Research in Autism Spectrum Disorders 8 (2014) 899–907

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

Journal homepage: http://ees.elsevier.com/RASD/default.asp

Review

A multisite trial of atomoxetine and parent training in children with autism spectrum disorders: Rationale and design challenges☆

Laura Silverman [a], Jill A. Hollway [b], Tristram Smith [a], Michael G. Aman [b], L. Eugene Arnold [b], Xueliang Pan [d], Xiaobai Li [d], Benjamin L. Handen [c,*]

[a] Strong Center for Developmental Disabilities, University of Rochester Medical Center, 601 Elmwood Avenue, Box 671, Rochester, NY 14642, United States
[b] Ohio State University's Nisonger Center for Developmental Disabilities, 1581 Dodd Drive, Columbus, OH 43210, United States
[c] University of Pittsburgh Medical Center, Merck Program, 1011 Bingham Street, Pittsburgh, PA 15203, United States
[d] Ohio State University's Center for Biostatistics, 2012 Kenny Road, Columbus, OH 43221, United States

ARTICLE INFO

Article history:
Received 12 December 2013
Received in revised form 13 March 2014
Accepted 14 March 2014

Keywords:
Atomoxetine (Strattera)
ADHD
Autism spectrum disorder
Drug trial
Parent training

ABSTRACT

Several randomized controlled trials (RCTs) involving children with autism spectrum disorder (ASD) have examined effectiveness of mono-therapies for problem behavior. However, results have not been as encouraging as in typically developing children. For example, when prescribed stimulants, children with ASD and hyperactivity/inattentiveness, show only moderately reduced symptoms, with frequent side effects. Therefore, alternative treatments or combinations of treatments are needed. The Children's Hyperactivity and Autism Research Treatment Study (CHARTS) is a randomized clinical trial comparing the individual and combined effects of atomoxetine and parent training to treat hyperactivity, inattentiveness, and noncompliance in children with ASD. Design challenges included the overall study design, targeting of different outcomes by different treatments, and data analysis. This article details options for addressing a number of these methodological issues in the context of conducting a large multicenter RCT with an ASD population.

Contents

1. Overview . . . 900
2. Study design and description . . . 900
3. Design challenges and rationale . . . 901
   3.1. Four treatment conditions . . . 902
   3.2. Acute trial . . . 902
   3.3. Twenty-four week extension . . . 902

☆ This work was supported by grants from the National Institute of Mental Health to Ohio State University (1R01MH079080-01A2), University of Pittsburgh (5R01MH079082-05), and University of Rochester (R01 MH083247) as well as support from Eli Lilly, who supplied active medication and matching placebo.

* Corresponding author. Tel.: +1 412 235 5445; fax: +1 412 235 5446.
E-mail address: handenbl@upmc.edu (B.L. Handen).

http://dx.doi.org/10.1016/j.rasd.2014.03.013
1750-9467/

3.4. Establishing and maintaining blindness to treatment assignment . . . 902
4. Selection of treatment options . . . 903
4.1. Psychopharmacological intervention: atomoxetine (Strattera) . . . 903
4.2. Psychosocial intervention: manualized parent management training . . . 903
5. Selection of two study outcomes . . . 904
5.1. Parent and teacher outcomes . . . 904
5.2. Observer-rated outcome measures . . . 904
5.3. Child cognitive assessments . . . 904
6. Statistical considerations . . . 905
6.1. Two outcome domains . . . 905
6.2. Multiple informants . . . 905
6.3. Different time points to optimal effects . . . 905
7. Discussion . . . 905
References . . . 906

1. Overview

Children with autism spectrum disorder (ASD) often have co-occurring behavior problems such as inattention, hyperactivity, irritability, anxiety and noncompliance (Lecavalier, 2006). Behavioral interventions, based on the principles of applied behavior analysis, can reduce these problems and increase adaptive skills (Howard, Ladew & Pollack, 2009; Smith, 2011). Certain medications are also effective for decreasing such problems (Hollander & Anagnostou, 2007). However, the available evidence provides little guidance on whether to select a behavioral intervention, medication, or both for an individual child with ASD.

To inform clinical decision-making, investigators have increasingly sought to examine the comparative and combined effects of psychosocial and psychopharmacological treatment in childhood mental health disorders. For example, the Multimodal Treatment Study of ADHD (MTA) compared stimulants (mostly methylphenidate), behavioral interventions, and their combination, in typically developing children with attention-deficit/hyperactivity disorder (ADHD) (The MTA Cooperative Group, 1999). Among children with ASD, the largest randomized clinical trial (RCT) of combined psychosocial and pharmacological treatments was conducted by the Research Units on Pediatric Psychopharmacology-Psychosocial Intervention (RUPP-PI) Autism Network. This RCT examined the effects of adding parent training (PT) in behavior management principles to risperidone to treat irritability and noncompliance in 124 children with ASD (Aman et al., 2009). This study showed that parent training augmented the therapeutic effects of medication alone. However, the investigators noted some methodological limitations, including (a) a medication-induced ceiling effect (the powerful effect of risperidone left little room for improvement for PT on behavioral outcomes), (b) no placebo control, and (c) no PT-alone condition (Aman et al., 2009, 2010). In the current investigation, the Children with Hyperactivity and Autism Research Treatment Study (CHARTS), we sought to refine the methods used in the RUPP-PI study and extend them to the treatment of ADHD symptoms in children with ASD.

A comparative effectiveness trial of two active treatments requires a more complex design than a trial comparing a single treatment to placebo. The purpose of this manuscript is to highlight some of the challenges that arose in conducting our trial in children with ASD and to explain how we addressed these difficulties. The challenges are divided into four categories: (a) overarching study design, (b) blinding, (c) measurement of treatment outcomes, and (d) data analytic plan.

2. Study design and description

Three sites were funded by the National Institute of Mental Health to conduct this five-year trial: the University of Pittsburgh Medical Center, the Ohio State University's Nisonger Center and the University of Rochester Medical Center. The trial included two phases. *Phase 1* was a 10-week, randomized, double-blind, placebo-controlled, 2×2 trial of atomoxetine (ATX) and parent training (PT). Treatment goals were to decrease hyperactivity and inattentiveness and to increase compliance in 128 children ages 5 through 13 years with ASD and ADHD symptoms. Participants were randomized to one of four possible treatment options: (a) PT and ATX, (b) PT and placebo, (c) ATX alone (no PT), or (d) placebo alone. Phase 2 of the study consisted of a 24-week extension period, explained below. During the acute trial (Phase 1), medication was titrated for the first six weeks, based on response and side effects, to a possible ceiling dose of 1.8 mg/kg/day and stabilized for the next four weeks. At the conclusion of the acute phase, subjects were classified as either responders or nonresponders. A responder was defined as: (a) a subject who showed a reduction of 30% or more in parent ratings for symptoms of ADHD, noncompliance, or both; and (b) a blinded clinician rating of *much* or *very much* improved ("1" or "2") on the Clinical Global Impression – Improvement (CGI-I) scale for ADHD, noncompliance, or both. All other subjects were considered nonresponders.

In Phase 2, responders continued their treatment without breaking the medication blind while nonresponders had the blind broken. "Placebo nonresponders" were offered 10-weeks of open-label ATX treatment and "ATX nonresponders" were treated clinically with the best available medication options for the next 24 weeks. This was done in order for those