ''problems in the morning'' or ''EMF Impairment'' (or similar wording). Further evidence for lack of bias regarding EMF impairment is the fact that our 77% rate of caregiver-reported moderate-to-severe EMF impairment severity is similar to the rate of 76% reported by Sallee (2015).

Conclusions

Within the constraints of these limitations, our findings show that the primary caregivers of stimulant-treated children and adolescents with ADHD report that inadequately controlled early morning ADHD symptoms and EMF impairments persist despite treatment. EMF impairments exert a pervasive and significantly negative emotional and functional burden, not only on the primary caregiver but also on the spouse/partner and siblings. This work, especially when considered in the context of similar findings by Sallee (2015), suggests that adequate ADHD symptom control during the early morning period may be an unmet need for school-age children with ADHD being treated with stimulant medications. More work is needed to confirm this finding, and to determine the degree to which symptom control at other times of day is also an unmet need.

Clinical Significance

What are the clinical implications of the fact that stimulant-treated children show evidence of EMF impairments that impact their family? One approach is seen in the data presented. About half the parents indicated that they had woken up their child with ADHD earlier than normal to administer ADHD medication and then let them go back to sleep, so that the medication would provide control in the early morning. Most who used this strategy said it had a very positive or somewhat positive effect. Thus, this is an option clinicians could communicate to parents. The early morning routine also provides a well-defined target for behavioral family therapy or, for adolescents, cognitive behavior therapy. Using organizational charts and reinforcing clearly defined early morning behaviors could alleviate many of these problems. This suggests that psychosocial treatment programs should develop modules aimed at EMF impairments.

Disclosures

In the past year, S.V.F received consulting income, travel expenses, and/or research support from Ironshore, Arbor, Shire, Akili Interactive Labs, Alcobra, VAYA, and Neurovance and research support from the National Institutes of Health (NIH). His institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards, or participated in continuing medical education programs sponsored by Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. S.V.F receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health*, Oxford University Press: *Schizophrenia: The Facts*, and Elsevier: ADHD: *Non-Pharmacologic Interventions*. R.A.B. is currently a consultant to Ironshore Pharmaceutical & Development, Inc. He has previously been a paid consultant to and/or speaker for Eli Lilly Co., Shire, Janssen, Medici, and Novartis. He receives book, rating scale, newsletter, and/or video royalties from Guilford Press, Premier Educational Seminars, Inc., J & K Seminars, and the American Psychological Association press. He also receives royalties for online CE courses he has written or recorded for ContinuingEdCourses.net and PsychContinuingEd.com. R. J. S. is a member of the Scientific Advisory Board of Ironshore Pharmaceuticals & Development, Inc. (''Ironshore''), has received consulting income or equity from ehave and Purdue Pharma and funding from Canadian Institutes for Health Research, Ontario Mental Health Foundation, and Ontario Brain Institute. His institution holds the rights for cognitive rehabilitation software for ADHD. In the past, he received consulting fees or was on the Advisory Board, or participated in medical education programs sponsored by the North American and Canadian Scientific Advisory Board of Strattera (Lilly).

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(*Appendices follow* →)

Appendix

Lightspeed GMI US Panel Demographic Profile (N = 1,269,000)

The profile of Lightspeed GMI US Panel participants overall reflects the demographic makeup of the United States. Key panel profile characteristics are shown below.

	%
Gender	
Male	31
Female	69
Household income	
Less than $25K	37
$25K–$49.9K	26
$50K–$74.9K	16
$75K–$99K	10
$100K+	12
Age	
18–24	19
25–34	28
35–44	21
45–54	17
55+	15
Region	
Midwest	21
Northeast	15
South	43
West	21
Race/ethnicity	
White/Caucasian	62
Black/African American	17
Hispanic/Latino	12
Other	9
Employment status	
House wife/house husband	8
Permanent full-time employment	26
Permanent part-time employment	8
Unpaid employment (e.g., volunteer work)/ full-time care of family member	1
Retired	3
Self-employed/freelance	6
Student, in school or apprenticeship	6
Temporary, seasonal, or occasional work	2
Unable to work/disabled	5
Without work or currently not working, and looking for work	10
No answer	25
Education	
Grade school	1
Some high school	5
Graduated high school or GED	19
Some college—no degree	20
Graduated college—associate's degree	7
Graduated college—bachelor's degree	12
Postgraduate degree—MS, MA, MBA, MD, DVM, DDS, etc.	5
Technical school/vocational training	5
Doctorate—PhD	1
No answer	25