# Aerobic Exercise vs. Pharmacotherapy in Adults with Attention Deficit Hyperactivity Disorder (ADHD): Pilot Study

Josh Oliel, MSc

August 2018

Department of Psychiatry, Faculty of Medicine

McGill University, Montreal

A thesis submitted to McGill University in partial fulfillment of the requirements for the degree of Master of Science in Psychiatry

Table of Contents

Abstract ..... I-II
Résumé ..... III-IV
Acknowledgments ..... V
Contribution of Authors ..... VI

Introduction ..... 1

Chapter 1 – Literature Review ..... 2
1.1 Diagnostic Classification and Clinical Presentation of ADHD in Adulthood ..... 2
1.2 Efficacy of Pharmacotherapy in Adults with ADHD ..... 5
1.3 Potential Therapeutic Benefits of Aerobic Exercise in ADHD ..... 8
1.4 Goals and Hypotheses ..... 12

Chapter 2 – Methods ..... 12
2.1 Ethics Review ..... 12
2.2 Participants and Recruitment ..... 12
2.3 Assessment of Attention Deficit Hyperactivity Disorder ..... 13
2.4 Protocol: Aerobic Exercise Only ..... 15
2.5 Protocol: Medication Only ..... 16
2.6 Protocol: Makeup Sessions ..... 17
2.7 Measures ..... 18

Chapter 3 – Data Analysis ..... 21
3.1 Therapeutic Efficacy: Mixed Linear Model ..... 21
3.2 Treatment Adherence and the Maintenance Effect ..... 24

Chapter 4 – Results ..... 25
4.1 Attrition Analysis ..... 25
4.2 Therapeutic Efficacy: Mixed Linear Model ..... 26
4.3 Treatment Adherence and the Maintenance Effect ..... 38

Chapter 5 – Discussion ..... 38
5.1 Principal Findings ..... 38
5.2 Secondary Findings ..... 41
5.3 Strengths, Limitations, and Future Direction ..... 42

Summary and Conclusion ..... 44

References ..... 45

APPENDIX A: Consent Form ..... 54
APPENDIX B: Scatter Plots:Treatment Adherence vs. Maintenance Effect ..... 64

**Abstract**

Stimulant medication (MED) is the principal treatment for adults diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), but non-pharmacological interventions have garnered attention. To date, no study has examined the effectiveness of aerobic exercise (AE) or compared its efficacy to conventional treatment in the adult patient population. Therefore, our primary goal was to examine the relative effectiveness of AE ($n$ = 21) and MED ($n$ = 10) following an eight-week intervention and six-month follow-up in adults diagnosed with ADHD. Clinical efficacy was ascertained on scales pertaining to ADHD symptoms, depression, anxiety, self-esteem, and functional impairment. The secondary goal was to assess maintenance of treatment effects within both cohorts. Patients assigned to AE attended two one-hour exercise sessions every week for eight consecutive weeks. Participants assigned to pharmacotherapy were first treated with stimulants and subsequently attended an eight-week intervention consisting of weekly educational classes on ADHD. Following the eight-week intervention, participants were asked to maintain their assigned treatment until the end of follow-up. Follow-up visits were conducted three (3M-PI) and six months (6M-PI) after the intervention. Primary mixed linear model (MLM) demonstrated that AE was efficacious in reducing patient and observer ratings of ADHD symptom severity post-intervention and treatment effects were maintained over follow-up; however, MED produced gains that were significantly greater than AE, particularly at the six-month follow-up point. Secondary MLM revealed that AE did not improve ratings of affective symptoms, self-esteem, or functional impairment post-intervention; however, MED produced gains that were marginally superior to AE post-intervention and largely attained significance (over exercise) at 6M-PI. Additional analyses revealed that medication displayed a superior adherence rate (94.50%) relative to exercise (59.10%) during the follow-up period. Overall, AE was effective as a stand-alone intervention in

the treatment of adults with ADHD; however, pharmacotherapy produced gains that were more pronounced than exercise on a greater number of outcome measures, especially during the follow-up period.

**Résumé**

Les médicaments stimulants (MED) sont le traitement principal pour les adultes diagnostiqués d'un trouble du déficit de l'attention avec ou sans hyperactivité (TDAH). Cependant, des traîtements non-pharmacologiques attire de plus en plus l'attention dont l'exercice d'aérobie. Mais à ce jour, aucune étude scientifique n'a pu démontrer la supériorité de l'efficacité de l'exercice d'aérobie (EA) par rapport aux traitements conventionnels pour les adultes. Par conséquent, l'objectif principal de cette étude est d'examiner l'efficacité relative de l'exercice d'aérobie (n = 21 par rapport aux médicaments stimulants (n = 10) après avoir suivi une intervention de huit semaines avec un suivi de six mois consécutifs dans les adultes diagnostiqués avec TDAH. L'efficacité clinique a été établie sur des échelles relatives aux symptômes de TDAH : dépression, anxiété, l'estime de soi et déficience fonctionnelle. L'objectif secondaire était d'évaluer le maintien des effets du traitement dans les deux cohortes. Pendant huit semaines consécutives, les patients dans la groupe EA ont assisté à deux séances d'exercices d'une heure, tandis que les patients dans la groupe MED ont d'abord été traités avec des stimulants et ont ensuite assisté à une session de huit semaines consécutives de cours hebdomadaire d'éducation sur le TDAH. À la suite de la session de huit semaines, il a été demandé aux participants de maintenir leur traitement jusqu'à la fin du suivi. Des visites de suivi ont été effectuées trois (3M-PI) et six mois (6M-PI) après l'intervention. Le modèle linéaire mixte primaire (MLM) a montré que la sévérité des symptômes de TDAH est moins prononcée après avoir suivi le traitement de EA, selon les observations des patients et des observateurs. Cependant, les effets bénéfiques liés à la MED sur les évaluations des patients étaient significativement plus importants que les effets indésirables constatés au cours du suivi. Un MLM secondaire a révélé que EA n'a pas amélioré les évaluations de symptômes affectifs,

l’estime de soi, ainsi que la déficience fonctionnelle post-intervention. Des analyses supplémentaires ont révélé que les médicaments affichaient un taux d'observance supérieur (94.5%) par rapport à l'exercice (59.10%) pendant la période de suivi. Dans l'ensemble, EA a été efficace en tant qu'intervention autonome dans le traitement des adultes atteints de TDAD. Toutefois, pharmacothérapie a produit des gains plus prononcés (par rapport à l'exercice) sur un plus grand nombre de mesures de résultats, en particulier pendant le suivi.

**Acknowledgments**

First and foremost, I would like to extend my deepest appreciation and gratitude to my supervisor Dr. Lily Hechtman who provided me tremendous support, guidance, and opportunity throughout this master's degree. I would also like to thank members of my research committee for invaluable feedback on the implementation of the current project. Further, I would like to thank my colleagues at the ADHD Research Program; Dr. Sivan Klil-Drori for envisioning, conducting, and, training me on the study; Joy Etcovitch for lending her clinical expertise and providing constructive feedback throughout this research. I would especially like to thank Tara Errington for her unwavering advice, guidance, mentorship, training, and support. She was truly integral to this thesis and the research program at large. Finally, I would like to thank my mother Rita Oliel, without whom none of this would be possible.

## Contribution of Authors

Dr. Lily Hechtman contributed her expertise in helping design the research project alongside Dr. Sivan Klil-Drori. Dr. Hechtman also acted by medicating participants assigned to pharmacotherapy, conducted diagnostic evaluations, and participated in revisions of the present document.

Tara Errington and Dr. Sivan Klil-Drori also contributed by supervising patient recruitment and implementation of the study protocol as well as conducted components of the ADHD evaluation.

I, Josh Oliel, contributed by recruiting participants, organizing/conducting the intervention and follow-up, as well as conducted the literature review and statistical analyses for the present thesis.

## Introduction

Attention deficit hyperactivity disorder (ADHD) is generally considered a childhood-onset neurodevelopmental disorder characterized by debilitating patterns of inattention, hyperactivity, and impulsivity (American Psychiatry Association (APA), 2013). Despite the early onset, ADHD symptoms persist into adulthood in 50-60% of cases (Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2013; Weiss & Hechtman, 1993). Stimulant medication (MED) is considered the first-line treatment for the adult patient population (Davidson, 2008; Kolar et al., 2008; NICE Guidelines on ADHD, 2008); however, non-pharmacotherapeutic interventions (i.e., cognitive behavioural therapy (CBT), neurofeedback, and psychoeducation) have been explored (Buitelaar, Kan, & Asherson, 2011).

Aerobic exercise (AE) is another non-pharmacological intervention that may be useful in the treatment of ADHD (see Den Heijer et al., 2017; Halperin, Berwid, & O'Neill, 2014; Klil-Drori & Hechtman, 2016 for full reviews). AE is understood as purposeful physical activity that increases pulse and respiration. Research supporting the potential utility of AE originates from studies using rodent models of ADHD and pediatric patients (Klil-Drori & Hechtman, 2016; Nestler & Hyman, 2010). However, the efficacy of AE as a stand-alone intervention or compared to conventional treatment (i.e., pharmacotherapy) in adults with ADHD remains unknown. The goal of the present study is to assess the relative efficacy of AE and stimulant medication following an eight-week intervention as well as determine whether clinical gains are maintained over a six-month follow-up. Investigating the utility of aerobic exercise is clinically important as if shown to be effective will add to the therapeutic options for this patient population.

## Literature Review

### 1.1. Diagnostic Classification and Clinical Presentation of ADHD in Adulthood

In North America ADHD is frequently diagnosed through the Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5). The DSM-5 classifies ADHD symptoms into three presentations: predominately inattentive presentation (ADHD-I), predominantly hyperactive/impulsive presentation (ADHD-H), and combined presentation (ADHD-C). To meet diagnostic threshold, adults must endorse five symptoms clustered under one of the presentations (American Psychiatric Association, 2013). Additionally, symptoms must have persisted for a substantial period (i.e. ≥ six-months) to a degree that clinically significantly impairs functioning and is developmentally inappropriate (APA, 2013). The DSM-5 also requires that symptoms are present in at least two settings such as school, work, or home. Finally, symptoms must have developed prior to twelve years of age and are not a result of other psychiatric/medical disorders (APA, 2013).

Research suggests that changes occur in the clinical presentation of core ADHD symptoms during adulthood. Specifically, hyperactive/impulsive symptoms tend to decrease with age, whereas inattentive symptoms become more problematic (Hechtman, French, Mongia, & Cherkasova, 2011; Kooij, 2012). Inattentive symptoms may become more problematic due to an increase in societal expectations to meet certain task demands (Hechtman et al., 2011; Kooij, 2012). Therefore, symptoms of inattention resulting in disorganization, procrastination as well as poor punctuality and planning, become more obvious and are strongly associated with functional impairment (Coles, Coon, Demuro, Mcleod, & Gnanasakthy, 2014; Kooij, 2012). Hyperactive/impulsive symptoms typically manifest in more subtle forms during adulthood, which may include persistent feelings of internal restlessness, agitation, or nervousness (Kooij,

2012). However, reports of external hyperactive/impulsive behaviours such as excessive talking or talking loudly as well as dangerous patterns of binge drinking, sexual promiscuity, and reckless driving have also been documented (Kooij, 2012; Lasser, Goodman, & Asherson, 2012).

### 1.1.1. Other Characteristics of ADHD: Comorbid Psychopathology, Functional Impairment, and Self-Esteem

Adults with ADHD are more liable to develop comorbid psychiatric conditions. Specifically, adults display a high incidence of depressive symptoms, with 36% to 50% of patients experiencing at least one episode of major depressive disorder during their lifetime (Sobanski, 2006; Barkley & Murphy, 2007). Subthreshold depressive symptomatology, such as agitation, anhedonia, poor concentration, sleep disturbances, and feelings of inadequacy, also co-occur in adults with ADHD (McIntosh et al., 2009; Torrente et al., 2011, 2014). Additionally, between 40% and 60% of patients are expected to develop at least one anxiety disorder, with social phobia and general anxiety being most prevalent (Sobanski, 2006). Individuals with ADHD symptoms also display elevated symptoms of anxiety as measured by the Beck Anxiety Inventory (BAI; Chao et al., 2008) and State-Trait Anxiety Inventory (STAI; Torrente, López, Lischinsky, Cetkovich-Bakmas, & Manes, 2017). The development of comorbid affective symptoms is highly pertinent as their onset is associated with poor clinical outcomes. Specifically, elevated anxious/depressive symptoms are associated with an increase in ADHD symptomatology (Jarett, 2016; Torrente et al., 2014), suicidality, and psychiatric hospitalizations (Biederman et al., 2008).

The combination of core ADHD symptoms and comorbid psychopathology commonly result in significant functional impairments in affected adults (Kooij, 2012). In terms of

academic performance, college students with ADHD display report study habits, such as difficulties with taking notes, planning for class assignments, and avoiding distractions. Consequently, students with ADHD are more likely to receive a lower GPA relative to controls (Advokat, Lane1, and Luo, 2011). Within the work environment, patients often struggle with following instructions as well as organizing their workload and schedule (Adamou et al., 2013). As a result, patients tend to earn negative performance evaluations, have poor relationships with their supervisors, and are more likely to be fired (Barkley & Murphy, 2010; Shifrin, Proctor, & Prevatt, 2010). Finally, patients report significant interpersonal dysfunctions, including difficulties in social interactions and relational impairments (Eakin et al., 2004; Friedman et al., 2003). With respect to social interactions, patients are less able to maintain conversations and display poor self-presentation skills (Friedman et al., 2003). Within marital contexts, spouses with ADHD tend to report poor marital adjustment, particularly in areas related to affectional expression, cohesion, consensus, and satisfaction (Eakin et al., 2004).

The aforementioned challenges across different functional domains commonly foster poor self-esteem in ADHD patients (Cook, Knight, Hume, & Qureshi, 2014; Kooij, 2012). Self-esteem is defined as a subjective cognitive appraisal regarding one's own self-worth and is influenced by a sense of achievement and competency (Guindon, 2010). Low self-esteem has several important clinical implications. First, poor self-esteem predicts the development of affective disorders that tend to occur in individuals with ADHD (Bajaj, Robins, & Pande, 2016; Sowislo & Orth, 2013). Additionally, self-esteem significantly mediates the relationship between ADHD symptoms and college adjustment (Shaw-Zirt, Popali-Lehane, Chaplin, & Bergman, 2005), as well as the relationship between ADHD symptoms and test anxiety (Cook et al., 2014;

Dan & Cas, 2015). The latter findings suggest that poor self-esteem may promote certain functional impairments within this patient population.

### 1.2. Efficacy of Pharmacotherapy in Adults with ADHD

Pharmacotherapy is considered the principal treatment for ADHD, with stimulants advocated as the medication of choice (Davidson, 2008; Kolar et al., 2008; NICE, 2008). Stimulants are typically classified as methylphenidate compounds (e.g., Biphentin, Concerta, Medikinet, and Ritalin) or amphetamine compounds (e.g., Adderall XR, Dexedrine, and Vyvanse; Kolar et al., 2008; Kooij, 2012). The following section will review research investigating the effectiveness of stimulant medication in adults with ADHD.

A large body of literature has assessed the efficacy of pharmacotherapy on core ADHD symptoms (see Castells et al., 2011; Fredriksen, Halmøy, Faraone, & Haavik, 2013 for full reviews). A study by Medori and colleagues (2008) evaluated the relative effectiveness of three fixed methylphenidate doses (18mg, 36mg, and 72mg) or placebo on ADHD symptoms after five-weeks of treatment. ADHD symptom severity was measured by self and observer versions of the Conner's Adult ADHD Rating Scale (CAARS). Stimulants (irrespective of dose) were more efficacious than placebo in reducing patient and observer ratings of inattentive symptom severity. However, findings were limited as researchers did not examine the long-term effectiveness of pharmacotherapy (Castells et al., 2011). Two separate investigations demonstrated that a 52-week intervention with stimulant medication resulted in significant reductions in patient and clinician ratings of ADHD symptom severity (Buitelaar et al., 2012; Fredriksen et al., 2013; Wender et al., 2011). However, these results were also limited as researchers did not use a control condition post-treatment. Therefore, clinical improvements could not be attributed exclusively to the effects of pharmacotherapy. Finally, a study by Rösler

and colleagues (2009) examined the efficacy of medication on ADHD symptoms in a six-month placebo-controlled trial. Results showed that medication was superior to placebo in reducing clinician (Wender-Reimherr Adult Attention Deficit Disorder Scale) and patient ratings (CAARS total score) of ADHD symptom severity (Fredriksen et al., 2013; Rösler et al., 2009). Overall, stimulants were effective in reducing core ADHD symptoms and medication-related gains were sustained over time.

Previous research has also shown that pharmacotherapy improves functional outcomes in adults with ADHD. Two separate placebo-controlled trials assessed the effect of stimulant medication on functional impairment in adult patients (Huss et al., 2014; Rösler et al., 2013). Functional outcomes were assessed via the Sheehan Disability Scale (SDS); a self-report measure of impairment in work/school, social life, and family life (Sheehan, Harnett-Sheehan, & Raj, 1996). Results showed that stimulant medication was superior to placebo in improving patient ratings of occupational and social functioning (Huss et al., 2014; Rösler et al., 2013). Finally, Wender and colleagues (2011) assessed functional outcomes following 52-weeks of pharmacotherapy. Treatment efficacy was ascertained via the Weissman Social Adjustment Scale; a semi-structured interview evaluating social adjustment. After 52-weeks of treatment, patients displayed significant improvements, relative to baseline, in marital, familial, and occupational adjustment (Fredriksen et al., 2013; Wender et al., 2011). The combination of these findings suggest that pharmacotherapy produced and sustained positive functional outcomes in adults with the disorder.

