Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Supplementary guanfacine hydrochloride as a treatment of attention deficit hyperactivity disorder in adults: A double blind, placebo-controlled study

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ARTICLE INFO

Article history:
Received 15 July 2015
Received in revised form
5 December 2015
Accepted 14 December 2015

Keywords:
Attention deficit hyperactivity disorder
Guanfacine hydrochloride
Placebo effect
Regression to the mean

ABSTRACT

The purpose of this study was to examine the efficacy of an extended release guanfacine hydrochloride supplement relative to a placebo supplement in adults (19–62) with ADHD and a sub-optimal response to a stimulant-only treatment program. The study's primary outcome measures were the Attention Deficit Hyperactivity Disorder Rating Scale and the Clinical Global Impression – Severity. Twenty-six adults who met criteria for attention deficit hyperactivity disorder and sub-optimal functioning were randomly assigned to supplement their existing psychostimulant treatment regimen with either a titrated dose (1–6 mg) of extended release guanfacine hydrochloride or a matching placebo for a 10-week trial. The data were analyzed with standard mixed model analysis of variance procedures, and participants in both the investigational agent group and the placebo group showed statistically significant improvement in their symptoms and functioning over the course of the trial. The treatments did not differ in terms of their efficacy, safety, or tolerability. Although these results do suggest that both treatments were associated with clinical improvement, the possible impacts of socially desirable responding and regression to the mean on these results are discussed.

1. Introduction

In recent years, adults with Attention Deficit Hyperactivity Disorder (ADHD) have begun to seek diagnostic consultation with greater frequency, but there has only recently been widespread interest in the developmental trajectories of patients with ADHD (Wilens et al., 2002). Although evidence certainly suggests that many children who have ADHD today will continue to need treatment when they reach adulthood (Kessler et al., 2005), the efficacy of treatment modalities across the lifespan is not yet fully understood (Mannuzza et al., 1998; McGough and Barkley, 2004; Murphy and Barkley, 1996). Today, the majority of FDA-approved pharmacological interventions for adults with ADHD are psychostimulant medications, but they can be sub-optimal treatments for a non-trivial subset of the treatment population (Barkley, 2006; Murphy and Gordon, 2006)

For children and adolescents, a safe and effective alternative to stimulants involves combining non-stimulants with stimulants, but it remains unclear whether adult populations could benefit from such regimen (Michelson et al., 2003). One combination that has proven to be effective with children with ADHD is the addition of extended release guanfacine hydrochloride (GH) to their existing psychostimulant regimen (Strange, 2008). GH is a selective alpha-2A agonist that is currently FDA-approved as a supplementary therapy to stimulants for the treatment of ADHD) in children and adolescents ages 6–17, but it has not been well researched as a treatment for ADHD in an adult population. The purpose of this trial was to study GH as a supplementary therapy to stimulants for the treatment of ADHD in adults age 18 and above. Specifically, the primary objective was to examine the efficacy of a GH supplement relative to a placebo supplement in adults with ADHD who were experiencing sub-optimal response to their current stimulant-only treatment program.

Half of participants in this present study were randomly

Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; ADHD – RS, Attention Deficit Hyperactivity Disorder Rating Scale; ASEX, Arizona Sexual Experience Questionnaire; CGI–I, Clinical Global Impression Scale—Improvement; CGI–S, Clinical Global Impression Scale—Severity; C-SSRS, Columbia Suicide Severity Rating Scale; FSI, Fatigue Symptom Inventory; HAM – A, Hamilton Anxiety Inventory; HAM – D, Hamilton Depression Rating Scale; RCBM, Rochester Center for Behavioral Medicine; PSQI, Pittsburgh Sleep Quality Index

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http://dx.doi.org/10.1016/j.psychres.2015.12.017
0165-1781/

assigned to the GH condition, in which their existing stimulant medication was paired with 1, 2, 3, 4, 5, or 6 mg of GH. The remaining participants were assigned to a placebo condition in which their existing stimulant medication was paired with a placebo. Participants' functioning was assessed pre-treatment, during treatment, and at the end of the study with two primary outcome measures: the Attention Deficit Hyperactivity Rating Scale (ADHD – RS) with adult prompts and the Clinical Global Impression—Severity (CGI—S). The ADHD – RS was included because it is a well-validated, widely-used assessment of ADHD symptoms (Zhang et al., 2005). The CGI was included because it is a well-validated, widely-used assessment of the impact of patients' global functioning (Forkmann et al., 2011; Guy, 2000). The secondary objective of this study was conduct a safety and tolerability analysis using the Arizona Sexual Experience Questionnaire, the Fatigue Symptom Index, the Pittsburgh Sleep Quality Index, the Hamilton Anxiety Inventory, the Hamilton Depression Rating Scale, and standard physiological measures of overall health (e.g., weight, blood pressure, etc.).

1.1. Hypotheses

It was hypothesized that participants in the GH group would show lower ADHD – RS and CGI – S scores over time than would those in the placebo group. It was also hypothesized that those in the GH group would show no differences over time from those in the placebo group on the safety and tolerability measures.

