DOCUMENT SUMMARY This research article published in the *Journal of Attention Disorders* presents post hoc analyses of two randomized, placebo-controlled studies on the efficacy of **SHP465 mixed amphetamine salts (MAS)** for treating **ADHD** in adults. The study specifically assesses improvements in **Executive Function (EF)** using the **Brown Attention-Deficit Disorder Scale (BADDS)**. Results indicate that treatment with **SHP465 MAS** led to significantly greater improvements in **EF**, with response rates approximately twice as high as those seen with a placebo.

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METADATA Category: RESEARCH Type: study Relevance: Reference Update Frequency: Static Tags: #adhd #adult-adhd #executive-function #badds #shp465 #amphetamine #pharmacotherapy #clinical-trial #research-study #thomas-brown Related Docs: This study should be cross-referenced with the clinical presentation by Dr. Thomas Brown on the **ADHD** motivation model, as it uses his **BADDS** scale. It also complements any documents discussing medication-based treatments for **ADHD** and the assessment of **Executive Function**.

FORMATTED CONTENT

Improved Executive Function in Adults Diagnosed With Attention-Deficit/Hyperactivity Disorder as Measured by the Brown Attention-Deficit Disorder Scale Following Treatment With SHP465 Mixed Amphetamine Salts Extended-Release: Post Hoc Analyses From 2 Randomized, Placebo-Controlled Studies

Journal of Attention Disorders 2022, Vol. 26(2) 256-266 **Thomas E. Brown, Jie Chen, and Brigitte Robertson**

Abstract

Objective: Assess **executive function (EF)** improvement with **SHP465 mixed amphetamine salts (MAS)** extended-release in adults with **attention-deficit/hyperactivity disorder (ADHD)** using responder analyses of the **Brown Attention-Deficit Disorder Scale (BADDS)**.

Methods: Post hoc analyses examined data from placebo-controlled **SHP465 MAS** dose-optimization (12.5-75 mg) and fixed-dose (25-75 mg) studies. Treatment response was assessed using two definitions (BADDS total score at endpoint <50 [no

EF impairment] vs. ≥50 [impaired]; **BADDS** total score at endpoint relative to the in-treatment 90% CI range for baseline total score [below the range = improved]).

Results: Response rates (**SHP465 MAS** vs. **placebo**) favored **SHP465 MAS** (all nominal p<.0001) in the dose-optimization (**BADDS** <50: 41.9% vs. 19.2%; below 90% CI range: 57.4% vs. 29.6%) and fixed-dose (**BADDS** <50: 51.9% vs. 16.7%; below 90% CI range: 70.6% vs. 32.3%) studies.

Conclusion: Improvement in **EF** measured by **BADDS** response rates was approximately 2-fold greater with **SHP465 MAS** than **placebo**.

Keywords: adults, **attention-deficit/hyperactivity disorder**, **Brown Attention-Deficit Disorder Scale**, **executive function**, **SHP465 mixed amphetamine salt**

Introduction

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Executive function" (EF), which is a component of the self-management system of the brain, is a term used to describe operations of brain circuits that prioritize, integrate, and regulate other cognitive functions.

EF provides a mechanism for "self-regulation".

> Questions related to
>
> **EF** ask how or whether a person goes about doing something (e.g., Will you do it and, if so, how and when?).

The diagnosis of

attention-deficit/hyperactivity disorder (ADHD) is currently based on criteria provided by the **Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)**. Those diagnostic criteria, which are based primarily on a collection of inattentive and/or hyperactive/impulsive symptoms, describe many, but not all, of the aspects of

EF that are important components of **ADHD**. As the

DSM criteria for **ADHD** were originally developed using data from research in children and adolescents rather than adults, normed rating scales can provide information that is useful for assessing the impact of **EF** impairment in adults diagnosed with **ADHD** beyond the **DSM** criteria alone.

Evidence for impaired

EF function in youth and adults with **ADHD** has been observed using batteries of neuropsychologic tests and normed self-report rating scales, with the latter providing an index of how impaired **EF** can influence daily activities. However, a meta-analysis of neuropsychologic

EF tests administered to adults with **ADHD** showed that only about 30% of those with **ADHD** showed significant impairment of **EF** when assessed with these tests. In contrast, >70% of adults diagnosed with

ADHD based on the **DSM, Fourth Edition (DSM-IV)** criteria were reported to exhibit some level of **EF** deficit when assessed using a range of normed **EF** measures that included three index scores from standardized tests of memory and cognitive abilities and five subscales of a normed self-report measure of **EF** impairments in daily life. Furthermore, studies have shown that when specific types of

EF impairment are combined with **DSM**-based **ADHD** adult diagnostic criteria a more robust assessment of **ADHD** is obtained compared with when **DSM** criteria alone are used. For example, an analysis of the physician-administered Adult

ADHD Clinical Diagnostic Scale showed that non-**DSM** symptoms of **EF** were found to be specific predictors of narrowly defined **ADHD** (difficulty prioritizing work, trouble planning ahead) and broadly defined **ADHD** (difficulty prioritizing work, cannot complete tasks on time, makes careless mistakes) in adults.