Researchers have also evaluated the effectiveness of pharmacotherapy on comorbid symptoms of depression and anxiety. A study by Mattos and colleagues (2013) demonstrated that a twelve-week intervention with stimulant medication reduced self-reported symptoms of anxiety

(STAI) and depression (Hamilton Depression Rating Scale; HAM-D). However, this study was limited as it did not include a control condition. Another study assessed the efficacy of medication or placebo on measures of anxiety (Hamilton Anxiety Inventory; HAM-A**)** and depression (HAM-D; Biederman et al., 2010). Results showed that pharmacotherapy was equally effective as placebo in reducing symptoms of depression and anxiety after six weeks of treatment (Biederman et al., 2010). Similarly, Jain and colleagues (2007) did not observe differences in reports of depression (HAM-D) or anxiety (HAM-A) between medication and placebo cohorts. Further complimenting this research, a six-month placebo-controlled study demonstrated no benefits of medication over placebo in reducing symptoms of anxiety or depression (Fredriksen et al., 2013; Rösler et al., 2010). These results suggest that stimulant medication may be suboptimal in treating affective symptoms within this patient population.

1.2.1. Limitations of Stimulant Medication

Although stimulant medication is effective in treating adults with ADHD, several pertinent limitations have also been reported. In clinical trials, effective response to pharmacotherapy is typically defined as 25% reduction in ADHD symptomatology (Hazell et al., 2011); however, some research suggests that symptomatic reductions exceeding 40% are more closely associated with clinically meaningful improvements (Hazell, Lewin, & Sly, 2005; Hazell et al., 2011; Gao, Zhao, Levine, & Allen, 2006). A meta-analysis examining the efficacy of methylphenidate showed that 54% of patients displayed the latter response rate (>40%) to the medication. Thus, a significant subset of patients may display a suboptimal response to stimulant medication (Hazell et al., 2011). Additionally, adults with ADHD show poor medication continuity rates, with mean treatment durations lasting approximately two months in community samples (Perwien, Hall, Swensen, & Swindle, 2004). Thus, adults with ADHD may be reluctant

to take stimulant medication and even when they do they do not seem to persist with this treatment. The combination of these findings underscores the necessity to evaluate novel therapeutic strategies to improve outcomes within this patient population.

### 1.3. Potential Therapeutic Benefits of Aerobic Exercise in ADHD

A growing body of research suggests that physical exercise (PE) may be useful in the treatment of ADHD (Den Heijer et al., 2017; Halperin, et al., 2014; Klil-Drori & Hechtman, 2016). Research on the efficacy of exercise on ADHD symptoms originates from rodent studies (Klil-Drori & Hechtman, 2016; Nestler & Hyman, 2010), pediatric patients (Den Heijer et al., 2017; Halperin, et al., 2014; Klil-Drori & Hechtman, 2016); and the adult population (Den Heijer et al., 2017).

Prior to expanding on the aforementioned research, one must first define physical exercise. PE is defined as a sequence of effortful movements that are performed to sustain or improve health (Den Heijer et al., 2017; Klil-Drori & Hechtman, 2016). PE is further subdivided into aerobic exercise (AE) and non-aerobic exercise. AE is defined as purposeful physical (e.g., running, cycling, and dancing) that elevates pulse and respiration; conversely non-aerobic involve activities (e.g., stretching) that do not produce a change in heartrate and respiration (Den Heijer et al., 2017). The following sections will only focus on research examining the efficacy of aerobic exercise.

#### 1.3.1. Aerobic Exercise in Rodent Models of ADHD

Some researchers use rodent models of psychiatric disorders as they allow for further investigations into neurobiological pathways that support pathological behaviours (Nestler & Hyman, 2010). The spontaneously hypertensive rat (SHR) is a frequently used model of ADHD as the strain displays similar behavioural, cognitive, and neurobiological features as adults with

the disorder (see Meneses et al., 2011 for a full review). Specifically, the SHR display hyperactive/impulsive traits, such as higher levels of locomotor activity and social behaviours (Heal, Smith, Kulkarni, & Rowley, 2008; Hsieh & Yang, 2008). Additionally, SHR show impairments on tasks pertaining to attention, working memory, spatial learning, and distractibility (Meneses et al., 2011; Robinson, Hopkins, & Bucci, 2011). Distractibility is commonly evaluated through measuring whether a rodent continuously responds (or orientates themselves) to an irrelevant or non-reinforced stimulus (Robinson et al., 2011). Finally, SHR show hypocatecholamine function, which may underlie ADHD-related behaviours (Meneses, et al., 2011; Robinson, et al., 2011).

Various studies have assessed the effect of physical activity on ADHD-like traits in SHR. In two separate investigations SHR were given free access to a running wheel for two (Hopkins, Sharma, Evans, & Bucci, 2009) or three weeks (Robinson et al., 2011; Rommel, Halperin, Mill, Asherson, & Kuntsi, 2013). Access to the running wheel resulted in significant reductions in hypersocial (i.e. hyperactivity/impulsivity) and orientating (i.e. distractibility) behaviours. However, exercise failed to reduce locomotor activity (Hopkins et al., 2009; Robinson et al., 2011; Rommel et al., 2013). Other studies utilized structured exercise protocols to assess the effectiveness of exercise or stimulant medication on ADHD-related behaviours. Researchers showed that a four-week treadmill protocol was as effective as methylphenidate in reducing hyper-social behaviours and locomotor activity (Cho, Baek, & Baek, 2014; Baek, Lee, & Baek, 2014). Further analyses revealed treatment with methylphenidate and exercise induced similar increases in the expression of the dopamine D2 receptor and tyrosine hydroxylase (an enzyme involved in the synthesis of dopamine) in the substantia nigra and striatum (Cho, et al., 2014; Baek, et al., 2014). These findings imply that aerobic exercise and methylphenidate both affect

ADHD-like behaviours through promoting activity in the dopaminergic system (Cho, et al., 2014; Baek, et al., 2014). However, ADHD is a complex disorder of the human central nervous system; consequently, it remains unclear whether the positive findings observed in rodents will translate to humans with the disorder.

1.3.2. Aerobic Exercise in Children with ADHD

Previous research investigated the utility of aerobic exercise in medication naïve children with ADHD symptomatology (Den Heijer et al., 2017; Halperin et al., 2014). In one study, a twelve-month sports program resulted in significant reductions in core ADHD symptoms (hyperactive/impulsive and inattentive symptoms), anxiety, restlessness, and aggression (Lufi & Parish-Plass, 2011; Halperin et al., 2014). However, the intervention also included a social skills training component. Therefore, it remains unclear whether these findings were a result of exercise, behavioural therapy, or the combination of the two. In another study, an eight-week aerobic exercise program produced significant improvements in parent/teacher ratings of inattention, hyperactivity, self-esteem, and social functioning. Additionally, participants displayed gains on a cognitive measure of inhibitory control (Smith et al., 2013; Halperin et al., 2014). Finally, Geladé and colleagues (2017) examined the relative efficacy of a ten-week aerobic exercise intervention or pharmacotherapy on cognition. Results indicated that both treatments were effective in improving performance on tasks measuring attention and inhibitory control; however, gains were more pronounced in the medication cohort (Geladé et al., 2017).

Overall, some pediatric research showed that aerobic exercise improved core ADHD symptoms, affective state, social functioning, and self-esteem. However, aerobic exercise may be sub-optimal to stimulants in treating ADHD-related impairment in children. The aforementioned findings must be interpreted with caution as adults with ADHD present unique challenges, such

as substance abuse and personality disorders, that predict poor treatment response (Retz & Retz-Junginger, 2014). Consequently, it remains unclear whether findings within the pediatric population will translate to adults.

1.3.3. Aerobic Exercise in Adults with ADHD

Research on the utility of aerobic exercise in medication naïve adults with ADHD is scarce (Den Heijer et al., 2017). Abramovitch, Goldzweig, & Schweiger (2013) assessed the relationship between exercise habits and psychopathology in adults diagnosed with ADHD. When compared to sedentary patients, those who were physically active reported lower levels of sadness, anxiety (less worrisome and intrusive thoughts), and impulsivity (Abramovitch et al., 2013). However, results were limited as the authors could not infer causation; perhaps adults who were less anxious or depressed were also more inclined to engage in physical activity (Abramovitch et al., 2013). Another study evaluated the effectiveness of a single 20-minute bout of cycling in adults who presented ADHD-like symptoms but were not diagnosed with the disorder. Following the routine participants reported elevated states of energy and motivation, with concomitant reductions in ratings of depression and fatigue (Fritz & O'Connor, 2016). These results imply that aerobic exercise may result in acute mood improvements in adults who display ADHD-related symptoms. However, it remains unclear whether exercise will be an effective therapeutic strategy in adults diagnosed with the disorder. Other lines of research have evaluated the efficacy of aerobic exercise in adults diagnosed with ADHD (Birchfield, 2014; Gapin, Labban, Bohall, Wooten, & Chang, 2015). However, research in adults was limited by practice effects on cognitive tests, did not control medication status, and did not examine the long-term effectiveness of exercise. The current research attempts to address some of these limitations.

### 1.4. Goals and Hypotheses

The goal of the present study is to assess the relative efficacy AE and MED after an eight-week intervention and determine whether therapeutic gains are maintained over a six-month follow-up. Specifically, it will examine treatment effects on ADHD and affective symptoms as well as on self-esteem, and functional impairment. The first hypothesis states AE will result in significant reductions in symptom severity (relative to baseline) post-intervention and after follow-up, but pharmacotherapy will be more efficacious than exercise post-treatment and post-follow-up. Finally, we hypothesize that continued treatment adherence will prove important in the maintenance of therapeutic gains.

## Methods

### 2.1. Ethics Review

The Montreal Children's Hospital Research Ethics Board (REB) approved the study protocol and the consent document.

### 2.2. Participants & Recruitment

***Power Analysis & Sample.*** The sample size for the current study was based on a power analysis. Results revealed that 36 patients per cohort will produce an 80% power level to detect a medium effect size (0.3) with $\alpha = 0.05$. Due to time constraints N = 31 adults meeting DSM-5 diagnostic criteria for ADHD were randomly assigned to aerobic exercise ($n = 21$) and medication ($n = 10$). Considering the underpowered nature of the study, this research was classified as a pilot study.

***Patient Recruitment***. Potential participants were referred to the research clinic by community/University health service centers, their health care provider, or by self-referral.

Additionally, research staff sent introduction letters and flyers to professionals and clinics to raise awareness of the study.

***Telephone Interview.*** The goal of the initial interview was twofold. First, study staff provided patients with detailed information regarding the intervention. If participants were interested in the study, they were asked a series of questions to determine eligibility. The inclusion/exclusion criteria of this study were based on prior research conducted by the ADHD Research Program (Cherkasova et al., 2016; Cumyn, French, & Hechtman, 2009; Errington, 2012). Exclusion criteria consisted of: 1) a history of neurological illness (i.e. chorea, epilepsy, head injury, seizures, multiple sclerosis, and stroke); 2) psychiatric comorbidities requiring treatment; 3) medical conditions that contraindicate the use of stimulant medication or aerobic exercise; 4) recreational drug use or 5) alcohol abuse; 6) a full-scale intelligence quotient (FSIQ) < 85 and 7) pregnancy or breast feeding (Cherkasova et al., 2016; Cumyn, et al., 2009; Errington, 2012). Additionally, participants were excluded if they were currently receiving treatment (pharmacological or non-pharmacological) for ADHD. Post-interview, patients were informed they would only be invited to the clinical trial if they received an ADHD diagnosis and received permission from their treating physician to perform aerobic exercise. In cases where a person was ineligible, they were provided a document detailing other support services and resources.

2.3. Assessment of Attention Deficit Hyperactivity Disorder

***Pre-Assessment Materials***. A standardized diagnostic protocol was implemented to assess the presence and severity of ADHD symptomatology in childhood and adulthood (Cherkasova et al., 2016; Cumyn et al., 2009; Errington, 2012). First, participants were required to obtain a referral that 1) requested an ADHD evaluation and 2) stated that they were fit to perform aerobic exercise. Following this, an electronic package of questionnaires measuring

childhood and current symptoms was sent to the participants. Each of the included questionnaires consisted of a patient and observer version of the document. Current ADHD symptoms were measured by the Conner's Adult ADHD Rating Scale (Conners, Erhardt, & Sparrow, 1999) and Barkley Current ADHD Symptoms Scale (Barkley & Murphy, 1998); whereas retrospective childhood symptoms were measured by the Barkley Childhood ADHD Symptom Scale (Barkley & Murphy, 1998) and Wender Utah Rating Scale (Cherkasova et al., 2016; Ward, Wender, & Reimherr, 1993). If results indicated a participant met diagnostic threshold, they were invited for a standardized ADHD assessment (Cumyn et al., 2009).

***Assessment Materials.*** The assessment was comprised of a psychopathological evaluation as well as neuropsychological and academic testing (Cherkasova et al., 2016; Cumyn et al., 2009; Errington, 2012). All assessments were conducted by a psychiatrist or a trained research assistant holding at least a master's degree in psychiatry, psychology, or a related field.

Psychopathology was measured by the Conners' Adult ADHD Diagnostic Interview-Part I and II **(**CAADID; Epstein, Johnson, & Conners, 2000), the Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2015), and the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD; First, Williams, Benjamin, & Spitzer, 2015). The CAADID-Part I collected information on: 1) demographic characteristics; 2) medical/psychiatric history; 3) ADHD-related risk factors; and 4) the developmental trajectory of ADHD symptoms (Epstein & Kollins, 2006). Part-II evaluated ADHD diagnostic information, such as symptomatic age of onset as well as the degree of symptom pervasiveness and impairment in childhood and adulthood (Epstein & Kollins, 2006). Finally, the SCID-5 and SCID-5-PD were respectively used to assess comorbid psychiatric disorders/syndromes (e.g., depressive disorders, anxiety

disorders, substance abuse disorders, and psychotic disorders) and comorbid personality disorders (e.g., Antisocial Personality Disorder and Borderline Personality Disorder).

Neuropsychological testing was conducted via subtests from the Wechsler Adult Intelligence Scale-IV (WAIS-IV; Wechsler, 2008). These subtests comprised the Verbal Comprehension Index (Information, Similarities, and Vocabulary), Working Memory Index (Digit Span and Arithmetic), Processing Speed Index (Coding and Symbol Search), and Perceptual Reasoning Index (Block Design, Matrix Reasoning, and Visual Puzzles; Lichtenberger & Kaufman, 2013). These four indices allowed for the calculation of the FSIQ. Finally, academic testing was performed on the arithmetic and reading subscales of the Wide Range Achievement Test-IV (WRAT-IV; Wilkinson, 1993).

***Post-Assessment.*** The study's psychiatrist evaluated the findings to determine if the participant met diagnostic criteria for ADHD, demonstrated an FSIQ > 85, and displayed no psychiatric comorbidities that demanded treatment. If this was the case, the patient was deemed eligible to participate in the clinical trial. A total of N = 51 were recruited and based on our criteria N = 31 were eligible and randomized into a treatment arm (See Figure 1 (page 22) for a flow of participants through the study).

2.4. Aerobic Exercise

***Eight-Week Intervention***. AE sessions were conducted twice a week for eight consecutive weeks and were led by a certified exercise instructor. The meetings took place in a large conference room within the hospital. Sessions were comprised of ten minutes of warm-up, forty minutes of aerobic exercise, and ten minutes of cooldown with stretches. The forty-minute of aerobic exercise component was subdivided into eight separate trials that each lasted five minutes. Within each trial, four minutes were dedicated to medium or high intensity aerobic

exercise and one minute was dedicated to rest. The instructor selected aerobic activities to perform during the trials; which included running, walk-lunges, high-knees, jumping-jacks, and walk-squats. Intensity of these trials was based on participant's maximum heart rate ($HR_{max}$; $HR_{max}$= 220 - age). Specifically, moderate exercise was defined as 50-60% of $HR_{max}$, whereas high intensity exercise was defined as 70-80% of $HR_{max.}$ (American College of Sports Medicine, 2010). The initial session consisted of six medium intensity trials (50-60% of $HR_{max}$) and two high intensity trials (70-80% of $HR_{max}$). The intensity of the sessions was gradually increased throughout the intervention; specifically, each week a medium intensity trial was substituted with one of high intensity. By the final week (of the intervention) the sessions were comprised exclusively of eight high intensity trials.

***Six-Month Follow-up.*** Patients were asked to continue performing two hours of weekly aerobic exercise for the entire follow-up period. Research staff provided participants a log to record the frequency, type, and intensity of activity performed during the week. Additionally, patients were asked to not start a new treatment for ADHD. However, if a patient wanted to begin pharmacotherapy (or a non-pharmacological treatment), they were asked to return to the clinic for an end-point evaluation. Finally, patients attended follow-up visits at the research clinic three and six months following the intervention.

