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A Multisite Trial of Atomoxetine and Parent Training in Children with Autism Spectrum Disorders: Rationale and Design Challenges

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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

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(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

randomized to PT to obtain all planned PT treatment sessions. Figure 1 shows the study flow chart for responders and nonresponders.

All study participants underwent a complete assessment to establish diagnosis of autistic disorder, pervasive developmental disorder – not otherwise specified (PDD-NOS), or Asperger's disorder based upon the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (*DSM-IV-TR*) (American Psychiatric Association, 2000). Also assessed were intelligence level, symptom severity and medical status. Randomization was stratified by site and balanced on two levels of mental age (above and below 6 years). Once randomized, participants were initially assessed at six weekly visits and then every other week until week 10. The Extension phase involved assessments every four weeks over a 24-week period. A blinded clinician rated therapeutic response. The treating physician, who monitored side effects and made dose adjustments, remained blind to treatment assignment unless clinical care required breaking the blind.

The study tested the following hypotheses: (a) participants receiving ATX alone would show greater improvement on *ADHD* measures over participants receiving placebo; (b) participants receiving PT would score significantly better on measures of *compliance* than participants not receiving PT; (c) participants receiving the combination of ATX and PT would show an additive effect and score significantly better on all outcome measures than participants in the other three groups; and (d) participants receiving ATX would experience minor and tolerable elevations in certain adverse events when compared with the placebo group. Table 1 illustrates the rationale and design decisions made when planning this study.

3. DESIGN CHALLENGES AND RATIONALE

The following section presents the design challenges we were confronted with when planning this RCT. We also highlight the methodological decisions that were ultimately made and the rationale behind them.

3.1 Four Treatment Conditions

One limitation of the RUPP-PI study was that it compared just two treatment conditions (i.e., medication and combined treatment) without a PT-only condition or a placebo condition (Aman, et al., 2009; van Haaren, 2009). We concluded that a PT-only group would enable us to evaluate the efficacy of PT as a stand-alone treatment for increasing compliant behavior. Likewise, a placebo-only group would enable us to evaluate the efficacy of ATX. Consequently, we included four treatment arms (ATX alone, PT alone, both interventions together, and a placebo condition), using a 2×2 factorial design.

3.2 Acute Trial

Once the overall design of the study was agreed upon, team members had to determine the appropriate length of the acute trial (Phase 1 of the study). This phase needed to be long enough to assess ATX efficacy adequately, but short enough that families of children who were on placebo or nonresponsive to active medication would be willing to maintain their children in the study. To limit side effects and allow for possibly greater sensitivity among children with ASD, a slow dose titration was planned (starting at 0.3 mg/kg vs. the 0.5

mg/kg recommended by the ATX package insert). In addition, if side effects were reported, adequate time was required to lower the ATX dose and then to “re-challenge” the child at the higher dose. Therefore, six weeks were allotted for dose titration, followed by four weeks at a steady dose. This was slightly longer than the eight-week trials typically conducted by researchers working with neurotypical children with ADHD (e.g., Michaelson et al., 2001; Newcorn et al., 2005).

3.3 Twenty-Four Week Extension

Another issue related to trial length involved the time required to observe positive effects of PT. In the RUPP-PI study (Aman et al., 2009), the impact of PT was not evident until 20 weeks of treatment. However, the target symptoms were different (severe irritability rather than noncompliance). In addition, risperidone had a more immediate and significant impact on behavior than we expected ATX to have. We did *not* predict near-universal reduction of behavioral symptoms with the use of ATX. Therefore, we anticipated that the effect of PT in CHARTS might exceed the effect seen in RUPP-PI. Nevertheless, based on RUPP-PI findings, we conservatively estimated that effects of PT might not be observable until after 10 weeks, with even greater impact during a 24-week follow-up phase (Phase 2 of the study).

Because of the possibility that behavioral effects of parent training might become apparent more slowly than medication effects, we decided to retain *all participants* (not just responders) until at least Week 10 of the Extension (i.e., *after an exposure of 20 weeks of PT*). Were we to retain responders alone, there was a strong chance that the number of control subjects (i.e., those receiving neither PT nor ATX) would be too low to enable a well-powered statistical comparison to take place. Additionally, such a control group might also be unrepresentative.

3.4 Establishing and Maintaining Blindness to Treatment Assignment

In order to maintain the blind during the study, ATX and visually identical placebo were dispensed. Staff members who dispensed the medication at each site were not involved in other study procedures. In addition, independence was maintained between researchers serving as prescribers, who might be tipped off by side effects, and those serving as blinded raters (independent evaluators who assessed behaviors at baseline and during subsequent study visits). Thus, the pharmacological intervention was delivered in a double-blind, placebo-controlled design, which deliberately isolated blinded raters from any knowledge of adverse events (AEs).