The

Brown Attention-Deficit Disorder Scale (BADDS) has been used to measure the effects of **ADHD** pharmacotherapy on **EF** in multiple studies of adults diagnosed with **ADHD**.

SHP465 mixed amphetamine salts (MAS) extended-release (**SHP465 MAS** [Mydayis; Shire, Lexington, MA, a member of the Takeda group of companies]) is a once-daily, single-entity **MAS** product for oral administration approved in the United States for the treatment of **ADHD** in individuals aged ≥13 years. Each

SHP465 MAS capsule contains three types of drug-releasing beads (one immediate-release bead and two different types of delayed-release beads) that contain equal amounts (by weight) of four salts (dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate, and amphetamine aspartate monohydrate), resulting in a 3:1 mixture of dextroamphetamine-to-levoamphetamine base equivalent.

The efficacy and safety of

SHP465 MAS were examined in a series of phase 3 studies in adults diagnosed with **ADHD**. In these studies,

SHP465 MAS significantly reduced **ADHD** Rating Scale, Fourth Edition (**ADHD-RS-IV**) total scores versus **placebo**. These studies also reported that the safety and tolerability profile of

SHP465 MAS was generally consistent with the profiles of other long-acting stimulants, with the most frequently reported treatment-emergent adverse events being insomnia, dry mouth, and decreased appetite. In two of the aforementioned

SHP465 MAS studies, the **BADDS** was included as a secondary efficacy endpoint. In these studies, treatment with

SHP465 MAS produced greater reductions in **BADDS** total and cluster scores than **placebo**. However, to date, there are no published reports of

SHP465 MAS treatment response rates based on **BADDS** total score in adults diagnosed with **ADHD**. Therefore, the objective of the current post hoc analyses was to examine

SHP465 MAS treatment response rates using two previously described definitions. The first definition examined

BADDS total score at endpoint, with **BADDS** total score ≥50 being used as an index of **EF** impairment. The second definition examined

BADDS total score at endpoint relative to the in-treatment 90% CI range for baseline total score, with total scores below the 90% CI range indicating improvement from baseline.

Methods

Study Design, Treatment, and Participants

These post hoc analyses included data from two studies of

SHP465 MAS in adults with **ADHD**. The methods have previously been described in detail elsewhere and are summarized here.

- **The dose-optimization study** was a 7-week, phase 3, randomized, double-blind, placebo-controlled study in which participants were randomized to **SHP465 MAS** (12.5-75 mg) or **placebo**. For each participant randomized to **SHP465 MAS**, treatment was initiated at 12.5 mg **SHP465 MAS** and titrated to 25 mg at Week 2, 50 mg at Week 3, and 75 mg at Week 4 until an optimal dose was reached. An optimal dose was defined as one that produced a ≥30% **ADHD-RS-IV** total score decrease from baseline and was well tolerated.
- **The fixed-dose study** was a 6-week, phase 3, randomized, placebo-controlled, double-blind study in which participants were randomized to **SHP465 MAS** (25, 50, or 75 mg) or **placebo**. All **SHP465 MAS** groups initiated treatment at 25 mg during Week 1. The 25 mg **SHP465 MAS** group received 25 mg throughout the study; the 50mg **SHP465** group received 37.5 mg during Week 2 and 50 mg during Weeks 3 to 6; the 75mg **SHP465 MAS** group received 37.5 mg during Week 2, 50mg during Week 3, and 75 mg during Weeks 4 to 6.

In both studies, eligible participants were men and non-pregnant/nonlactating women (aged 18-55 years) who had satisfactory medical assessments. Participants were also required to meet

DSM-IV, Text Revision (DSM-IV-TR) criteria for **ADHD** and to have **ADHD-RS-IV** baseline total scores ≥24 (for the dose-optimization study) or ≥32 (for the fixed-dose study).

Endpoint

The primary efficacy endpoint in both studies was change from baseline on the

ADHD-RS-IV. The

BADDS was included as a secondary efficacy endpoint in these studies and was assessed at baseline and at the final study visit. This report focuses on the results of post hoc responder analyses.

The

BADDS is a 40-item, validated, self-report scale administered by a clinician or appropriately trained individual that assesses aspects of **EF** that are conceptually related to **ADHD**. The items assessed in the

BADDS include all of the symptoms of inattention for **ADHD** listed in the **DSM-IV**, along with wide coverage of symptoms of **EF** not included in the **DSM-IV ADHD** criteria.