2.5. Medication Only

***Medication Titration*.** Patients randomly allocated MED underwent a standardized titration protocol (Cherkasova et al., 2016), which lasted until optimal dose was attained. Optimal dosage was defined as the lowest dose of medication that produced the greatest benefits with the least side effects. At the start of medication titration, patients were prescribed a low dose of an amphetamine or methylphenidate compound. Following this, participants were asked to

attend follow-up visits to determine if adjustments to the medication were required. Medication dose was modified in accordance with patient reports of medication efficacy and side effects (via the CADDRA Patient ADHD Medication form; http://www.caddra.ca/pdfs/caddraGuidelines2011_Toolkit.pdf) as well as changes in vital signs (heart rate and blood pressure) and weight (Cherkasova et al., 2016). Of the participants who attained optimal dose, six were prescribed a methylphenidate compound (Concerta (*n*=3) or Biphentin (*n*=3) and two were prescribed an amphetamine compound (Adderall XR (*n*=2)).

***Eight-Week Intervention.*** Following titration, participants attended education sessions on ADHD which were conducted on a weekly basis. Each session lasted sixty minutes and did not include therapeutic techniques found in behavioural therapy. The education sessions were held to control for the potential effects of non-exercise factors (e.g., peer support) occurring in AE-only. The education sessions were on the following subjects. 1) The presentation of ADHD in adulthood and 2) co-occurring psychopathology. 3) The neurobiology of ADHD. The effects of ADHD symptoms on 4) relationships and 5) familial life. 6) Examinations into the positive aspects of ADHD. 7) Available treatments for adults with the disorder and 8) summary of the information.

***Six Month Follow-up.*** Participants were asked to continue their prescribed treatment, limit aerobic activity to one hour a week, and log daily medication use. Patients were asked to return to the research clinic for a medication visit at 3M-PI and 6M-PI. During these visits medication efficacy was ascertained and dosage was modified if necessary. Once participants completed the follow-up they were referred to their treating physician. If a patient wanted to suspend medication use (or drop-out prior to study completion), they were required to return to the clinic for a final safety visit and an end-point evaluation.

2.6 Makeup-Sessions During the Intervention.

Participants were allowed to attend a maximum of three makeup sessions throughout the eight-week intervention. Makeup sessions were scheduled in accordance with the availability of the exercise space, the aerobics instructor, and the patients.

2.7. Measures

Assessments pertaining to psychopathological and functional outcomes was conducted at several points: baseline (BL), post-intervention (PI), three-months post-intervention (3M-PI), and six-months post intervention (6M-PI). The following section provides a description of instruments used at each assessment period.

***Barkley ADHD Current Symptom Scale (Barkley & Murphy, 1998).*** Patient and informant versions of the Current Symptom Scale (CSS-S/O) were used to assess frequency (i.e. never or rarely, sometimes, often, and very often; Barkley & Murphy, 1998) of diagnostic ADHD symptoms over the preceding week. The CSS is comprised of 18 items that are equally divided into the inattentive (i.e., poor attentional control, executive function, and distractibility) and hyperactive/impulsive subscale (i.e., poor impulse control, disinhibition, and restlessness (Aycicegi, Dinn, & Harris, 2003; Knouse, Traeger, O'Cleirigh, & Safren, 2013). A total score exceeding 24 is indicative of clinically significant ADHD symptomatology (Cherkasova et al., 2016). Psychometric properties of the CSS include adequate test-retest reliability ($r$ = 0.85 to 0.90; Dupaul, Power, Anastopoulos, & Reid, 1998), convergent validity (Rodriguez & Simon-Dack, 2013) and items demonstrate good internal consistency on the inattentive ($\alpha = 0.71$) and hyperactive/impulsive subscales ($\alpha = 0.83$; Knouse, et al., 2013).

***Beck Depression Inventory-II (Beck, Steer, & Brown, 1996).*** The Beck Depression Inventory-II (BDI-II) is a 21-item measure of depressive symptomatology occurring over the

previous week (Steer, Ranieri, Kumar, & Beck, 2003). The BDI-II demonstrates moderate discriminant validity ($r$ = 0.47), suggesting it adequately distinguishes symptoms of depression from anxiety (Strohmeier, Rosenfield, Ditomasso, & Ramsay, 2016). The BDI-II also displays strong test-retest reliability (r = 0.93) and convergent validity ($r$ = 0.75; Wang & Gorenstein, 2013).

***Beck Anxiety Inventory (BAI; Beck & Steer, 1990).*** The BAI is 21-point instrument evaluating the severity of (psychological and somatic) anxiety symptoms over the past week (Beck & Steer, 1990; Gloster et al., 2008). Symptom severity is ascertained through participants ranking experienced symptoms on a four-point scale ranging from 0 (not at all) to 3 (severely; Beck & Steer, 1990; Strohmeier et al., 2016). The BAI shows high internal consistency ($\alpha$ = 0.92) and moderate convergent validity ($r$ = 0.51) with other anxiety scales (Beck, Epstein, Brown, & Steer, 1988; Strohmeier et al., 2016). Finally, the BAI shows proficient discriminant validity ($r$ = 0.25) with the HAM-D (Beck et al., 1988; Strohmeier et al., 2016).

***Sheehan Disability Scale (SDS; Sheehan et al., 1996)***. The SDS is a self-report measure of functional impairment. The instrument consists of three scales that evaluate the extent symptoms of an illness disrupt activities in areas related to work/school, social life, and family life (Huss et al., 2014). The SDS shows good test-retest reliability ($r$ = 0.72) and internal consistency ($\alpha$ = 0.79; Coles et al., 2014). Additionally, the subscales of the instrument (work/school, social life, and family life) correlate well with clinician ratings of ADHD symptom severity. The latter findings suggest instrument is sensitive to ADHD-related functional impairment (Coles et al., 2014).

***Index of Self-Esteem (ISE; Hudson, 1982; Abell, Jones, & Hudson, 1984).*** The ISE is a 25-item self-report instrument of self-esteem. All items on the scale are ranked on a five-point

scale, with scores exceeding 30 indicating significant psychological distress (Normann-Eide, Johansen, Normann-Eide, Egeland, & Wilberg, 2015). The ISE shows high internal validity ($\alpha = 0.95$) and correlates well with other measures of self-esteem (Taylor, 2005).

## Data Analysis

### 3.1. Therapeutic Efficacy of AE and MED: Mixed Linear Model

***Study Design, Participants, & Baseline Characteristics.*** The current study implemented a multi-period design throughout an eight to ten-month period. Therefore, to assess rate of symptomatic change over time participants with ≤ 1 observation point were excluded from the analysis (see Figure. 1 (page 22) for a flow chart of patients through the study). The primary analysis was comprised of N = 23 and patients were subdivided into AE (*n* = 15) and MED (*n* = 8). Group differences in baseline characteristics were assessed via parametric (independent-samples *t*-test) or non-parametric tests (Mann-Whitney U) and categorical variables were evaluated by chi-squared test.

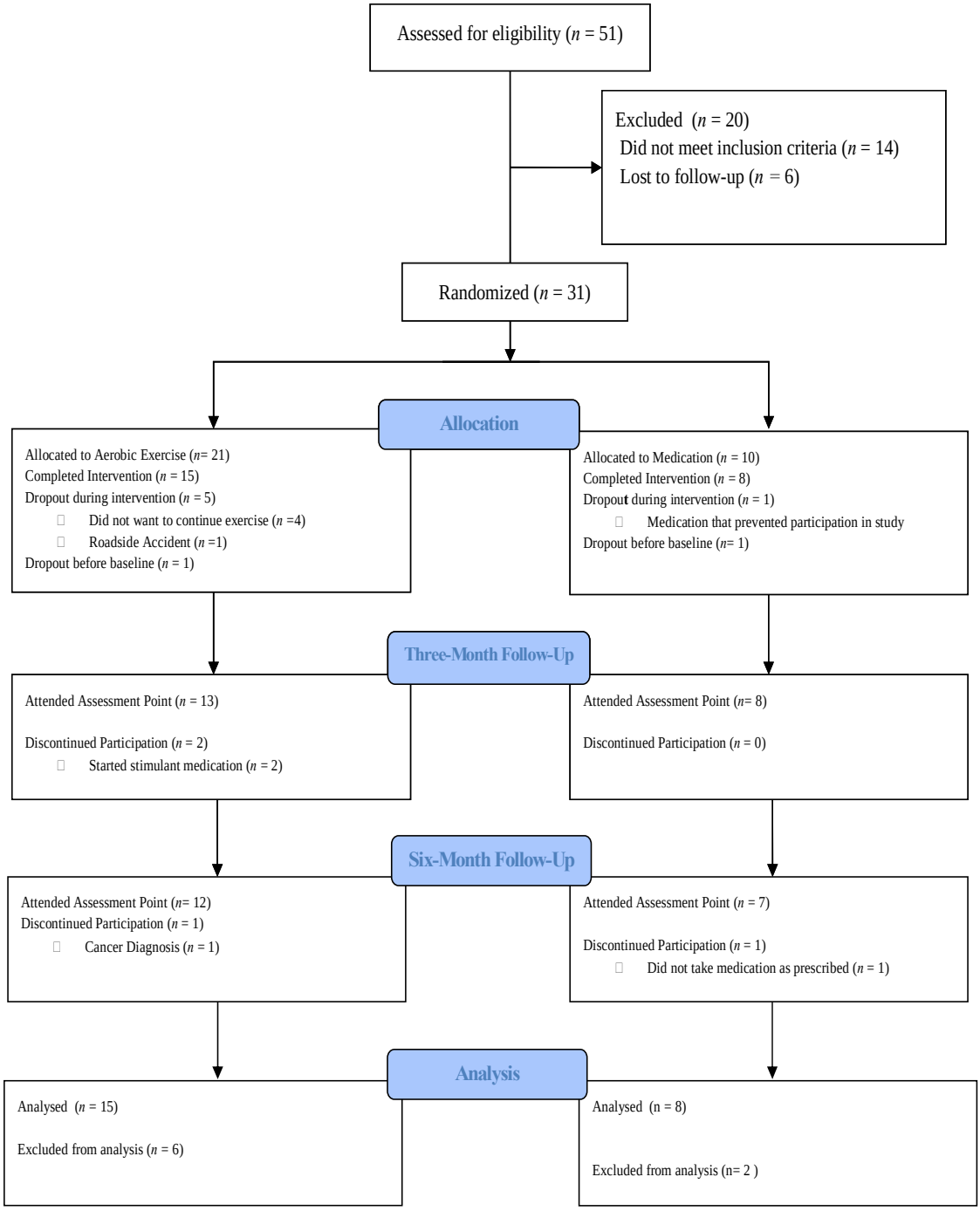



Figure 1. Flow of participants included in Mixed Linear Model

***Statistical Protocol.*** The statistical protocol was adapted from a prior study evaluating the relative efficacy of cognitive behavioural therapy (CBT) or CBT+MED following a twelve-week intervention and six-month follow-up (Cherkasova et al., 2016). Data analysis was performed on SPSS Version 23 (IBM Corporation). Mixed linear model was conducted on each dependent variable by using the restricted maximum likelihood procedure. This statistical analysis was selected as it accounts for missing data; thus, a greater number of participants were included in the analysis and no imputation techniques were required (Hoifodt et al., 2013). Fixed effects were imputed as Treatment ($T_x$), assessment point (AP), and $T_x \times AP$. Repeated effects was defined as assessment point (i.e., Baseline (BL), Post-Intervention (PI), Three-Months Post-Intervention (3M-PI), and Six-Months Post-Intervention (6M-PI)) and a first order auto-regressive covariance structure was utilized. Finally, random effects were accounted for by calculating intercepts for each patient.

***Treatment Effect.*** To examine treatment effects, a priori comparisons that assessed symptomatic change in [outcome variable] from baseline to post-intervention within both cohorts were constructed. An additional a priori comparison was constructed between cohorts at PI to ascertain relative therapeutic efficacy. Note that the above contrasts were conducted with estimated means (*EMs*) generated by the mixed linear model.

***Maintenance Effect.*** To determine the maintenance of therapeutic gains, planned contrasts that assessed symptomatic change in [outcome variable] were constructed from PI to 6M-PI within both groups. An additional a priori comparison was conducted between cohorts at the six-month follow-up to determine relative therapeutic efficacy. Note that the above comparisons were performed with *EMs* that were produced by the mixed linear model. To limit the number of comparisons and select the most important ones regarding the maintenance effect,

the three-month time point was not used as a contrast. Specifically, comparisons from PI to 3M-PI, 3M-PI to 6M-PI, and group differences at 3M-PI were omitted. Therefore, our selected maintenance effect (PI to 6M-PI) alludes to overall symptomatic change across the six-month follow-up.

Significance threshold for primary variables (i.e., patient and observer versions of the ADHD Current Symptom Scale) was set at $\alpha = 0.05$; whereas secondary outcomes (i.e., Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI), Sheehan Disability Scale (SDS), and Index of Self Esteem (ISE)) was set at $\alpha = 0.008$ (Cherkasova et al., 2016). The latter α-level was Bonferroni-corrected (divided by the number of contrast ($k = 6$) for each dependent variable) to control family-wise error ("IBM, Calculation of Bonferroni-Adjusted p-Values", 2016; Cherkasova et al., 2016). Secondary variables with $p$-values < 0.05 but > 0.008 were considered trends (Cherkasova et al., 2016).

***Test of Normality***. Shapiro-Wilk's Test of Normality was conducted on standardised residuals of each model to ensure the data did not violate normality (Sainani, 2012). Square-root transformations ($\sqrt{(x)}$) were applied to each value in the dataset if normality was violated ($p < 0.05$). Secondary mixed linear models were then constructed with the transformed data and standardised residuals were reassessed for normality.

3.2 Secondary Hypothesis: Treatment Adherence and the Maintenance Effect

The following analysis was only conducted on participants who provided data during the follow-up period, AE: $n = 12$ and MED: $n = 7$.

Rate of treatment adherence during the follow-up was ascertained via patient logs. Within aerobic exercise, maximum adherence to treatment (i.e., 100%) was set at a minimum of two hours (or 120 minutes) of weekly activity. Within medication, total adherence (i.e., 100%) was

defined as daily medication use throughout the follow-up period. Rate of adherence was calculated by averaging weekly patient-recordings of treatment use (AE: Activity time (in minutes); MED: Number of days medication was consumed) and dividing it by the recommended regimen (AE: 120 minutes of aerobic activity; MED: seven days of medication use). Thus, the larger the percentage, the greater adherence to the recommended treatment.

We had hoped to conduct Pearson correlation to assess the relationship between rate of adherence and maintenance of treatment effects on ADHD symptoms (difference in CSS-S score from PI to 6M-PI). However, scatter plots showed great variability in adherence, particularly in aerobic exercise. That coupled with the small sample size made correlational analyses non-feasible (See page 38 for further elaboration). However, independent samples *t*-test was performed to assess group differences in rate of adherence during the six-month follow-up.

## Results

### 4.1. Attrition Analysis

Multiple linear regression was applied to the entire dataset (N = 31) to identify variables (i.e., group assignment, sex, and age) that predicted dropout. None of these factors were significant predictors of attrition ($p > 0.05$). Rate of attrition from baseline was as follows: PI (AE: 25%; MED: 11.1%), 3M-PI (AE= 35%; MED = 11.1%), and 6M-PI (AE= 40%; MED = 22.2%). Although attrition rates were larger in exercise, chi-squared tests revealed no significant difference in attrition between cohorts: post-intervention ($p = 0.39$), 3M-PI ($p = 0.18$), and 6M-PI ($p = 0.35$).

### 4.2. Therapeutic Efficacy of AE and MED: Mixed Linear Model

The following analyses reflect participants included in the mixed linear model (N = 23; AE: $n = 15$; MED: $n = 8$).

***Baseline Analysis & Participation.*** Group differences in demographic characteristics (i.e., sex, age, and education level) were assessed. Sex ratio, age, and level of education did not differ between groups ($p > 0.05$). Additionally, no group differences were observed in diagnostic status, IQ, ADHD symptomatology, and anxious/depressive symptom severity ($p > 0.05$; See Table. 1 (page 27) for descriptive statistics of baseline characteristics). Group differences in participation during the eight-week intervention was also examined. In terms of attendance, MED displayed a greater attendance rate ($M$=100%, SD = 0.0) than AE ($M$ = 91.2%, SD = 7.7), t (21) = -3.02, $p < 0.05$. However, Mann-Whitney U-test revealed no difference in attendance to makeup sessions between cohorts ($p > 0.05$).

***Primary Analysis.*** The following section details results of a priori contrasts, model values reflect estimated means (*EM*) generated by the mixed linear model. Please see Table 2 (page 28) for descriptive statistics and results of planned comparisons.