As for the psychosocial intervention, we were unable to maintain the double-blind since both participants and therapists were aware of treatment assignment. However, we were able to maintain the blind with the independent evaluators, through the *management of communication* among study personnel, families and blinded raters. PT therapists were not permitted to discuss their patients with other study personnel or to share information about scheduling, lest they disclose treatment assignment. In addition, PT therapists saw study parents in a different physical space than other research personnel. This was done so that independent evaluators would not inadvertently encounter study patients or see them with

PT clinicians. Parents were instructed not to discuss PT-related content with blinded staff. Likewise, parents were also warned to avoid language or terminology included in the PT intervention when talking to other study personnel. Finally, PT therapists held conference calls that were separate from the rest of the leadership group. This allowed clinical issues to be discussed without unblinding researchers responsible for medication management or assessment of behavioral outcomes.

4. SELECTION OF TREATMENT OPTIONS

4.1 Psychopharmacological Intervention: Atomoxetine (Strattera)

Psychostimulants are the first line of treatment for ADHD symptoms in typically developing children (Arnold, 2000). RCT's have shown that these medications also improve ADHD symptoms in some children with ASD, but have much *lower response rates* and much *higher rates of AEs* than reported in typically developing children (Aman, 1996; Handen et al., 2000; Quintana et al., 1995; RUPP Autism Network, 2005). Early studies examining stimulants in ASD reported AEs, including paradoxical overactivity and stereotypic behavior (Schmidt, 1982); fearfulness, separation anxiety, rapid pulse and increased hyperactivity (Realmuto et al., 1989); delusional ideas and fragmented thinking (Sporn & Pinkser, 1981); and agitation, stereotypies, aggression, and motor and phonic tics (Volkmar, Hoder, & Cohen, 1985). Although these side effects were seen in only five patients, this reflects approximately 14% of study enrollment. The RUPP Autism Network reported intolerable AEs in response to methylphenidate in 18% of their sample, with the most significant effect being irritability. Similarly, in a double-blind, placebo-controlled crossover study, significant side effects of methylphenidate included increased levels of social irritability, withdrawal, crying, tantrums and skin picking, especially at a higher doses (0.6 mg/kg; Handen et al., 2000). Alpha₂-adrenergic receptor agonists, such as clonidine and guanfacine have also been tested in ASD, as alternatives to stimulants, for children who either show little response or significant side effects. RCTs using these medications documented drowsiness, decreased activity and irritability (Handen, Sahl & Harden, 2008; Jaselskis, Cook, Fletcher, & Leventhal, 1992).

Endeavoring to achieve a more favorable treatment profile, we decided to investigate the efficacy of ATX, a non-stimulant medication. At that time, a literature search revealed only limited data regarding the safety and efficacy of ATX's use in ASD. We found only four relevant reports, of which three were open label and one was a small, double-blind study. In general, the effects of atomoxetine on the symptoms of ADHD in children with ASD appeared to be positive. The small placebo-controlled, cross-over trial of ATX noted fewer intolerable side effects than generally seen in response to stimulant medication (Arnold et al., 2006). The most common AEs were mild upper gastrointestinal symptoms, including upset stomach and/or nausea and vomiting. More recently, we conducted another review of the literature in subjects with developmental disabilities, which reinforced our original conclusions (Aman, et al., in review). Several studies showed that ATX also had a number of additional practical advantages over stimulants.

The primary human subjects concern was that atomoxetine has a "black box" warning because, in rare instances, it may be associated with an increased risk of suicidality. Because

children with ASD have impairments in social communication, suicidality is particularly difficult to assess for them. We implemented a number of safeguards to address this concern. First, study teams at all sites included both child psychiatrists and clinical psychologists to ensure that experts on suicidality were available if needed. Second, in our screening evaluation, we conducted a mental health assessment that included a parent-completed symptom checklist and interviews with the parent and child; we excluded children with past or current bipolar disorder, major depression, or suicidality. In addition, we highlighted mood swings and agitation on the side-effect review forms collected at each visit during the double-blind and extension phases, and we followed up with families if these were reported by either the parent or the teacher. Independent evaluators also met with parents at each visit and asked them to rate the severity of their child's mood swings, agitation, self-injury, anxiety and depression on a scale from 1 to 10, with additional follow-up if parents reported an increase in any of these behaviors. Finally, our independent Data and Safety Monitoring Board included a patient advocate to assess side-effects from the perspective of a family member and two psychiatrists to advise us on safety issues.

4.2 Psychosocial Intervention: Manualized Parent Management Training

The CHARTS manual was designed for use with a broad range of children with ASD, including children who were high functioning and verbal, and those who were lower-functioning with limited expressive language. The PT manual that was written for the RUPP-PI study (Aman et al., 2009) was also used in the CHARTS study. The manual was modified slightly, with some minor revisions to the sequence and content of sessions, based on the therapists' previous clinical experience. We chose this intervention because (a) limited information was available on its impact on ADHD symptoms (especially in children with ASD), and (b) most children with ADHD also displayed noncompliance. PT had been shown to reduce noncompliance in populations other than ASD. However, most studies of PT for noncompliance in ASD had been small-N investigations of unstandardized PT protocols (Bearss et al., 2013).

To monitor clinician fidelity, forms were created for every session, identifying the key teaching points and activities that needed to be implemented by the clinician. Fidelity scores of 80% or above were set as the expectation. All sessions were videotaped and a random subset of videos was sent to an independent clinician at a different site to check self-ratings of fidelity. Cross-site clinician conference calls were held monthly to discuss questions regarding how best to implement interventions.