BADDS items are grouped into five clusters (organizing and activating to work, sustaining attention and concentration, sustaining energy and effort, managing affective interference, utilizing working memory and accessing recall). Cluster scores are generated by summing item scores within each cluster, and total score is generated by summing all item scores; higher cluster scores and total scores indicate greater levels of impairment in

EF. The items of the

BADDS are scored on a 4-point Likert scale (0=never; 1=once a week or less; 2=twice a week; 3=almost daily), with total score ranging from 0 to 120. Based on psychometric analyses, a

BADDS total score ≥50 has been suggested to be indicative of impaired **EF**, and posttreatment total score shifts below the pretreatment 90% CI range are considered an index of improved **EF**.

BADDS Structure and Scoring

- **Total Score (score range: 0-120)**
    - **Cluster 1: Organizing and Activating to Work (score range: 0-27)**
        - Item 2: Has difficulty getting started
        - Item 3: Feels overwhelmed
        - Item 10: Has difficulty setting priorities
        - Item 11: Procrastinates excessively
        - Item 13: Has difficulty getting organized
        - Item 19: Is slow to react
        - Item 21: Is excessively rigid; a perfectionist
        - Item 27: Is hard to wake up in the morning
        - Item 39: Misunderstands directions
    - **Cluster 2: Sustaining Attention and Concentration (score range: 0-27)**
        - Item 1: Tries to pay attention but mind drifts
        - Item 4: "Spaces out" when reading
        - Item 5: Becomes sidetracked easily
        - Item 6: Loses track in required reading, must reread
        - Item 8: Has difficulty grasping main idea in reading

        - Item 23: Gets lost in daydreaming
        - Item 26: Becomes distracted easily
        - Item 32: Stares off into space; seems "out of it"
        - Item 36: Doesn't seem to be listening; gets complaints
    - **Cluster 3: Sustaining Energy and Effort (score range: 0-27)**
        - Item 12: Feels sleepy during the day
        - Item 14: Needs extra time
        - Item 16: Is criticized as lazy
        - Item 17: Produces inconsistent quality of work
        - Item 22: Does not work to potential
        - Item 25: Begins but effort fades quickly
        - Item 34: Has sloppy, hard-to-read penmanship
        - Item 37: Needs reminders for tasks
        - Item 40: Does not finish tasks
    - **Cluster 4: Managing Affective Interference (score range: 0-21)**
        - Item 9: Is excessively impatient
        - Item 18: Is sensitive to criticism
        - Item 20: Becomes irritated easily; short-fused
        - Item 24: Has difficulty expressing anger
        - Item 29: Exhibits depressed mood
        - Item 30: Tends to be a loner among peers
        - Item 31: Appears apathetic
    - **Cluster 5: Utilizing Working Memory and Accessing Recall (score range: 0-18)**
        - Item 7: Is excessively forgetful
        - Item 15: Intends to do things but forgets
        - Item 28: Makes repeated restarts in writing
        - Item 33: Misplaces words/letters in writing
        - Item 35: Loses track of items
        - Item 38: Has difficulty memorizing

Statistical Analysis and Data Presentation

All analyses were conducted in the overall intent-to-treat (ITT) population. These post hoc analyses assessed

SHP465 MAS treatment response rates at study endpoint using two previously described definitions.

1. **BADDS** total score at endpoint (<50 [no clinically impaired **EF**] vs. ≥50 [some level of **EF** impairment]) was used to assess the percentage of participants in each treatment group exhibiting **EF** impairment.
2. **BADDS** total score at endpoint relative to the in-treatment 90% CI range for baseline total score was used to assess the percentage of participants exhibiting improved **EF** (total score at endpoint below the 90% CI range), no change in **EF** (total score within the 90% CI range), or worsening of **EF** (total score at endpoint above the 90% CI range).

Results

Participant Disposition and Demographics

The ITT population consisted of 268 participants in the dose-optimization study (

SHP465 MAS, n=136; **placebo**, n=132) and 405 participants in the fixed-dose study (all **SHP465 MAS**, n=302; **placebo**, n=103). Most participants in each study were white and had the combined

ADHD subtype. In both studies, the

SHP465 MAS and **placebo** groups had comparable **ADHD-RS-IV** total scores and **BADDS** total scores at baseline.