Table 1. Demographics and Baseline Score of Participants Included in Mixed Linear Model

| | AE | MED | Test-Statistic | *p* |
|---|---|---|---|---|
| Age *M*(SD) | *32.53* (8.83) | 35.64 (13.15) | t (21) = -0.68 | 0.51 |
| Sex (n) | | | $\chi^2$ (1, N = 23) = 1.06 | 0.30 |
| Males | 6 | 5 | | |
| Females | 9 | 3 | | |
| Level of Education Attained or in Progress (*n*) | | | $\chi^2$ (5, N = 23) = 6.38 | 0.27 |
| Highschool | 1 | 0 | | |
| Trade School | 0 | 1 | | |
| College/CEGEP | 3 | 4 | | |
| University-Undergraduate | 8 | 1 | | |
| University- Graduate | 2 | 1 | | |
| No Data | 1 | 1 | | |
| Subtype (*n*) | | | $\chi^2$ (2, N = 23) = 0.008 | 0.93 |
| Combined | 4 | 2 | | |
| Inattentive | 11 | 6 | | |
| Hyperactive | 0 | 0 | | |
| Full Scale IQ *M*(SD) | *97.33* (9.86) | *105.50* (12.78) | t(21) = -1.70 | 0.10 |
| Baseline Scores *M*(SD) | | | | |
| ADHD Current Symptoms Scale-Self (CSS-S) | *31.80* (9.30) | *28.13* (6.15) | t(21) = 1.01 | 0.33 |
| ADHD Symptoms-Observer (CSS-O) | *28.47* (11.42) | *23.38* (9.87) | t(21) = 0.11 | 0.28 |
| Beck Depression Inventory (BDI) | *11.87* (8.85) | *8.88* (6.56) | t(21) = 0.837 | 0.41 |
| Beck Anxiety Inventory (BAI) | *8.13* (5.55) | *4.75* (5.20) | t(21) = 1.42 | 0.17 |
| Sheehan Disability Scale (SDS) | *13.53* (6.42) | *15.88* (5.69) | t(21) = -0.86 | 0.40 |
| Index of Self Esteem (ISE) | *46.80* (15.23) | *34.13* (13.25) | t(21) = 1.98 | 0.06 |

Note. AE = Aerobic Exercise; MED = Medication; ADHD CSS-S/O = ADHD Current Symptoms Scale- Self/Observer; BDI = Beck Depression Inventory; Beck Anxiety Inventory (BAI); SDS = Sheehan Disability Scale; ISE = Index of Self-Esteem.

Table 2. Descriptive Statics and a Priori Comparisons from Mixed Linear Model

| | BL | PI | Pre/Post Treatment: *Within Group* | AE *vs*. MED at PI *Between Group* | PI | 6M-PI | Pre/Post Follow-up *Within Group* | AE *vs*. MED at 6M-PI *Between Group* |
|---|---|---|---|---|---|---|---|---|
| | *EM*(SE) | *EM*(SE) | *p* | *p* | *EM*(SE) | *EM*(SE) | *p* | *p* |
| **CSS-S** | | | | 0.06 | | | | 0.001** |
| AE | *31.80*(2.32) | *23.13*(2.32) | $p < 0.0001$** | | *23.13*(2.32) | *20.79*(2.43) | 0.34 | |
| MED | *28.13*(3.17) | *15*.5(3.17) | $p < 0.0001$** | | *15.50*(3.17) | *6.84*(3.31) | 0.011* | |
| **CSS-O** | | | | 0.026* | | | | 0.035***** |
| AE | *28.47*(2.84) | *21.38*(2.95) | 0.015* | | *21.38*(2.95) | *20.11*(3.00) | 0.63 | |
| MED | *23.38*(3.88) | *10.00*(3.88) | 0.0010** | | *10.00*(3.88) | *9.20*(3.98) | 0.81 | |
| **BAI** | | | | 0.040***T*** | | | | 0.001***bc*** |
| AE | *2.70(0.30)* | *2.22 (3.0)* | 0.17 | | *2.22 (3.0)* | 2.66(0.33) | 0.24 | |
| MED | *1.76(0.40)* | *1.12 (0.40)* | 0.18 | | *1.12 (0.40)* | 0.78(0.43) | 0.50 | |
| **BDI-II** | | | | 0.33 | | | | 0.014***T*** |
| AE | *3.14*(0.36) | *2.63*(0.36) | 0.12 | | *2.63*(0.36) | *2.96*(0.38) | 0.32 | |
| MED | *2.76*(0.50) | *2.01*(0.51) | 0.10 | | *2.01*(0.51) | *1.32*(0.51) | 0.13 | |
| **SDS** | | | | 0.018 ***T*** | | | | 0.011***T*** |
| AE | *13.53*(1.47) | *9.80* (1.47) | 0.06 | | *9.80*(1.47) | *9.84*(1.58) | 0.99 | |
| MED | *15.88*(2.01) | *3.75* (2.01) | $p < 0.0001$***bc*** | | *3.75*(2.01) | *2.97*(2.09) | 0.75 | |
| **ISE** | | | | 0.049 ***T*** | | | | 0.002***bc*** |
| AE | *46.80(*3.99) | *44.13*(3.99) | 0.33 | | *44.13*(3.99) | 43.65(4.14) | 0.87 | |
| MED | *34.13*(5.47) | *30.25*(5.46) | 0.30 | | *30.25*(5.46) | 20.20(5.57) | 0.012***T*** | |

Descriptive values reflect estimated means (*EM*) and standard error (SE) in aerobic exercise (AE) and medication (MED). ADHD Current Symptom Scale Self/Observer (CSS-S/O); Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI), Sheehan Disability Scale (SDS), Index of Self Esteem (ISE). Assessment point defined as Baseline (BL), Post Intervention (PI), and Six-Months Post-Intervention (6M-PI).

Primary Variables (ADHD-S/O):
* = Statistically significant (not Bonferroni corrected) at $p < 0.05$
** = Statistically significant (not Bonferroni corrected) at $p < 0.01$

Secondary Variables (BAI, BDI-II, SDS, ISE):
***bc*** = Statistically significant (Bonferroni corrected) at $p < 0.008$
***T*** = Trend-status (Bonferroni corrected) at $0.05 > p > 0.008$.

4.2.1. Primary Variables: Patient and Observer Ratings of ADHD Symptomatology

**Patient *Version of the CSS.*** Aerobic exercise and medication produced significant improvements from baseline in patient ratings of ADHD symptomatology following the intervention (AE: $p < 0.0001$; MED: $p < 0.0001$); however, MED-related gains were marginally superior to exercise at PI ($p = 0.06$). Analysis of the maintenance effect revealed that AE did not display significant changes (progressive or regressive) in ADHD ratings over the six-month follow-up ($p = 0.34$). Conversely, medication produced further reductions on the CSS-S from PI to 6M-PI ($p = 0.011$) and MED-related gains were significantly greater than exercise at the final assessment point ($p = 0.001$; See Table 2 (page 28) for estimated means and results of planned contrasts). Treatment patterns across time revealed that both cohorts improved post-intervention; however, exercise largely maintained therapeutic gains whereas medication facilitated further improvement from PI to the three-month follow-up and maintained gains until 6M-PI (See Figure 2.A (page 31) for a graph examining the relative efficacy of AE and MED on patient ratings of ADHD symptoms across assessment points).

***Observer Versions of the CSS.*** Aerobic exercise and pharmacotherapy promoted significant reductions (from baseline) in observer ratings of ADHD symptom severity post-intervention (AE: $p = 0.015$; MED: $p = 0.0010$); however, MED-related gains were significantly larger than AE at PI ($p = 0.026$). A priori contrasts examining maintenance of treatment effects revealed that neither cohort displayed significant changes in symptom severity from PI to 6M-PI ($p > 0.05$). Additionally, medication-related gains were significantly larger than exercise at the six-month evaluation point ($p = 0.035$; See Table 2 (page 28) for *EMs* and results of a priori comparisons). Both groups displayed a pattern of symptomatic improvement post-intervention and treatment effects were largely maintained

until the final assessment point (See Figure 2.B (page 31) for a graph examining the efficacy of AE and MED across time on observer-ratings of ADHD Symptoms).

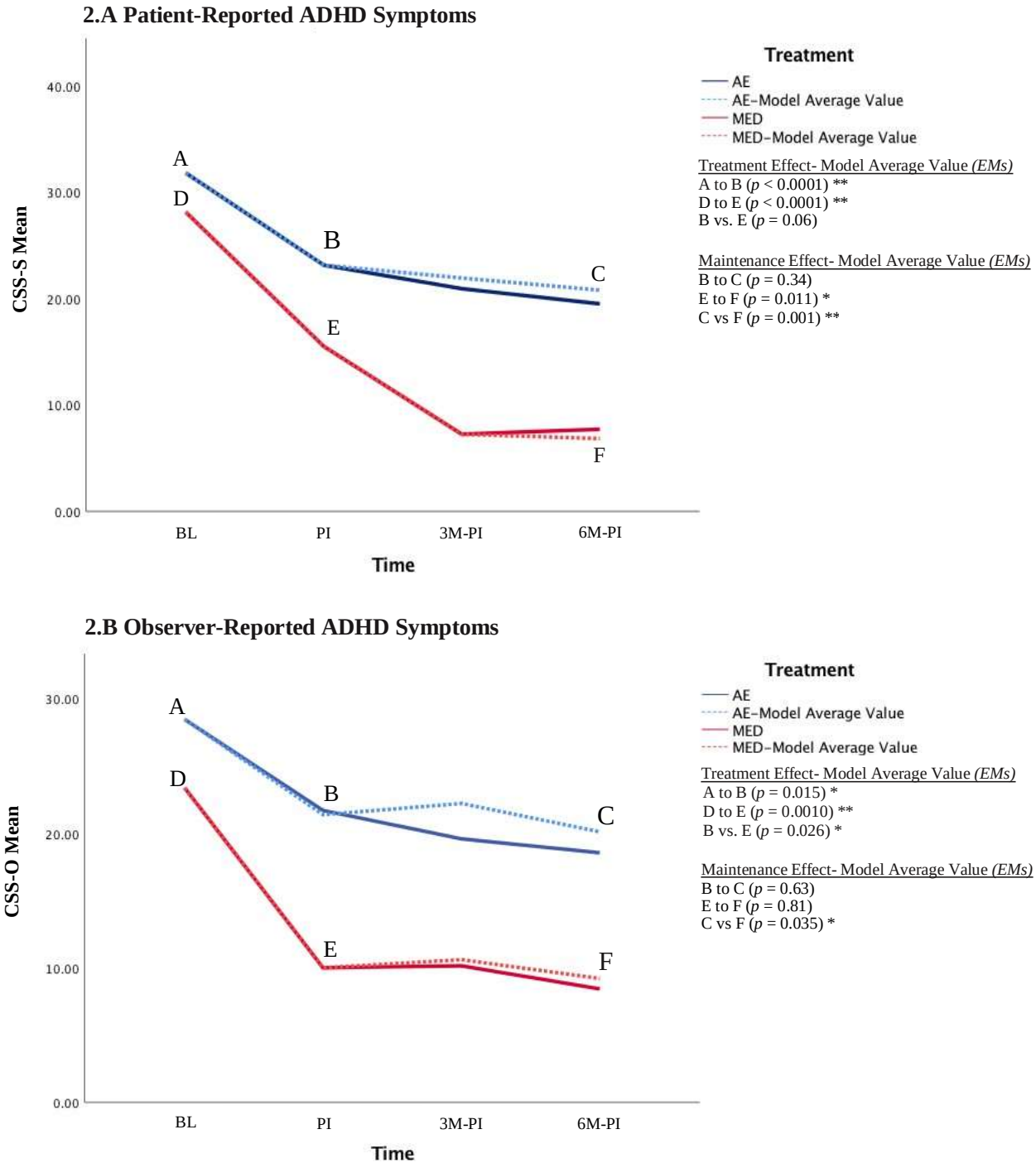



**Figure 2.** Relative Effectiveness of AE and MED on ADHD Symptomatology Across Assessment Points

Patient (2.A) and observer (2.B) reported CSS throughout the intervention- lower scores are indicative of reduced ADHD symptom severity. Solid lines reflect means of raw data, dotted lines reflect estimated means generated by the mixed linear model. Assessment periods: Baseline (BL) = AE (A) and MED (D); Post Intervention (PI) = AE (B) and MED (E); Three Months Post-Intervention (3M-PI); and Six Months Post-Intervention (6M-PI) = AE (C) and MED (F). No significant differences were observed between groups at baseline (A vs D).

2.A Planned Contrasts for ADHD Current Symptoms Scale-Patient (CSS-P)

Treatment Effect: A to B ($p < 0.0001$) **, D to E ($p < 0.0001$) **, B vs. E ($p = 0.06$)

Maintenance Effect: B to C ($p = 0.34$), E to F ($p = 0.011$) *, C vs F ($p = 0.001$) **

2.B A-priori Comparisons for Current Symptoms Scale-Observer (CSS-O)

Treatment Effect: A to B ($p = 0.015$) *, D to E ($p = 0.0010$) **, B vs. E ($p = 0.026$) *

Maintenance Effect: B to C ($p = 0.63$), E to F ($p = 0.81$); C vs F ($p = 0.035$) *



* = Statistically significant (not Bonferroni corrected) at $p < 0.05$

** = Statistically significant (not Bonferroni corrected) at $p < 0.01$

4.2.2. Secondary Variables: Anxiety, Depression, Functional Impairment, and Self-Esteem

***Beck Anxiety Inventory***. Shapiro-Wilk Test of Normality demonstrated $p < 0.01$; therefore, √(x) transformations were applied. Results of normality test on transformed data revealed that the dataset was normally distributed ($p = 0.18$). Neither cohort displayed significant reductions (relative to baseline) in anxiety ratings following the intervention ($p > 0.05$). However, MED-related effects were marginally superior to exercise post-intervention ($p = 0.040$). Analysis of the maintenance effect revealed that neither condition showed significant changes in ratings of anxiety from PI to 6M-PI ($p > 0.05$); however, MED-related effects were significantly larger than exercise at the final assessment point ($p = 0.001$; See Table 2 (page 28) for descriptive statistics and results of planned comparisons). Medication produced gradual patterns of decline in anxiety scores from baseline to 3M-PI and gains were largely maintained until 6M-PI. Conversely, exercise produced patterns of decline post-intervention, maintained treatment effects until 3M-PI, and showed deterioration from 3M-PI to 6M-PI. This deterioration of the maintenance effect (within AE) may explain why medication-related effects were significantly greater than exercise post-follow-up (See Figure 3.A (page 34) for a graph on the relative effectiveness of AE and MED on BAI-score throughout the study).

***Beck Depression Inventory.*** Shapiro-Wilk Test of Normality revealed $p < 0.01$; therefore, √(x) transformations were implemented. Test of normality on transformed data showed $p > 0.05$. Aerobic exercise and medication did not produce significant improvements (from baseline) following the intervention and therapeutic gains did not differ between cohorts ($p > 0.05$). A priori comparisons evaluating maintenance of clinical gains revealed no change in depressive ratings from PI to 6M-PI in either cohort ($p > 0.05$); however, medication produced improvements that were marginally superior to AE at the

six-month assessment point ($p = 0.014$; See Table 2 (page 28) for estimated means and results of a priori comparisons). Treatment patterns revealed that pharmacotherapy resulted in gradual patterns of decline from baseline to 3M-PI and showed slight deterioration from 3M-PI to 6M-PI. Conversely, AE displayed a pattern of decline following the intervention, maintained gains until 3M-PI, and slight deterioration from 3M-PI to 6M-PI (See Figure 3.B (page 34) for a graph depicting treatment effects on BDI-II-score across time).

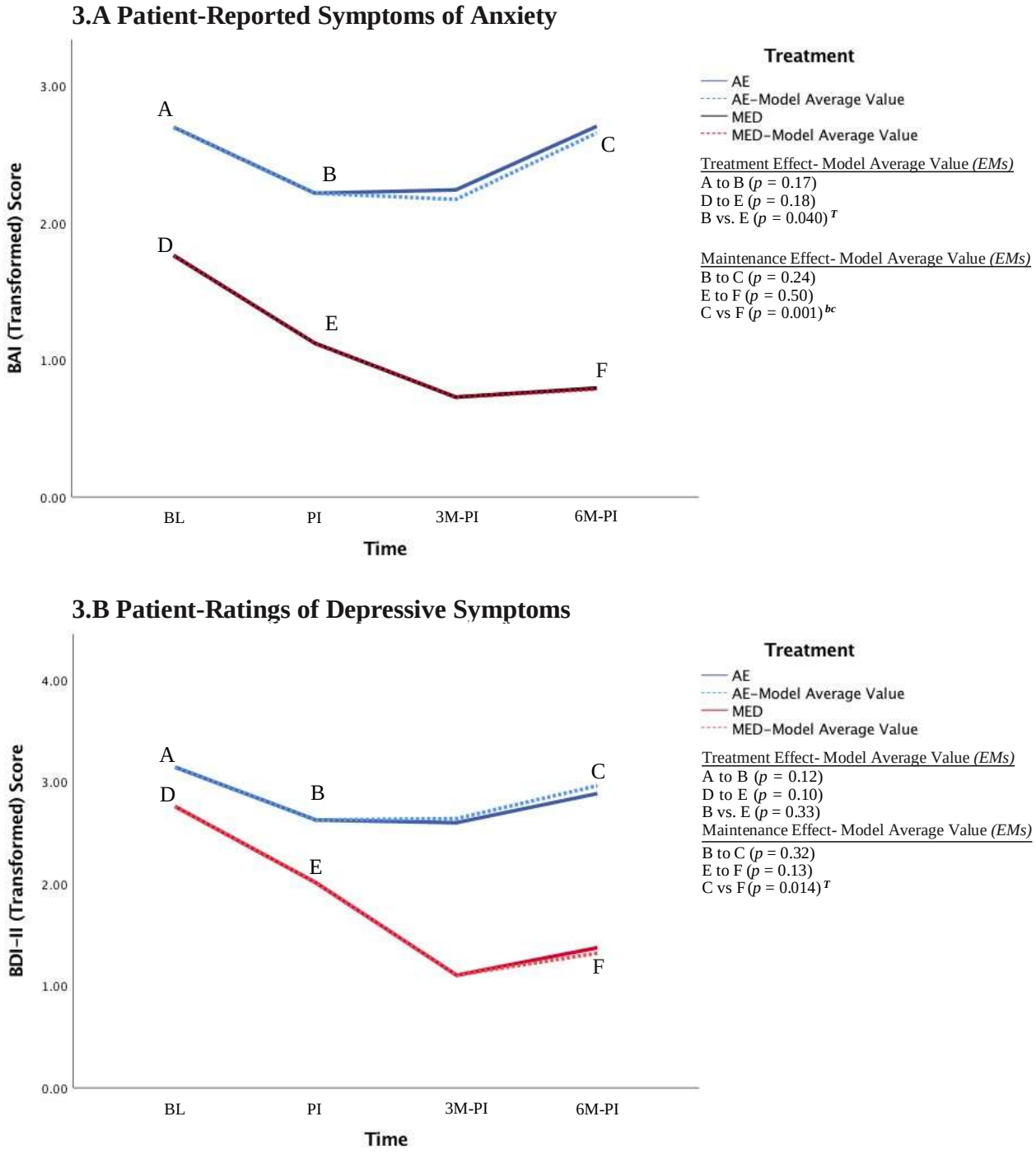



**Figure 3.** Relative Effectiveness of AE and MED on Anxious/Depressive Symptoms across Evaluation Points
Rate of change in patient ratings of (3.A) anxious (Beck Anxiety Inventory) and (3.B) depressive symptoms (Beck Depression Inventory-II) reported throughout the intervention- lower scores are indicative of reduced psychopathology. Solid lines reflect means of raw data, while dotted lines reflect estimated means generated by the mixed linear model. Assessment periods: Baseline (BL) = AE (A) and MED (D); Post Intervention (PI) = AE (B) and MED (E); Three Months Post-Intervention (3M-PI); and Six Months Post-Intervention (6M-PI) = AE (C) and MED (F). No significant differences were observed between groups at baseline (A vs. D).