2. Methods

The study was conducted at the Rochester Center for Behavioral Medicine (RCBM), a research and treatment center in suburban Detroit, MI, USA. RCBM actively participates in clinical care and new medication investigations. Clinical trials include multi-centered national trials and single site, investigator-initiated studies. The research unit is led by a board-certified psychiatrist and supported by an experienced team of clinical coordinators. Study medications were obtained from Shire's Investigator Sponsored Trial Operations Office. The Western Institutional Review Board (WIRB) oversaw the study and guided informed consent procedures.

2.1. Patient population

Study participants were recruited from local advertisements and the clinic's existing patient population. Participants ($N=26$) ranged in age from 19–62 ($M=37.54$, $SD=12.22$). Fourteen participants were female, and 12 were male. Twenty-two (84.6%) were Caucasian, three (11.5%) were African-American, and one (3.8%) was listed as "other." A screening period of up to 30 days was used to determine the participants' eligibility to participate in the study and to engage in the appropriate washout of any excluded medications.[1]

[1] All investigational medications, tricyclic antidepressants, STRATTERA®, antipsychotics, neuroleptics, psychostimulants (other than entry defined use of VYVANSE™, CONCERTA®, RITALIN™, FOCALIN™, and/or ADDERALL™) were prohibited. These included sympathomimetics, appetite suppressants, modafinil, cough/cold preparations containing stimulants, other medications containing amphetamine, clonidine and guanfacine, monoamine oxidase inhibitors, anticonvulsant medications, any antibiotics with a CNS effect were prohibited. Any herbal preparations that have CNS effect, affect cognitive performance, and/or affect BP, HR, or prolong QT/QTc interval were also prohibited. Medications known to be CYP3A4/5 inducers or inhibitors that may interact with GH were prohibited. The use of any new CYP3A4/5 inhibitors or inducers after Visit 1 was prohibited unless use was planned for the duration of the study, and a stable dose had been established for at least 14 days prior to Visit 1. In those cases the treatment was to be given concomitantly throughout the study, with no planned changes in use.

2.2. Inclusion criteria

All participants had a current ADHD diagnosis derived from the diagnostic criteria for adult ADHD (inattentive, hyperactive/impulsive, or combined subtypes), as specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (APA, 2000). These criteria were assessed by psychiatric intake and use of appropriate symptom checklists. Participants were required to be on a current treatment regimen of stimulant medications at the time of the screening interview, and all who were selected had reported a lengthy pharmaceutical treatment history for ADHD (years to decades). Their current primary ADHD medications included Vyvanse ($n=9$, $M_{dose}=56.67$ mg), Adderall XR ($n=8$, $M_{dose}=31.88$ mg), Adderall ($n=6$, $M_{dose}=15.83$ mg), Ritalin ($n=2$, $M_{dose}=15$ mg), and Concerta ($n=1$, $M_{dose}=81$ mg). Each participant presented at Visit 1 with a sub-optimal response to their treatment regimen. Sub-optimal response was defined by the participant's dissatisfaction with his/her clinical progress, a Visit 1 baseline score of greater than or equal to 28 using the ADHD – RS, or a CGI – S score greater than or equal to 4 at Visits 1.

In addition to these hypothesis-specific inclusion criteria, more general inclusion criteria were also specified. Participants, in the opinion of the investigator, must have been able to understand and comply with protocol requirements, including assessments, prescribed dosage regimens, and discontinuation of concomitant medications. Participants were able to provide written, personally signed and dated informed consent to participate in the study in accordance with the International Conference on Harmonisation, Good Clinical Practice Guideline E6, and applicable regulations before completing any study related procedures. They demonstrated a typical level of intellectual functioning without evidence of significant general intellectual deficit, and they were able to swallow intact tablets. Finally, women were required to have a negative urine pregnancy test at Visit 1, and they agreed to use medically accepted means of contraception during the study.

2.3. Exclusion criteria

Participants with severe comorbid psychiatric diagnoses (e.g., Axis I disorders such as mood disorders, anxiety disorders, post-traumatic stress disorder, obsessive compulsive disorder, etc.) were excluded, as were participants with a history of psychosis, pervasive developmental disorders, severe Axis II disorders or severe substance dependence. The determination of participants' comorbidities was made subjectively through clinical interview and objectively through the Adult Self-Report Inventory-4. Participants were also excluded if they had a chronic or an acute medical condition or illness that could have been negatively affected by the study medication. Those with a history of hypothyroidism, hypertension, or a resting systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg were ineligible. Participants who were directly affiliated with the study team, and those who were receiving treatment with an unregulated medication or had participated in a clinical trial within 30 days prior to screening, were also excluded. Individuals could not participate if they weighed less than 30 kg or more than 120 kg at the time of informed consent.

2.4. Study design

This was a randomized, single-center, double-blind, placebo-controlled study. Participants were recruited within the Rochester Center for Behavioral Medicine (RCBM) clinic and the Detroit metropolitan area through outreach to professionals involved in the treatment of adult ADHD, advertisements in local newspapers and circulars, and internet social networking sites. At the

Please cite this article as: Butterfield, M.E., et al., Supplementary guanfacine hydrochloride as a treatment of attention deficit hyperactivity disorder in adults: A double.... Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.12.017