	Dose-optimization study			Fixed-dose study					
	Placebo (n = 132)	**SHP465 MAS (n=136)**	**All (N=268)**	**Placebo (n = 103)**	**25 mg (n=103)**	**50mg (n=101)**	**75 mg (n=98)**	**All SHP465 MAS (n=302)**	**All (n=405)**
Mean SD age, y	37.1 ± 10.26	36.1 ± 10.08	36.6 ± 10.16	35.6 ± 9.82	37.8 ± 9.84	38.0 ± 9.77	37.2 ± 9.51	37.6 ± 9.68	37.1 ± 9.74
Women, n (%)	65 (49.2)	67 (49.3)	132 (49.3)	46 (44.7)	50 (48.5)	35 (34.7)	45 (45.9)	130 (43.0)	176 (43.5)
Race, n (%) White	110 (83.3)	117 (86.0)	227 (84.7)	88 (85.4)	95 (92.2)	87 (86.1)	83 (84.7)	265 (87.7)	353 (87.2)
ADHD subtype, n (%) Combined	95 (72.0)	95 (69.9)	190 (70.9)	83 (80.6)	86 (83.5)	78 (79.6)	80 (79.2)	244 (80.8)	327 (80.7)
Mean SD BADDS total score	79.7 ± 17.08	77.7 ± 18.89	ND	83.0 ± 18.20	80.1 ± 16.30	81.5 ± 16.88	83.3 ± 16.66	81.6 ± 16.61	ND

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BADDS Responder Analyses

BADDS Total score at endpoint: The percentage of participants with **BADDS** total scores <50 at endpoint was greater and the percentage with **BADDS** total score ≥50 at endpoint was smaller with **SHP465 MAS** compared with **placebo** in both the dose-optimization study (nominal p<.0001) and the fixed-dose study (nominal p<.0001).

- In the dose-optimization study, 41.9% of the **SHP465 MAS** group scored <50 compared to 19.2% of the **placebo** group.
- In the fixed-dose study, 51.9% of the **SHP465 MAS** group scored <50 compared to 16.7% of the **placebo** group.

BADDS Total Score at Endpoint Relative to the Baseline In-Treatment 90% CI Range: The percentage of participants with **BADDS** total scores at endpoint that were below the baseline in-treatment 90% CI range (an index of improved **EF** from baseline) was greater with **SHP465 MAS** than **placebo** in both studies.

- In the dose-optimization study, 57.4% of the **SHP465 MAS** group fell below the 90% CI range, compared to 29.6% of the **placebo** group.
- In the fixed-dose study, 70.6% of the **SHP465 MAS** group fell below the 90% CI range, compared to 32.3% of the **placebo** group.

Level of EF Impairment (BADDS Score ≥50)	Dose-optimization study		Fixed-dose study				
BADDS total score at endpoint, n (%)	**Placebo (n=125)**	**SHP465 MAS (n=129)**	**Placebo (n=96)**	**25 mg (n=99)**	**50 mg (n=98)**	**75 mg (n=96)**	**All SHP465 MAS (n=293)**
<50	24 (19.2)	54 (41.9)	16 (16.7)	42 (42.4)	56 (57.1)	54 (56.3)	152 (51.9)
50-59	13 (10.4)	18 (14.0)	7 (7.3)	10 (10.2)	17 (17.2)	7 (7.3)	34 (11.6)
60-69	15 (12.0)	20 (15.5)	15 (15.6)	12 (12.2)	11 (11.1)	13 (13.5)	36 (12.3)
≥70	73 (58.4)	37 (28.7)	58 (60.4)	29 (29.3)	22 (22.9)	20 (20.4)	71 (24.2)

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Discussion

This paper describes improvement of

EF in adults diagnosed with **ADHD** following treatment with **SHP465 MAS**, as measured by the **BADDS**. Normed rating scales for

ADHD are one well-recognized way of assessing **EF** impairments, which many researchers consider the underlying core problem in **ADHD**.

> For example, Castellanos (1999) observed that "the unifying abstraction that best encompasses the faculties principally affected in
>
> **ADHD** has been termed **executive function**..there is now impressive empirical support for its importance in **ADHD**."

There are two conflicting ways of describing and measuring

EF. One view sees

EF as being defined by low scores on a battery of neuropsychological tests. However, a meta-analysis of such

EF tests administered to adults with **ADHD** showed that only about 30% of those with **ADHD** showed significant impairments of **EF** functions when assessed with these tests. The alternative view, advocated by Barkley and Brown, is that

EF impairments associated with **ADHD** are best assessed by use of normed rating scales for **ADHD** utilized in combination with clinical interviews and **DSM** criteria for **ADHD**. They claim that rating scales are more valid ecologically because they gather data on the individual's functioning in a variety of settings and situations of daily life over a more protracted time frame than can be assessed by neuropsychological tests of

EF. In support of this view, it has been reported >70% of adults diagnosed with

ADHD based on the **DSM-IV** criteria exhibit some level of **EF** deficit when assessed using a range of normed **EF** measures.

One key finding of these analyses is that nominally greater percentages of participants treated with

SHP465 MAS compared with **placebo** had **BADDS** total scores <50, which is indicative of the absence of significantly impaired **EF**. The second key finding is that nominally greater percentages of participants treated with

SHP465 MAS compared with **placebo** had **BADDS** total scores at endpoint that were below the baseline in-treatment 90% CI range, which is indicative of improved **EF** from baseline.