3.A. A-priori Contrasts for Beck Anxiety Inventory (BAI)
Treatment Effect: A to B ($p$ = 0.17), D to E ($p$ = 0.18), B vs. E ($p$ = 0.040) $^{T}$
Maintenance Effect: B to C ($p$ = 0.24), E to F ($p$ = 0.50), C vs F ($p$ = 0.001) $^{bc}$

3.B. A-priori Comparisons for Beck Depression Inventory (BDI-II)
Treatment Effect: A to B ($p$ = 0.12), D to E ($p$ = 0.10), B vs. E ($p$ = 0.33)
Maintenance Effect: B to C ($p$ = 0.32), E to F ($p$ = 0.13), C vs F ($p$ = 0.014) $^{T}$



$^{bc}$ = Statistically significant, Bonferroni corrected, at $p < 0.008$
$^{T}$ = Trend-status, Bonferroni corrected, at $0.05 > p > 0.008$.

***Sheehan Disability Scale.*** AE promoted non-significant reductions from baseline in ratings of functional impairment post-intervention ($p = 0.06$); whereas medication produced significant reductions in SDS-ratings following the intervention ($p < 0.0001$). Moreover, MED-related gains were marginally greater than AE at PI ($p = 0.018$). Analysis of the maintenance effect demonstrated that neither condition displayed significant changes in ratings of functional impairment from PI to 6M-PI ($p > 0.05$); however, medication-related gains were marginally superior to exercise at 6M-PI ($p = 0.011$; See Table 2 (page 28) for estimated means and results of a priori contrasts). Medication produced a pattern of symptomatic improvement post-intervention and treatment gains were largely maintained until the end of follow-up. Aerobic exercise also displayed a pattern of symptomatic improvement post-intervention; but showed patterns of maintenance from PI to 3M-PI and slight deterioration from 3M-PI to 6M-PI (See Figure 4.A (page 37) for a graph on the relative efficacy of AE and MED on ratings of functional impairment).

***Index of Self-Esteem*.** Pharmacotherapy and aerobic exercise did not produce significant improvements in ratings of self-esteem post-intervention ($p > 0.05$); however, medication-related effects were marginally superior to AE at PI ($p = 0.049$). Analyses examining maintenance of therapeutic effects revealed that exercise did not produce significant changes on the ISE post-intervention ($p > 0.05$); whereas, medication resulted in marginally significant improvements from PI to 6M-PI ($p = 0.012$). Finally, MED-related effects were significantly greater than exercise at the six-month evaluation point ($p = 0.002$; See Table 2 (page 28) for estimated means and results of a priori comparisons). Medication produced a gradual pattern of symptomatic improvement across the assessment periods. Conversely, AE displayed an initial pattern of slight improvement from BL to 3M-PI and some deterioration during follow-up. This weakening of

the maintenance effect (within AE) may explain why medication attained significance over exercise at 6M-PI (See Figure 4B (page 37) for a graph on the relative effectiveness of treatments on the ISE).

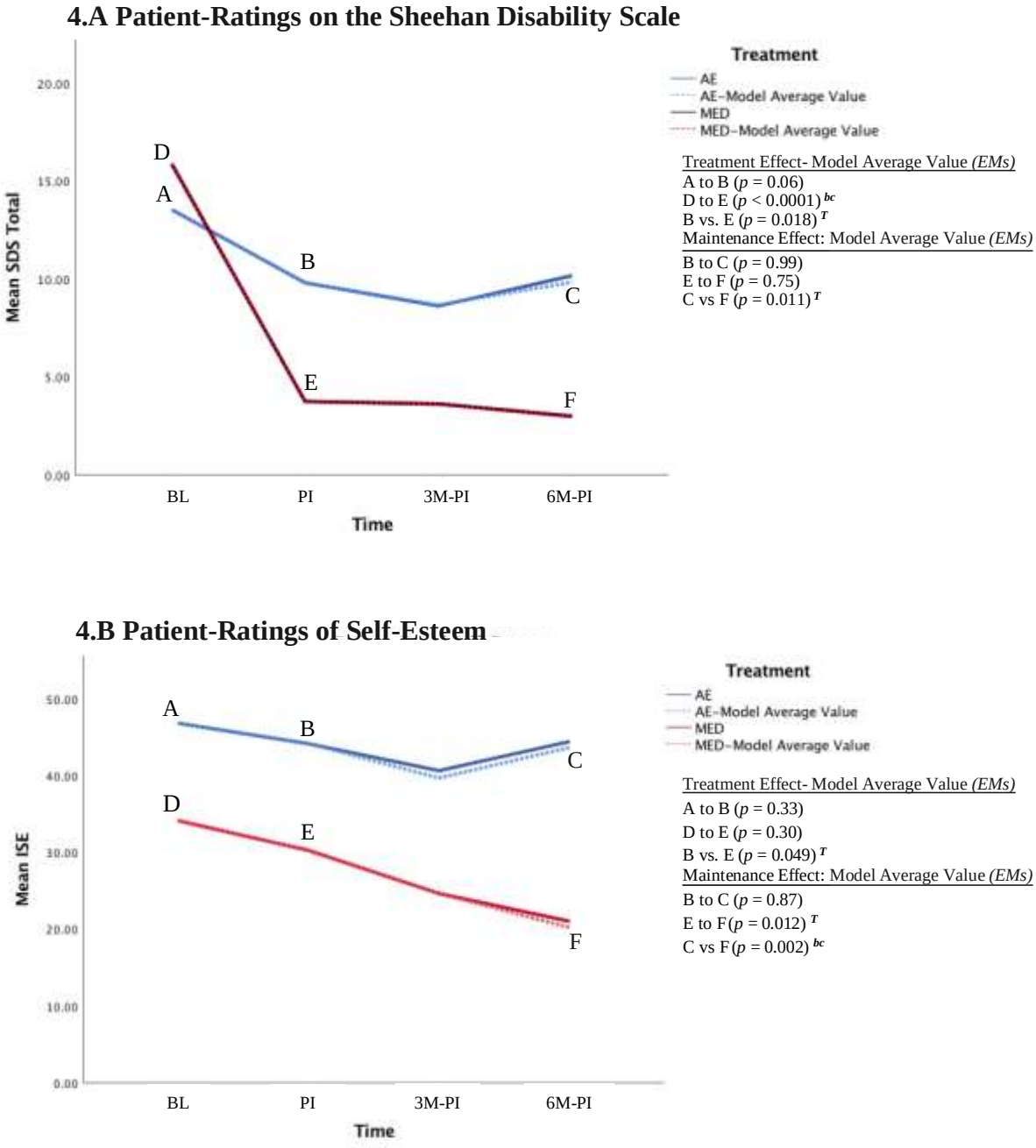



**Figure 4.** Relative Effectiveness of AE and MED ADHD on Functional Impairment and Self Esteem
Rate of change in patient ratings of (4.A) functional impairment (Sheehan Disability Scale-Total Score) and (4.B) self-esteem (Index of Self-Esteem) throughout the intervention- lower scores are indicative of more optimal functioning. Solid lines reflect means of raw data, while dotted lines reflect estimated means generated by the mixed linear model. Assessment periods defined as: Baseline (BL) = AE (A) and MED (D); Post Intervention (PI) = AE (B) and MED (E); Three Months Post-Intervention (3M-PI); and Six Months Post-Intervention (6M-PI) = AE (C) and MED (F). No significant differences were observed between groups at baseline (A vs. D).

4.A. A-priori Contrasts for Sheehan Disability Scale (SDS)
Treatment Effect: A to B ($p$ = 0.06), D to E ($p$ < 0.0001) $^{bc}$, B vs. E ($p$ = 0.018) $^{T}$
Maintenance Effect: B to C ($p$ = 0.99), E to F ($p$ = 0.75), C vs F ($p$ = 0.011) $^{T}$

4.B. A-priori Contrasts for Index of Self Esteem (ISE)
Treatment Effect: A to B ($p$ = 0.33), D to E ($p$ = 0.30), B vs. E ($p$ = 0.049) $^{T}$
Maintenance Effect: B to C ($p$ = 0.87), E to F ($p$ = 0.012) $^{T}$ , and C vs F ($p$ = 0.002) $^{bc}$

$^{bc}$ = Statistically significant, Bonferroni corrected, at $p$ < 0.008
$T$ = Trend-status, Bonferroni corrected, at 0.05 > $p$ > 0.008.

4.3. Treatment Adherence and Maintenance Effect

***Treatment Adherence During the Six-Month Follow-up.*** Pharmacotherapy displayed an average adherence rate of 94.50% with a range of scores from 86% to 100%; whereas, aerobic exercise displayed an average adherence rate of 59.10% with a range of scores from 10% to 92%. Independent samples t-test revealed that pharmacotherapy ($M$ = 94.50%, SD = 5.50) displayed a significantly larger adherence rate than aerobic exercise ($M$ = 59.10%, SD = 21.07), t(17) = 3.49 , $p$ = 0.0028.

***Correlational Analysis.*** Prior to conducting Pearson's correlation, scatter plots were constructed (within both cohorts) to ascertain the presence of a linear relationship between treatment adherence (during follow-up) and maintenance of ADHD symptoms (See Appendix B for scatter plots constructed in AE and MED; Rochford, 2017). Visual inspection of scatter plots revealed no apparent linear relationship between the variables in either group (See Appendix B for scatter plots in AE and MED). This may have occurred as a function of distinct data distribution patterns in adherence rate (i.e., a ceiling effect within MED and widespread variability within AE) and the small sample size (AE: $n$ = 12; MED: $n$ = 7). Due to the absence of a linear relationship, we could not reliably conduct correlational analysis to determine whether treatment adherence was associated with the maintenance effect (Rochford, 2017).

## Discussion

The current pilot study assessed the relative efficacy of aerobic exercise and pharmacotherapy in adults diagnosed with ADHD. Treatment efficacy was ascertained following an eight-week intervention and throughout a six-month follow-up. Additional analyses examined group differences in treatment adherence across the follow-up period.

5.1. Primary Hypothesis: Relative Efficacy of AE and MED in Adults With ADHD

Results revealed that aerobic exercise and medication were effective in reducing patient-reported ADHD symptom severity from baseline after the intervention. Moreover, estimated means suggested that reductions in both cohorts fell below pathological threshold (i.e., < 24 on the CSS-S) following the intervention. However, exercise promoted gains that were maintained until the final assessment point; whereas, pharmacotherapy promoted further improvements from PI to 6M-PI that were superior to AE at the final assessment point. Similar results were found with observer-ratings of ADHD symptom severity. Specifically, exercise and medication produced reductions in scores post-intervention and clinical gains were sustained until the end of follow-up. However, unlike the CSS-S, medication did not produce further improvements in observer ratings from PI to 6M-PI. The discordance between the patient and observer scale may be attributed to increased error on the latter outcome measure. Error on the CSS-O may have been introduced as a function of missing responses (i.e., observers who did not return questionnaires) and discordant raters across the assessment points. Overall, both treatments produced clinically significant improvements post-intervention; however, medication-related gains were largely improved on during follow-up to a degree greater than exercise.

Analyses of the SDS (Sheehan Disability Scale) and ISE (Index of Self Esteem) revealed that medication produced significant or trend-level improvement (respectively) over exercise post-intervention. During follow-up, MED-related gains were sustained on the SDS such that ratings trended over exercise at 6M-PI; conversely, medication-related gains on the ISE gradually improved across follow-up to an extent that attained statistical significance (over exercise) at the final assessment point. Overall, the later findings suggest that MED-related effects may translate better than exercise to functional improvement.

Analyses of affective scales revealed that medication was more effective than exercise in improving anxious and depressive symptom severity. Specifically, pharmacotherapy produced marginally significant reductions in anxiety ratings post-intervention and MED-related effects were significantly greater than exercise at the six-month assessment point. With relation to depressive ratings, medication displayed trends of improvement (relative to exercise) at the end of the follow-up period. The later results imply that medication demonstrated greater clinical efficacy than exercise on anxious/depressive symptoms following prolonged treatment and affective symptomatology may be resistant to the effects of exercise within this patient population. The aforementioned findings must be interpreted cautiously. First, values on affective scales required $\sqrt{(x)}$ transformations as the original data violated normality. Therefore, one may postulate that reducing scores on these scales obscured potential treatment effects. Additionally, participants were assessed for and excluded if they expressed comorbid psychopathological symptoms requiring treatment; consequently, findings only pertain to mildly affected individuals.

By and large patterns of the graphs for the two treatment groups were different. For AE, there was a decline in symptoms from BL to PI followed by a maintenance of gains until the end of follow-up (e.g., CSS-S/O) or a pattern of deterioration from 3M-PI to 6M-PI (e.g., BAI, BDI, ISE, and SDS). For medication, one pattern revealed improvement from BL to PI, further improvement to 3M-PI, and maintenance of gains to 6M-PI (e.g., CSS-S, BAI, BDI, and ISE). An additional pattern revealed a decline from baseline to PI, followed by symptomatic maintenance until the end of follow-up (e.g., CSS-O and SDS). However, patterns of deterioration during the follow-up period were seldom observed in the medication cohort.

5.2. Secondary Analyses: Treatment Adherence within AE and MED

We also examined group differences in treatment compliance throughout the six-month follow-up. Results revealed that pharmacotherapy displayed a significantly larger rate of adherence (94.50%) than aerobic exercise (59.10%). The later finding implies that patients assigned to MED were more inclined to maintain a daily medication regimen, whereas those assigned to AE were less inclined to maintain the (two hours per week) exercise routine during follow-up. Our results differ from other studies demonstrating medication adherence rates (in adults with ADHD) ranging from 50-60% (see Adler & Nierenberg, 2010 for a full review). This may be attributed other studies implementing more objective measures of therapeutic adherence (e.g., pharmacy log) and a larger sample size. Our results must be interpreted cautiously as analyses were conducted on a fraction of the original cohort and relied exclusively on patient-reported accounts of treatment use; consequently, reported adherence rates may be inflated.

Additionally, we could not reliably conduct correlational analyses to assess the relationship between treatment adherence and therapeutic maintenance within AE and MED. Despite this, prior research using a larger sample size revealed that continuity of treatment (i.e., medication) correlated positively with symptomatic improvement (Adler & Nierenberg, 2010). Therefore, one may speculate that greater adherence to treatment (particularly within medication) may largely explain some of our results. First, medication only produced gains on certain scales (i.e., CSS-S, BAI, and ISE) that were significantly larger than exercise at the follow-up assessment point; perhaps greater treatment adherence (throughout follow-up) potentiated pharmacotherapeutic efficacy. Additionally, group differences in therapeutic adherence may underlie the discordance in treatment patterns. Specifically, one may speculate that poor therapeutic adherence (as observed in AE) increases susceptibility to a pattern of deterioration in the maintenance effect; whereas greater compliance to treatment (as observed in MED) protects

against deterioration. However, a larger sample size and the implementation of more objective measures (e.g., pharmacy logs or gym attendance logs completed by a fitness instructor) are necessary to elucidate the relationship between treatment adherence and symptomatic maintenance.

5.3 Implications, Strengths Limitations, and Future Directions.

***Implications & Strengths.*** Our findings are the first to show that aerobic exercise is effective in treating ADHD-related symptoms in adults diagnosed with the disorder. Specifically, this was the first study to show that exercise promotes acute clinical gains (following the intervention) and symptomatic improvements are sustained over time. Our findings expanded on prior literature that showed a positive relationship between activity level and psychopathology (Abramovitch et al., 2013) as well as other studies that used participants without a formal ADHD diagnosis (Fritz & O'connor, 2016) or did not assess the long-term efficacy of exercise (Birchfield, 2014; Gapin et al., 2015). Another strength of the study was that it controlled for the effects of concomitant treatment (i.e., exercise, medication, and psychotherapy) during the intervention and six-month follow-up. This increased specificity of treatment effects and improved on other exercise-interventions that did not account for participants' treatment status (Birchfield, 2014; Gapin et al., 2015). Finally, this was the first study that compared the effectiveness of aerobic exercise to conventional treatment (i.e., pharmacotherapy) in the adult patient population with ADHD. Our analyses bolstered stimulant medication as the standard for the treatment of adults with the disorder; however, results also suggested that non-pharmacological treatment avenues (such as aerobic exercise) demonstrates clinical efficacy.

***Limitations and Future Directions.*** The implications of our findings must be interpreted within the context of the study limitations. As previously discussed, primary analyses to assess

relative therapeutic efficacy were conducted on a small sample size, N = 23 (AE: *n* = 15; MED; *n* = 8). Therefore, comparisons between cohorts may have been non-significant as a function of increased variability. Additionally, the current study largely relied on patient-ratings to ascertain treatment efficacy and adherence. Future research should implement more objective measures such as a clinician rating scale (e.g., Clinical Global Impression (CGI), neuropsychological test of attention, and pharmacy/gym attendance logs. Moreover, the current study excluded patients with comorbid psychiatric disorders; therefore, our results may not generalise to a substantial subset of adults with ADHD. Moreover, the current study did not utilize a non-therapeutic cohort (e.g., waitlist control), as such it remains unclear whether observed treatment effects were a result of treatment or participation in a clinical trial. Finally, the present study did not control/account for lifestyle habits (e.g., physical activity routine) at baseline.

Although this study provided preliminary evidence that AE may be effective in the treatment of ADHD, the efficacy of a combination intervention (AE and MED) remains elusive. Prior research evaluated the utility of aerobic exercise as an adjunct to stimulant medication in children with ADHD (Den Heijer et al., 2017). Specifically, two clinical trials assessed the efficacy of a six-week aerobic exercise intervention or an educational course in medicated patients (Choi, Han, Kang, Jung, & Renshaw, 2015; Kang, Choi, Kang, & Han, 2011; Den Heijer et al., 2017). Results revealed that aerobic exercise was superior to education in improving ADHD symptomatology and neuropsychological performance, which was associated with an increase in the activation of the right frontal and temporal lobes (Choi et al., 2015; Kang et al., 2011). The combination of these findings imply that aerobic exercise may potentiate the efficacy of pharmacotherapy on ADHD- related impairment. Furthermore, aerobic exercise may exert this therapeutic effect through increasing neural activity within the frontotemporal network. Future

studies should evaluate whether exercise enhances pharmacotherapeutic efficacy in adults as well as implement neuroimaging techniques (e.g., fMRI) to examine physiological changes associated with treatment.

**Summary of Findings and Conclusions.**

Our findings are the first to show that aerobic exercise is effective in treating ADHD-related symptoms and treatment effects are maintained over a substantial period of time. Despite this, pharmacotherapy produced gains that were significantly greater than exercise on scales pertaining to ADHD, anxiety, and self-esteem; but the later improvements were largely seen during the follow-up period. Moreover, results revealed that pharmacotherapy elicited greater therapeutic compliance (relative to exercise) throughout the six-month follow-up. These findings allow for the speculation that greater treatment adherence (within medication) facilitated the aforementioned improvements during the follow-up period. Overall, aerobic exercise was effective in the treatment of ADHD, but medication-related gains were more pronounced (especially during the maintenance period) on a greater number of outcome measures.

## References

Abell, N., Jones, B. L., & Hudson, W. W. (1984). Revalidation of the Index of Self- Esteem. *Social Work Research and Abstracts*, *20*, 11-16.

Abramovitch, A., Goldzweig, G., & Schweiger, A. (2013) Correlates of Physical Activity with intrusive Thoughts, Worry and Impulsivity in Adults with Attention–Deficit/Hyperactivity Disorder: A Cross- Sectional Pilot Study. *Israel Journal of Psychiatry Related and Related Sciences, 50*, 47–54.

Aycicegi, A., Dinn, W. M., & Harris, C. L. (2003). Assessing Adult Attention-Deficit/Hyperactivity Disorder: A Turkish Version of the Current Symptoms Scale. *Psychopathology, 36*, 160-167.

Adler, L. D., & Nierenberg, A. A. (2010). Review of Medication Adherence in Children and Adults with ADHD. *Postgraduate Medicine, 122*, 184-191.

Advokat, C., Lane, S. M., & Luo, C. (2011). College students with and without ADHD: Comparison of Self-Report of Medication Usage, Study Habits, and Academic Achievement. *Journal of attention Disorders, 15*, 656-666.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th Ed.). Arlington, VA: American Psychiatric Publishing.

American College of Sports Medicine. (2010). *ACSM's Guidelines for Exercise Testing and Prescription*. Pennsylvania, Philadelphia: Lippincott Williams & Wilkins.

Adamou, M., Arif, M., Asherson, P., Aw, T. C., Bolea, B., Coghill, D., & Pitts, M. (2013). Occupational Issues of Adults with ADHD. *BioMed Central Psychiatry, 13*, 59-67.

Bajaj, B., Robins, R. W., & Pande, N. (2016). Mediating Role of Self-Esteem on the Relationship Between Mindfulness, Anxiety, and Depression. *Personality and Individual Differences, 96*, 127-131.

Baek, D. J., Lee, C. B., & Baek, S. S. (2014). Effect of Treadmill Exercise on Social interaction and Tyrosine Hydroxylase Expression in the Attention-Deficit/Hyperactivity Disorder Rats. *Journal of Exercise Rehabilitation, 10*, 252-257.

Barkley, R. A., & Murphy, K. R. (2010). Impairment in Occupational Functioning and Adult ADHD: The Predictive Utility of Executive Function (EF) Ratings Versus EF Tests. *Archives of Clinical Neuropsychology, 25*, 157-173.

Barkley, R. A., & Murphy, K. R. (1998). *Attention Deficit Hyperactivity Disorder: A Clinical Workbook* (2 Ed.). New York, NY: Guilford Publications.

Barkley, R. A., & Murphy, K. R. (2007). Comorbid Psychiatric Disorders in Adults with ADHD. *ADHD Report, 15*, 1–7.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for Measuring Clinical Anxiety: Psychometric Properties. *Journal of Consulting and Clinical Psychology*, *56*, 893-897.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory-II.* San Antonio, *78*, 490-498.

Beck, A. T., & Steer, R. A. (1990). *Manual for the Beck Anxiety Inventory*. San Antonio, TX: Psychological Corporation.

Biederman, J., Ball, S. W., Monuteaux, M. C., Mick, E., Spencer, T. J., Mcreary, M., & Faraone, S. V. (2008). New insights into the Comorbidity Between ADHD and Major Depression in Adolescent and Young Adult Females. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*, 426-434.

Biederman, J., Mick, E., Surman, C., Doyle, R., Hammerness, P., Kotarski, M., & Spencer, T. (2010). A Randomized, 3-Phase, 34-Week, Double-Blind, Long-Term Efficacy Study of Osmotic-Release Oral System-Methylphenidate in Adults with Attention-Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology*, *30*, 549-553.

Birchfield, N. (2014). *The Effects of Assisted Cycle Therapy on Executive and Motor Functioning in Young Adult Females with Attention-Deficit Hyperactivity Disorder*. Arizona State University.

Buitelaar, J. K., Kan, C. C., & Asherson, P. (2011). *ADHD in Adults: Characterization, Diagnosis, and Treatment*. Cambridge University Press.

Buitelaar, J. K., Trott, G. E., Hofecker, M., Waechter, S., Berwaerts, J., Dejonkheere, J., & Schäuble, B. (2012). Long-Term Efficacy and Safety Outcomes with OROS-MPH in Adults with ADHD. *International Journal of Neuropsychopharmacology*, *15*, 1-13.

Castells, X., Ramos-Quiroga, J. A., Rigau, D., Bosch, R., Nogueira, M., Vidal, X., & Casas, M. (2011). Efficacy of Methylphenidate for Adults with Attention-Deficit Hyperactivity Disorder. *Central Nervous System Drugs*, *25*, 157-169.

Coles, T., Coon, C., Demuro, C., Mcleod, L., & Gnanasakthy, A. (2014). Psychometric Evaluation of the Sheehan Disability Scale in Adult Patients with Attention-Deficit/Hyperactivity Disorder. *Neuropsychiatric Disease and Treatment*, *10*, 887-895.

Conners, C. K., Erhardt, D., & Sparrow, E. (1999). *Conner's Adult ADHD Rating Scales: Technical Manual*. Multi-Health Systems incorporated (MHS).

Cook, J., Knight, E., Hume, I., & Qureshi, A. (2014). The Self-Esteem of Adults Diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD): A Systematic Review of the Literature. *ADHD Attention Deficit and Hyperactivity Disorders*, *6*, 249-268.

Chao, C. Y., Gau, S. S., Mao, W. C., Shyu, J. F., Chen, Y. C., & Yeh, C. B. (2008). Relationship of Attention-Deficit–Hyperactivity Disorder Symptoms, Depressive/Anxiety Symptoms, and Life Quality in Young Men. *Psychiatry and Clinical Neurosciences, 62*, 421-426.

Cherkasova, M. V., French, L. R., Syer, C. A., Cousins, L., Galina, H., Ahmadi-Kashani, Y., & Hechtman, L. (2016). Efficacy of Cognitive Behavioral therapy with and without Medication for Adults with ADHD: A Randomized Clinical Trial. *Journal of Attention Disorders, 43*, 831-842.

Cherkasova, M., Sulla, E. M., Dalena, K. L., Pondé, M. P., & Hechtman, L. (2013). Developmental Course of Attention Deficit Hyperactivity Disorder and Its Predictors. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 22*, 47.

Cho, H. S., Baek, D. J., & Baek, S. S. (2014). Effect of Exercise on Hyperactivity, Impulsivity and Dopamine D2 Receptor Expression in the Substantia Nigra and Striatum of Spontaneous Hypertensive Rats. *Journal of Exercise Nutrition & Biochemistry, 18*, 379-384.

Choi, J. W., Han, D. H., Kang, K. D., Jung, H. Y., & Renshaw, P. F. (2015). Aerobic Exercise and Attention Deficit Hyperactivity Disorder: Brain Research. *Medicine & Science in Sports & Exercise, 47*, 33-39.

Cumyn, L., French, L., & Hechtman, L. (2009). Comorbidity in Adults with Attention-Deficit Hyperactivity Disorder. *The Canadian Journal of Psychiatry, 54*, 673-683.

Dan, O., & Cas, S. (2015). the Relationships Among ADHD, Self-Esteem, and Test Anxiety in Young Adults. *Journal of Attention Disorders, 19*, 231-239.

Davidson, M. A. (2008). Literature Review: ADHD in Adults: A Review of the Literature. *Journal of Attention Disorders, 11*, 628-641.

Den Heijer, A. E., Groen, Y., Tucha, L., Fuermaier, A. B., Koerts, J., Lange, K. W., & Tucha, O. (2017). Sweat It Out? the Effects of Physical Exercise on Cognition and Behavior in Children and Adults with ADHD: A Systematic Literature Review. *Journal of Neural Transmission, 124*, 3-26.

Dupaul, G., Power, T. J., Anastopoulos, A. D., & Reid, R. (1998). *ADHD Rating Scale–IV: Checklists, Norms, and Clinical interpretation.* New York, NY: Guilford.

Eakin, L., Minde, K., Hechtman, L., Ochs, E., Krane, E., Bouffard, R., & Looper, K. (2004). The Marital and Family Functioning of Adults with ADHD and their Spouses. *Journal of Attention Disorders, 8*, 1-10.

Epstein, J. N., Johnson, D., & Conners, C. K. (2000). *Conners' Adult ADHD Diagnostic Interview for DSM-IV.* North Tonawanda, NY: Multi-Health Systems, inc

Epstein, J. N., & Kollins, S. H. (2006). Psychometric Properties of An Adult ADHD Diagnostic interview. *Journal of Attention Disorders, 9*, 504-514.

Errington, T. A. (2012). *The Treatment of Adults with Attention-Deficit/Hyperactivity Disorder (ADHD): The Impact on Marital Relationships and Family Functioning*. Mcgill University, Montreal, QC.

First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2015). *Structured Clinical interview for DSM-5 Disorders, Clinician Version (SCID-5-CV).* Arlington, VA: American Psychiatric Association.

First, M. B., Williams, J. B. W., Benjamin, L. S., & Spitzer, R. L. (2015). *User's Guide for the SCID-5-PD (Structured Clinical interview for DSM-5 Personality Disorder*). Arlington, VA, American Psychiatric Association,

Fredriksen, M., Halmoy, A., Faraone, S. V., & Haavik, J. (2013). Long-Term Efficacy and Safety of Treatment with Stimulants and Atomoxetine in Adult ADHD: A Review of Controlled and Naturalistic Studies. *European Neuropsychopharmacology*, *23*, 508-527.

Friedman, S. R., Rapport, L. J., Lumley, M., Tzelepis, A., Vanvoorhis, A., Stettner, L., & Kakaati, L. (2003). Aspects of Social and Emotional Competence in Adult Attention-Deficit/Hyperactivity Disorder. *Neuropsychology*, *17*, 50.

Fritz, K. M., & O'Connor, P. J. (2016). Acute Exercise Improves Mood and Motivation in Young Men with ADHD Symptoms. *Medicine and Science in Sports and Exercise*, *48*, 1153-1160.

Gapin, J. I., Labban, J. D., Bohall, S. C., Wooten, J. S., & Chang, Y. K. (2015). Acute Exercise Is Associated with Specific Executive Functions in College Students with ADHD: A Preliminary Study. *Journal of Sport and Health Science*, *4*, 89-96.

Geladé, K., Bink, M., Janssen, T. W., Van Mourik, R., Maras, A., & Oosterlaan, J. (2017). An RCT into the Effects of Neurofeedback on Neurocognitive Functioning Compared to Stimulant Medication and Physical Activity in Children with ADHD. *European Child & Adolescent Psychiatry*, *26*, 457-468.

Gao, H., Zhao, Y., Levine, L., & Allen, A. (2006). *Determining Cut-Points for Clinically Meaningful Improvement: A Receiver Operating Characteristic Approach*. Scientific Proceedings of the 53rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry, pp. 201, Washington, DC: American Academy of Child and Adolescent Psychiatry.

Gloster, A. T., Rhoades, H. M., Novy, D., Klotsche, J., Senior, A., Kunik, M., Stanley, M. A. (2008). Psychometric Properties of the Depression Anxiety and Stress Scale-21 in Older Primary Care Patients. *Journal of Affective Disorders*, *110*, 248–259.

Guindon, M. H. (2010). *Self-Esteem Across the Lifespan: Issues and interventions*. New York. NY: Routledge.

Hazell, P., Lewin, T., & Sly, K. (2005). What Is A Clinically Important Level of Improvement in

Symptoms of Attention-Deficit/ Hyperactivity Disorder? *Australian and New Zealand Journal of Psychiatry, 39*, 354-358.

Hazell, P. L., Kohn, M. R., Dickson, R., Walton, R. J., Granger, R. E., & Wyk, G. W. (2011). Core ADHD Symptom Improvement with Atomoxetine Versus Methylphenidate: A Direct Comparison Meta-Analysis. *Journal of Attention Disorders, 15*, 674- 683.

Heal, D. J., Smith, S. L., Kulkarni, R. S., & Rowley, H. L. (2008). New Perspectives from Microdialysis Studies in Freely-Moving, Spontaneously Hypertensive Rats on the Pharmacology of Drugs for the Treatment of ADHD. *Pharmacology, Biochemistry and Behavior, 90*, 184–197.

Hechtman, L., French, L. R., Mongia, M., & Cherkasova, M. V. (2011). Diagnosing ADHD in Adults: Limitations To DSM-IV and DSM-5 Proposals and Challenges Ahead. *Neuropsychiatry, 1*, 579-590.

Hsieh, Y. L., & Yang, C. C. (2008). Age-Series Characteristics of Locomotor Activities in Spontaneously Hypertensive Rats: A Comparison with the Wistar-Kyoto Strain. *Physiology and Behaviour, 93*, 777–882.

Hopkins, M. E., Sharma, M., Evans, G. C., & Bucci, D. J. (2009). Voluntary Physical Exercise Alters Attentional Orienting and Social Behavior in A Rat Model of Attention-Deficit/Hyperactivity Disorder. *Behavioral Neuroscience, the*, 599-606.

Hudson, W. W. (1982). *The Clinical Measurement Package: A Field Manual*. Home-Wood, IL: The Dorsey Press.

Halperin, J. M., Berwid, O. G., & O'Neill, S. (2014). Healthy Body, Healthy Mind?. *Child and Adolescent Psychiatric Clinics, 23*, 899-936.

Huss, M., Ginsberg, Y., Tvedten, T., Arngrim, T., Philipsen, A., Carter, K., & Kumar, V. (2014). Methylphenidate Hydrochloride Modified-Release in Adults with Attention Deficit Hyperactivity Disorder: A Randomized Double-Blind Placebo-Controlled Trial. *Advances in Therapy, 31*, 44-65.

Hoifodt, R. S., Lillevoll, K. R., Griffiths, K. M., Wilsgaard, T., Eisemann, M., Waterloo, K., & Kolstrup, N. (2013). the Clinical Effectiveness of Web-Based Cognitive Behavioral therapy with Face-To-Face Therapist Support for Depressed Primary Care Patients: Randomized Controlled Trial. *Journal of Medical Internet Research, 15*, 1-22.

Jain, U., Hechtman, L., Weiss, M., Ahmed, T. S., Reiz, J. L., Donnelly, G. A., & Darke, A. C. (2007). Efficacy of A Novel Biphasic Controlled-Release Methylphenidate Formula in Adults with Attention-Deficit/Hyperactivity Disorder: Results of A Double-Blind, Placebo-Controlled Crossover Study. *Journal of Clinical Psychiatry, 68*, 268-277.

Jarett, M. A. (2016). Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms, Anxiety Symptoms, and Executive Functioning in Emerging Adults. *Psychological Assessment, 28*, 245-250.

Kang, K. D., Choi, J. W., Kang, S. G., & Han, D. H. (2011). Sports therapy for Attention, Cognitions and Sociality. *international Journal of Sports Medicine*, *32*, 953-959.

Klil-Drori, S., & Hechtman, L. (2016). Potential Social and Neurocognitive Benefits of Aerobic Exercise as an Adjunct Treatment for Patients with ADHD. *Journal of Attention Disorders*, 1-15

Knouse, L. E., Traeger, L., O'Cleirigh, C., & Safren, S. A. (2013). Adult Attention Deficit Hyperactivity Disorder Symptoms and Five-Factor Model Traits in A Clinical Sample: A Structural Equation Modeling Approach. *The Journal of Nervous and Mental Disease, 201*, 848-854.

Kooij, J. J. S. (2012). *Adult ADHD: Diagnostic Assessment and Treatment*. London: Springer.

Kolar, D., Keller, A., Golfinopoulos, M., Cumyn, L., Syer, C., & Hechtman, L. (2008). Treatment of Adults with Attention-Deficit/Hyperactivity Disorder. *Neuropsychiatric Disease and Treatment*, *4*, 389-404.

Lasser, R. A., Goodman, D. W., & Asherson, P. (2012). Lifespan Persistence of ADHD: the Life Transition Model and Application. *Journal of Clinical Psychiatry*, *73*, 192-201.

Lichtenberger, E. O., & Kaufman, A. S. (2013). *Essentials of WAIS-IV Assessment.* Hoboken, NJ: John Wiley & Sons.

Lufi, D., & Parish-Plass, J. (2011). Sport-Based Group Therapy Program for Boys with ADHD or with Other Behavioral Disorders. *Child & Family Behavior Therapy*, *33*, 217-230.

Mattos, P., Louzã, M. R., Palmini, A. L. F., Oliveira, I. R. D., & Rocha, F. L. (2013). A Multicenter, Open-Label Trial to Evaluate the Quality of Life in Adults with ADHD Treated with Long-Acting Methylphenidate (OROS MPH) Concerta Quality of Life (Conqol) Study. *Journal of Attention Disorders*, *17*, 444-448.

Mcintosh, D., Kutcher, S., Binder, C., Levitt, A., Fallu, A., Rosenbluth, M. (2009). Adult ADHD and Comorbid Depression: A Consensus-Derived Diagnostic Algorithm for ADHD. *Neuropsychiatric: Disease and Treatment*, *5*, 137–150.

Medori, R., Ramos-Quiroga, J. A., Casas, M., Kooij, J. J. S., Niemelä, A., Trott, G. E., & Buitelaar, J. K. (2008). A Randomized, Placebo-Controlled Trial of Three Fixed Dosages of Prolonged-Release OROS Methylphenidate in Adults with Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *63*, 981-989.

Meneses, A., Perez-Garcia, G., Ponce-Lopez, T., Tellez, R., Gallegos-Cari, A., & Castillo, C. (2011). Spontaneously Hypertensive Rat (SHR) As an Animal Model for ADHD: A Short Overview. *Reviews in the Neurosciences*, *22*, 365-371.

National Institute for Health and Clinical Excellence. (2008). *Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults*. Retrieved From Http://Www.Nice.Org.Uk/Nicemedia/Live/12061/42060/42060 .Pdf.

Nestler, E. J., & Hyman, S. E. (2010). Animal Models of Neuropsychiatric Disorders. *Nature Neuroscience, 13,* 1161- 1169.

Norwalk, K., Norvilitis, J. M., & Maclean, M. G. (2009). ADHD Symptomatology and Its Relationship To Factors Associated with College Adjustment. *Journal of Attention Disorders, 13,* 251-258.

Normann-Eide, E., Johansen, M. S., Normann-Eide, T., Egeland, J., & Wilberg, T. (2015). Personality Disorder and Changes in Affect Consciousness: A 3-Year Follow-Up Study of Patients with Avoidant and Borderline Personality Disorder. *Plos One, 10,* 1-18.

Perwien, A. R., Hall, J., Swensen, A., & Swindle, R. (2004). Stimulant Treatment Patterns and Compliance in Children and Adults with Newly Treated Attention-Deficit/Hyperactivity Disorder. *Journal of Managed Care Pharmacy, 10,* 122-129.

Retz, W., & Retz-Junginger, P. (2014). Prediction of Methylphenidate Treatment Outcome in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD). *European Archives of Psychiatry and Clinical Neuroscience, 264,* 35-43.

Robinson, A. M., Hopkins, M. E., & Bucci, D. J. (2011). Effects of Physical Exercise on ADHD-Like Behavior in Male and Female Adolescent Spontaneously Hypertensive Rats. *Developmental Psychobiology, 53,* 383-390.

Rochford, J. (2017). Correlational Analysis. (PDF) Retrieved from Https://Mycourses2.Mcgill.Ca/D2l/Le/Content/279881/Home,

Rodriguez, P. D., & Simon-Dack, S. L. (2013). Factor Analysis of Five Adult ADHD Self-Report Measures: Are they All the Same? *Journal of Attention Disorders, 17,* 64-69.

Rösler, M., Fischer, R., Ammer, R., Ose, C., Retz, W. (2009). A Randomised, Placebo-Controlled, 24-Week, Study of Low-Dose Extended-Release Methylphenidate in Adults with Attention-Deficit/Hyperactivity Disorder. *European Archives of Psychiatry and Clinical Neuroscience. 259,* 120–129.

Rösler, M., Retz, W., Fischer, R., Ose, C., Alm, B., Deckert, J., & Ammer, R. (2010). Twenty-Four-Week Treatment with Extended Release Methylphenidate Improves Emotional Symptoms in Adult ADHD. *The World Journal of Biological Psychiatry, 11,* 709-718.

Rösler, M., Ginsberg, Y., Arngrim, T., Adamou, M., Niemelä, A., Dejonkheere, J., Van, O. J., Schäuble, B. (2013). Correlation of Symptomatic Improvements with Functional Improvements and Patient-Reported Outcomes in Adults with Attention-Deficit/Hyperactivity Disorder Treated with OROS Methylphenidate. *The World Journal of Biological Psychiatry, 14,* 282-290.

Rommel, A. S., Halperin, J. M., Mill, J., Asherson, P., & Kuntsi, J. (2013). Protection from Genetic Diathesis in Attention-Deficit/Hyperactivity Disorder: Possible Complementary Roles of Exercise. *Journal of the American Academy of Child & Adolescent Psychiatry, 52,* 900-910.

Sainani, K. L. (2012). Dealing with non-normal data. *Pm & R : the Journal of Injury, Function, and Rehabilitation, 4,* 1001-1005.

Shaw-Zirt, B., Popali-Lehane, L., Chaplin, W., Bergman, A. (2005). Adjustment, Social Skills, and Self-Esteem in College Students with Symptoms of ADHD. *Journal of Attention Disorders, 8,* 109–120.

Sheehan, D. V., Harnett-Sheehan, K., & Raj, B. A. (1996). the Measurement of Disability. *International Clinical Psychopharmacology, 11,* 89-95.

Shifrin, J. G., Proctor, B. E., & Prevatt, F. F. (2010). Work Performance Differences Between College Students with and without ADHD. *Journal of Attention Disorders, 13,* 489-496.

Smith, A. L., Hoza, B., Linnea, K., Mcquade, J. D., Tomb, M., Vaughn, A. J., & Hook, H. (2013). Pilot Physical Activity Intervention Reduces Severity of ADHD Symptoms in Young Children. *Journal of Attention Disorders, 17,* 70-82.

Sobanski, E. (2006). Psychiatric Comorbidity in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD). *European Archives of Psychiatry and Clinical Neuroscience, 256,* 26-31.

Steer, R. A., Ranieri, W. F., Kumar, G., & Beck, A. T. (2003). Beck Depression inventory-II Items Associated with Self-Reported Symptoms of ADHD in Adult Psychiatric Outpatients. *Journal of Personality Assessment, 80,* 58-63.

Strohmeier, C. W., Rosenfield, B., Ditomasso, R. A., & Ramsay, J. R. (2016). Assessment of the Relationship Between Self-Reported Cognitive Distortions and Adult ADHD, Anxiety, Depression, and Hopelessness. *Psychiatry Research, 238,* 153-158.

Sowislo, J. F., & Orth, U. (2013). Does Low Self-Esteem Predict Depression and Anxiety? A Meta-Analysis of Longitudinal Studies. *Psychological Bulletin, 139,* 213-240.

Taylor, E. H. (2005). Using Self-Rating Scales for Assessing the Severely Mentally Ill Client: A Clinical and Psychometric Perspective. *Journal of Human Behavior in the Social Environment, 11,* 23-40.

The Calculation of Bonferroni-Adjusted P-Values. (2016). Retrieved June 12, 2018, From Https://Www-01.Ibm.Com/Support/Docview.Wss?Uid=Swg21476685

Torrente, F., Lischinsky, A., Torralva, T., López, P., Roca, M., Manes, F. (2011). Not Always Hyperactive? Elevated Apathy Scores in Adolescents and Adults with ADHD. *Journal of Attention Disorders. 15*, 545–556.

Torrente, F., Lopez, P., Alvarez Prado, D., Kichic, R., Cetkovich-Bakmas, M., Lischinsky, A., Manes, F. (2014). Dysfunctional Cognitions and their Emotional, Behavioral, and Functional Correlates in Adults with Attention Deficit Hyperactivity Disorder (ADHD): Is the Cognitive-Behavioral Model Valid? *Journal of Attention Disorders, 18,* 412–424.

Torrente, F., López, P., Lischinsky, A., Cetkovich-Bakmas, M., & Manes, F. (2017). Depressive Symptoms and the Role of Affective Temperament in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD): A Comparison with Bipolar Disorder. *Journal of Affective Disorders*, *221*, 304-311.

Wang, Y. P., & Gorenstein, C. (2013). Psychometric Properties of the Beck Depression Inventory-II: A Comprehensive Review. *Revista Brasileira De Psiquiatria*, *35*, 416-431.

Ward, M. F., Wender, P. H., & Reimherr, F. W. (1993). The Wender Utah Rating Scale: An Aid in the Retrospective Diagnosis of Childhood Attention Deficit Hyperactivity Disorder *American Journal of Psychiatry, 150,* 885-890.

Weiss, G., & Hechtman, L. T. (1993). *Hyperactive Children Grown Up: ADHD in Children, Adolescents, and Adults*. New York, NY: Guilford Press.

Wender, P. H., Reimherr, F. W., Marchant, B.K., Sanford, M.E., Czajkowski, L.A., Tomb, D.A. (2011). A one Year Trial of Methylphenidate in the Treatment of ADHD. *Journal of Attention Disorders*, 15, 36–45.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV).* San Antonio, TX: NCS Pearson inc.

Wilkinson, G. S. (1993). *The Wide Range Achievement Test: Manual (3rd Ed.).* Wilmington, DE: Jastak Association.

## Appendix A: Consent Form

Centre universitaire de santé McGill
McGill University Health Centre

☒ HME MCH ☒ HGM MGH ☒ HRV RVH
☒ HNM MNH ☒ ITM MCI ☒ CL LC

*FMU-9997*

**- INFORMATION AND CONSENT DOCUMENT -**

**STUDY TITLE: THE RELATIVE EFFICACY OF AEROBIC EXERCISE IN THE TREATMENT OF ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) VERSUS MEDICATION ONLY AND THE COMBINATION OF THE TWO A PILOT STUDY.**

**MUHC OR MCGILL STUDY CODE: MUHC-15-226**

**PRINCIPAL INVESTIGATOR**: Dr. Lily Hechtman

**CO-INVESTIGATORS:** Dr. Sivan Klil-Drori

**DEPARTMENT/DIVISION**: Montreal Children's Hospital, Department of Psychiatry

**STUDY SPONSOR:** **Montreal Children's Hospital Foundation via Shire Endowment Fund**

## A. INFORMATION ABOUT THE STUDY

**INTRODUCTION:**

We are inviting you to take part in a research study because you have been diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) as part of the "Adults with ADHD: Symptomatology and Functioning" study that is conducted in the Montreal Children's Hospital ADHD research program. This study will explore the effect of aerobic exercise on adults with ADHD. Before you decide whether or not to participate, please take your time to carefully read and understand the following information regarding the study. This form may contain information or words that are unfamiliar. Please ask the investigator to explain any word or information that you do not understand.

**NATURE AND OBJECTIVES OF THE STUDY:**

The aim of the present study is to compare the usefulness of different treatments for adults with Attention-Deficit/Hyperactivity Disorder (ADHD). One treatment will involve stimulant medication, which has been proven useful in treating adults with ADHD. The second treatment will involve aerobic exercise, which has been shown to be effective in treating children with ADHD, in improving self esteem, reducing anxiety and depressive symptoms, and effective in

treating cardiovascular diseases in adults. The third treatment will be a combination of both treatments. The main purpose of the study is to evaluate the relative usefulness of each therapy alone (medication, aerobic exercise), or the combination of aerobic exercise and medication for treating adults with ADHD.

In total, we expect approximately 70 participants in this study.

**STUDY PROCEDURES:**

Once you have read the consent form and had the study explained to you, you will be asked to sign the consent form. If you agree to participate and are eligible, you will be asked to complete the following procedures:

You will be randomly assigned (by chance) to one of three treatments. Randomly means like the flip of a coin, so you have a chance of one in three of receiving any of the three treatments in this study.

The three treatments are:
1. Medication.
2. Aerobic exercise.
3. Combined medication and aerobic exercise.

You must be willing and able to be assigned to any of the three groups.

Questionnaires examining your feelings, behaviour and functioning will be completed at the following time points:

1. Before the beginning of the treatment
2. At the beginning of the 8 weeks of intervention *
3. At the end of the 8 weeks of intervention.
4. Three months after the end of intervention.
5. Six months after the end of intervention.

* This time point is only for groups involving medication treatment.

Duration of Participation in the Study

The duration of participation will differ for each group of treatment, as well as each participant. In general, participants can expect to participate in this study for a minimum of 9 months from the initial recruitment until the last follow up period.

Centre universitaire de santé McGill
McGill University Health Centre

☒ HME MCH ☒ HGM MGH ☒ HRV RVH
☒ HNM MNH ☒ ITM MCI ☒ CL LC

*FMU-9997*

Study Interventions

Medication Intervention Group

If you are randomly assigned to the medication group, you will meet a psychiatrist to discuss the different medication options. The possible benefits, limitations, and possible side effects of the medication will be reviewed and explained. The location of the medication appointments will be held in the Centre of Innovative Medicine of the Montreal Children's Hospital.

Prior to beginning any medication, a thorough personal and family medical history will be obtained. Special emphasis will be put on identifying medical conditions that may be dangerous in combination with ADHD medication(such as cardiovascular diseases, hypertension, arteriosclerosis, glaucoma, cardiac abnormalities, or an allergy to the drug). You will be asked to identify an activity which requires concentration that you need to carry out every day while the medication is active. You will need to monitor your performance on that activity to determine how effective the medication is in improving your concentration. Before beginning any medication, baseline ADHD symptoms and side effect scales will be completed, these will be completed before each medication visit. At each medication visit your weight, blood pressure and heart rate will be measured. You will be asked to have an observer rate your ADHD symptoms at baseline and before each medication visit.
The preferred type of medication for ADHD are long acting compounds, as they have shown to have less side effects and are easier to use.

However, long acting compounds are more expensive. Therefore, if you do not have private medical insurance, we may consider less expensive compounds for economic considerations. The dose will be increased systematically by the psychiatrist , from the lowest recommended dose. The gradual increase will continue until optimal dose is reached. Optimal dose is that dose above which further improvement is not achieved, and side effects are manageable. When you reach your optimal dose you will be asked to remain on that optimal dose with regular follow-up assessments and will get a prescription for the medication.

During the intervention and the follow-up period you will be asked to complete a daily log of the medication for ADHD taken daily.

Once you have reached your optimal dose of medication, you will participate in 8 weekly educational group meetings. Each group will have between 10 and 15 participants and will meet once a week for 8 consecutive weeks. Each meeting will last approximately 60 minutes and will cover different educational topics related to ADHD. The location of the educational group meetings will be held in a conference room at the Montreal Children's Hospital, at the end of a work day between 6:00-7:30 pm.

Aerobic Exercise Intervention Group

If you are randomly assigned to the aerobic exercise only group, you will be asked to participate twice a week in an aerobic exercise group for 8 consecutive weeks. Each meeting will last 60 minutes that will be divided into a 10 minute warm-up, a 40 minute of aerobic exercise with music, and a 10 minute cool down with stretches. The intensity will be measured separately for each participant, calculated from the maximal heart rate of each individual. There will be approximately 10-15 participants in a group. The meetings will take place in a big enough conference room in the Montreal Children's Hospital, with furniture that can be moved aside in order to create an open-space room, suitable for exercise. During the follow-up period, you will be expected to continue to follow a similar aerobic exercise program twice a week, on your own or with a group, for example in a local community center. You will also be expected not to begin another treatment for ADHD.The group intervention will begin once all participants for this group are recruited. During the intervention and the follow-up period you will be asked to complete a daily log in which to fill the aerobic exercise type and duration you practice each day.

Combined Aerobic Exercise and Medication Group

If you are randomly assigned to the combined medication and exercise group, you will follow the same procedures for the medication treatment. Once you will be on your optimal dose of medication, you will begin the aerobic exercise treatment intervention, instead of attending the educational meetings. The aerobic exercise group meetings will take place in a big enough conference room in the Montreal Children's Hospital, with furniture that can be moved aside in order to create an open-space room, suitable for exercise.
During the intervention and the follow-up period you will be asked to complete a daily log in which to fill the aerobic exercise type and duration you practice each day and the medication for ADHD taken daily.

Follow up procedures for all three arms

The period of time for follow-up will be from the end of the 8 weeks of intervention, for 6 months. After you complete the 8 weeks of intervention, you will be asked to attend 2 follow-up meetings. The follow-up meetings will be 3 months and 6 months after the end of the 8 week intervention. During the intervention and follow-up periods, you will be asked to continue with the treatment you were assigned to in the study, and not to begin a new treatment for ADHD other than that treatment. After the end of the follow-up period, you will be referred back to your medical doctor.

**PARTICIPANT RESPONSIBILITIES:**

Aerobic Exercise Only Group
If you are randomly assigned to the aerobic exercise only group, you will be asked to attend the scheduled meetings, follow the instructions given to you by the study staff, participate, complete the study questionnaires and daily logs, and to approach the study staff about any questions or problems regarding the study that you may have.

Medication Only Group
If you are randomly assigned to the medication group, you will be asked to cooperate with the psychiatrist and report any differences after changing the medication dose, and report any side effects.
Most importantly report if you have any difficulties in taking the medication or any desire to stop taking it. You will be asked to attend and participate in the meetings (medication, medication follow-up and educational meetings), complete the study questionnaires and daily logs, and to approach the study staff about any questions or problems regarding the study that you may have.

Combined Aerobic Exercise and Medication
If you are randomly assigned to the combined exercise and medication group, you will be asked to attend and participate in the meetings (medication, medication follow-up and exercise meetings), follow the instructions given to you by the study staff, complete the study questionnaires and daily logs, and to approach the study staff about any questions or problems regarding the study that you may have.

**RISKS OF HARM:**

Risks Associated with the Medication Treatment

The side effects associated with regular use of stimulants by patients being treated for ADHD are listed below.

<u>The most common (greater than 10%, 10 out of 100 people) side effects are:</u>
Sore throat and runny nose, decreased appetite, nervousness, dry mouth, nausea, and difficulty falling asleep.

<u>Common ( 1% - 10% of patients, 1 out of 100 to 10 out of 100 people) side effects are:</u>
Headache, fatigue, dizziness, sleep disturbances, restlessness, changes in blood pressure (usually increase), skin rash, itchy rash and hives, fever, hair loss, anxiety, changes in heart rate (usually increase), vomiting, stomach pain, upset stomach, indigestion, toothache, cough, excessive sweating, joint pain, decreased weight, feeling jittery.

Severe Side Effects:

<u>The following severe side effects are rare, and were seen in greater than 0.01 % but less than 0.1 % of patients (between 1 out of 10, 000 to 1 out of 1000 of patients):</u>
Symptoms of visual disturbances, blurred vision, and painful and prolonged erections-because of the potential lasting damage of this side effect, it should be evaluated by a doctor immediately.

<u>The following severe side effects are very rare, and were seen in less than 0.01% of patients (less than 1 out of 10, 000 patients):</u>
Circulation problems in fingers and toes, such that the fingers or toes may feel numb, cool, painful, and/or may change color. Psychotic symptoms: including hallucinations (seeing or hearing things that are not real), delusion (strongly held belief despite clear evidence that this belief is actually false) or mania (mental and physical hyperactivity and disorganization of behavior with mood swings). Seizures, uncontrolled speech and body movements (Tourette's syndrome), aggressive behavior, stroke, abnormal liver function including liver coma, anemia, low white blood and platelet count.
Cases of sudden death, stroke and heart attack have been reported in adults taking stimulant drugs at usual doses for ADHD- although the role of stimulants in these adult cases is unknown, adults have a greater likelihood than children of having serious cardiovascular (heart) disorders.

Hypersensitive reactions :
With any medication, there is a risk of allergic reactions, such as hives, swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing, and if not treated promptly could become life-threatening. If you experience the symptoms of an allergic reaction, please go to the nearest hospital emergency department.

Stimulant drugs may lead to dependency and/or abuse. Moreover, alcohol can make their side effects worse. For your safety, you must refrain from taking alcohol containing products during the study.

**Addressing Side Effects**
In general, the side effects are temporary and will disappear in about two weeks of taking the medication on a daily basis.
The medication treatment will be carefully followed, and if any side effects develop, they will be addressed appropriately, for example- dose adjustment; timing and amount; for decreased appetite - increased food intake when medication is not active; for sleep problems- sleep hygiene, etc.

Potential Risks - Aerobic Exercise:
Aerobic exercise has a minimal risk for physical injury, and it is also time consuming.

Centre universitaire de santé McGill | McGill University Health Centre

☒ HME MCH ☒ HGM MGH ☒ HRV RVH
☒ HNM MNH ☒ ITM MCI ☒ CL LC

*FMU-9997*

**RISKS OF HARM ASSOCIATED WITH PREGNANCY:**

**There is limited data regarding utero exposure to stimulant and non-stimulant medications for ADHD, and limited data regarding potential short and long term behavioral teratogenicity, therefore we cannot safely recommend the use of stimulant or non-stimulant medications during pregnancy and breastfeeding. For these reasons, pregnancy or breastfeeding are exclusion criteria of the study.**

**INCONVENIENCIES:**

You may experience discomfort, stress, and frustration related to completing the questionnaires involved in the study. You will also need to anticipate transportation costs, travelling time, and the time devoted to the intervention. Additionally, the meetings are time consuming.

**POSSIBLE BENEFITS:**

Potential Benefits - Aerobic Exercise:
The aerobic exercise in the study is designed for beginners who do not exercise regularly. You may benefit from doing aerobic exercise, as it has been proven to be useful in treating and preventing chronic diseases such as cardiovascular diseases and improving the quality of life.
Additionally, the information learned from the study may help add to medical knowledge in this area and better treatment for people in the future.

Potential Benefits - Medication:
Medication therapy for ADHD has been shown to improve ADHD symptoms, and by that you may feel improvement in your functioning. In addition, you may benefit from the ADHD educational meetings by understanding much more about ADHD from professionals and having the opportunity for discussion and asking questions.

**VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW:**

Your participation in this research is voluntary. You are therefore free to refuse to participate. You may also withdraw from the project at any time, without giving any reason, by informing the research team.

Your decision not to participate in the project or to withdraw from it will have no impact on the quality of care and services to which you are entitled.
The researcher, the McGill University Health Centre (MUHC) Research Ethics Board (REB), the institution or the sponsor may put an end to your participation without your consent, if new findings or

information indicate that your participation is no longer in your interest, if you do not follow the project instructions, or if there are administrative reasons that force the termination of the project.

However, before you withdraw from the project, we ask you to come back to the clinic for a final evaluation and safety visit.

If you withdraw or are withdrawn from the project, the information and biological material collected during the project will be stored to ensure the project's follow-up.
Any new findings obtained during the research project that may have an impact on your decision to continue participation will be communicated to you rapidly.

**CONFIDENTIALITY:**

During your participation in this project, the researcher and his or her team will collect and record information about you in a study file. Only the information required to meet the scientific goals of the project will be collected.

This information may include information from your medical chart concerning your past and present health condition, your lifestyle, as well as the results of all the tests, exams and procedures that you will have to undergo as part of this research project.

Your research file could also contain other information, such as your name, sex, and date of birth.

All the information collected will remain confidential to the extent required by law. In order to protect your identity and the confidentiality of your information, you will only be identified by a code number. The key to the code linking your name to your study file will be kept by the researcher.

The researcher will use these data for research purposes, in order to achieve the project's scientific goals that are described in this consent form.
The research data will be stored for at least 25 years by the researcher. The research data may be published in medical journals or discussed during scientific meetings; however it will not be possible to identify you.

The research data may also be used for further analysis related to the project or to help in the development of future research projects.

For the purpose of surveillance, control, protection, safety and marketing of the study drug, your study file as well as your medical charts may be examined by a person mandated by regulatory authorities such as Health Canada, in Canada or internationally, as well as by

representatives of the sponsor, the institution or the MUHC REB. All these individuals and organization adhere to a policy on confidentiality.

You have the right to consult your study file in order to verify the information collected and to have it corrected as necessary.

A description of this research project will be available in this website:
http://www.clinicaltrials.gov
This website will not include information that can identify you. At most, the website will include a summary of results. You can search this website at any time.

**STUDY FUNDING:**

Montreal Children's Hospital Foundation via Shire Endowment Fund

**COMPENSATION IN THE CASE OF INJURY OR LOSS AND THE RIGHTS OF THE PARTICIPANT:**

If you suffer any injury following drug administration or any other procedure related to the research project, you will receive the appropriate care and services for your medical condition. By accepting to participate in this project, you are not waiving any of your legal rights nor discharging the researchers, granting agency, or the institution of their civil and professional responsibility.

**COMPENSATION OR REIMBURSEMENT FOR PARTICIPATION:**

There will be no compensation or reimbursement for participation in this study.

**CONTACT INFORMATION FOR QUESTIONS:**

At any time during the course of the study, if you have any questions concerning your participation in the study, you may contact Dr. Lily Hechtman at 514-412-4400 ext. 22167 for more information. You may also call Dr. Sivan Klil-Drori at 514-412-4400 ext. 23286.

For additional information regarding your rights as a research participant, you may contact the hospital's ombudsman at (514) 412-4400 ext. 22223, who is independent of the investigator, and works to protect patients' rights.

Centre universitaire de santé McGill
McGill University Health Centre

☒ HME MCH ☒ HGM MGH ☒ HRV RVH
☒ HNM MNH ☒ ITM MCI ☒ CL LC

*FMU-9997*

**OVERSIGHT OF THE ETHICAL ASPECTS OF THE STUDY:**

**THE MCGILL UNIVERSITY HEALTH CENTRE RESEARCH ETHICS BOARD (MUHC REB) HAS REVIEWED AND APPROVED THIS STUDY AND IS RESPONSIBLE OF FOLLOWING THE STUDY AND ENSURING THAT YOU ARE PROTECTED. BEFORE ANY CHANGE IS MADE TO THIS STUDY OR CONSENT DOCUMENT, IT MUST BE REVIEWED AND APPROVED BY THE MUHC REB).**

## B. DECLARATION OF CONSENT

**PARTICIPANT'S CONSENT:**

I have read this information and consent form and have had the opportunity to ask questions which have been answered to my satisfaction before signing my name. I acknowledge that I will receive a copy of the Information and Consent Form for future reference. I agree to participate in the research study. A copy of your consent form will be added to your medical chart and as a result it will be available to all individuals or organizations that access your medical chart in the future.

Participant:_____ sign: _____

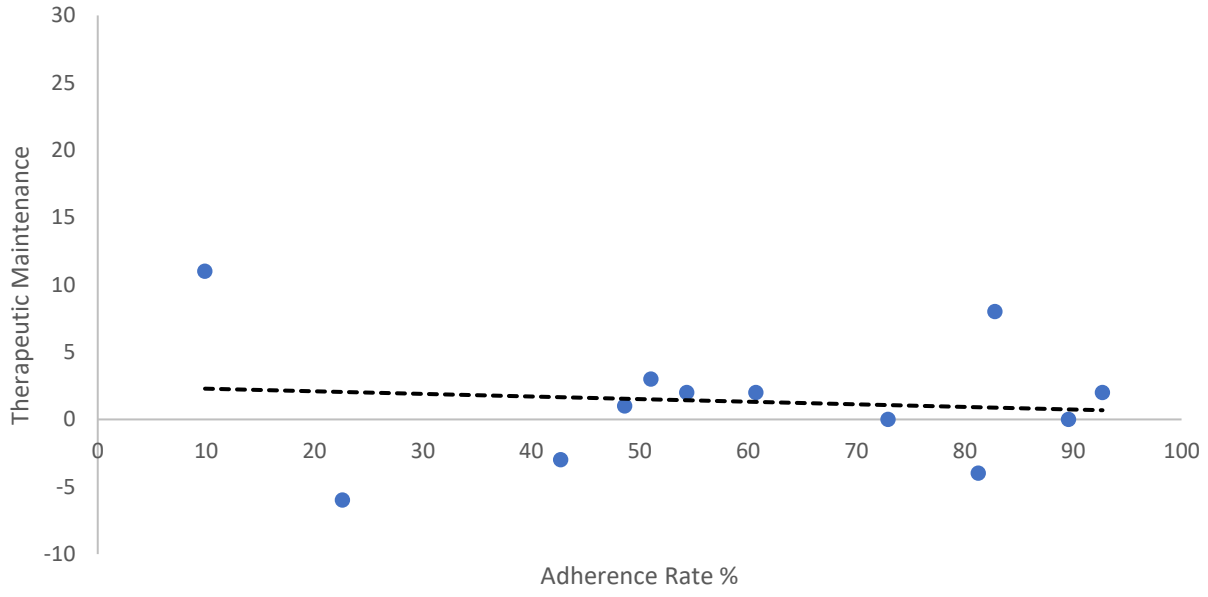
Date: _____

Person who obtained consent: _____ sign: _____

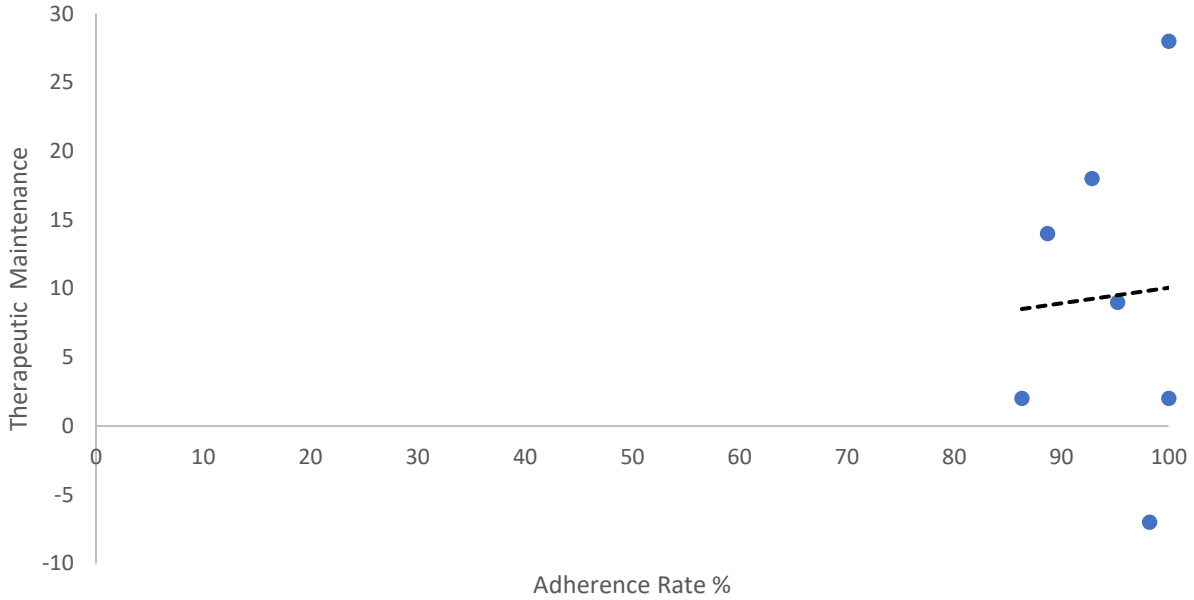
Date: _____

**Appendix B.** Scatter Plot Depicting the Relationship Between Treatment Adherence Rate and Maintenance of Therapeutic Effects in Aerobic Exercise (A) and Medication (B)

## A. Aerobic Exercise




## B. Medication




**Appendix B.** The above scatter plots show no apparent linear relationship between adherence to treatment (during the follow-up period) and the maintenance effect. Scatter plots were constructed in aerobic exercise (A; *n* =12) and medication (B; *n* =7).