5. SELECTION OF TWO STUDY OUTCOMES

Typically, a single primary target symptom is selected in RCTs. However, in the current study we chose to focus on two treatments for two target areas: ADHD symptoms and noncompliance. While both ATX and PT were expected to affect both target areas, we hypothesized that ATX would have a greater impact on ADHD symptoms, whereas PT would have greater impact on noncompliance. This is in contrast to other studies of combined psychosocial/psychopharmacological treatment, which have designated a single primary outcome measure (e.g., Abikoff et al. 2004; March et al., 2004; POTS, 2004).

5.1 Parent and Teacher Outcomes

Parent and Teacher Swanson, Nolan, and Pelham, Questionnaire – Fourth Edition (SNAP-IV) (Swanson, 1992)—For comparability with our prior studies and with many studies of ADHD among typically developing children, the SNAP-IV Parent and Teacher Rating Scales were used to measure ADHD at home and school. The SNAP-IV comprises the 18 DSM-IV symptoms of ADHD (nine hyperactive/impulsive items and nine inattention items) on a 0-3 metric scale. A mean item score of >1.5 on the Parent and Teacher SNAP-IV 18 ADHD symptoms *or* the 9-symptom hyperactive-impulsive items, *or* the 9 symptom inattentive items was used for study inclusion. The SNAP-IV was also used to measure change.

Home and School Situations Questionnaires (HSQ and SSQ) (Altepeter & Breen, 1989; Barkley, Edwards, & Robin, 1994)—The HSQ and SSQ, which were originally designed to assess the severity of noncompliance in typically developing children, were selected to measure noncompliance in CHARTS. The RUPP-PI Autism Network (Aman et al., 2009) adapted the HSQ for measuring noncompliance in ASD by adding five items, yielding a total of 25 items (Chowdhury et al., 2010). The SSQ was used in its original 9-item form.

5.2 Observer-Rated Outcome Measures

Standard Observation Analogue Procedure (SOAP) (Johnson et al. 2009)—While the primary outcome measures were derived from standardized questionnaires, we also conducted direct observations. The SOAP consisted of three conditions: (a) a 3-minute free-play/social attention control condition (demand-free interaction between parent and child), (b) a 10-minute high-demand condition (involving 10 parental requests) and (c) a 3-minute clean up Condition (Handen et al., 1999; Hanley, Iwata, & McCord, 2003; Kennedy et al., 2000; Repp & Horner, 1999). The high-demand condition was intended to simulate typical parent-child interactions, in which multiple requests and restrictions were placed on the child. Sessions were 16 minutes long and used two sets of standardized toys and materials. One set of demands was for higher-functioning participants and another for lower-functioning participants; parents selected items from the demand set that they considered to be representative of home. Details of the procedure can be found in Handen et al. (2013), including procedures for coding mother and child behaviors.

Clinical Global Impressions of ADHD and Noncompliance (Guy, 1976)—These measures provided clinician-rated global ratings of a study participant's condition prior to and during medication dosing (Busner & Targum, 2007, 2009). We decided to conduct two global assessments, one for ADHD and one for noncompliance. This made achievement of inter-rater reliability more difficult than when there is a single target behavior. As with other outcome ratings, the CGI was completed by a blinded rater insulated from knowledge of AEs and dosing. To develop a common “culture” for rating CGIs, we developed guidelines and scored vignettes for review by blinded clinicians. Finally, we reviewed all subjects' outcome scores and arrived at consensus CGI scores monthly on Steering Committee calls.

5.3 Child Cognitive Assessments

Cognitive Tests—Subjects were assessed using a computer-controlled battery for cognitive

performance on tasks tapping sustained attention, visual selective attention and inhibition. A paper and pencil *cancellation task* was also administered to measure sustained attention. The battery was chosen to detect relevant drug effects; however, this may be the first study in which cognitive tests have been used to assess the potential impact of PT on child cognitive performance. Although unintended originally, this could be a unique contribution of this study.

6. STATISTICAL CONSIDERATIONS

6.1 Two Outcome Domains

The first analytic challenge was the dual outcome domain. There were two primary outcome measures: (a) *ADHD symptoms rated by parent and teacher* using the SNAP-IV (i.e., 18 items), which we planned to use to assess medication efficacy and which involved comparisons of ATX vs. Placebo, and (b) noncompliance rated by parent and teacher on the Home and School Situation Questionnaires (HSQ/SSQ), which we intended to use as a primary outcome for comparison of PT vs. no PT. This posed the problem of multiple tests for related but conceptually independent domains. To resolve this, we proposed to test the two primary hypotheses using Hochberg's procedure (Hochberg, 1988). If both outcomes were to reveal a p -value of <0.05 , both would be considered significant. If one revealed a p -value of <0.025 and the other >0.05 , the first would be considered significant. However, if one were to have a p -value of >0.05 and the other >0.025 , *neither* would be considered significant. This risked the possibility that a significant finding between 0.025 and 0.05 on one would be lost because the other was >0.05 . We felt that this risk was worth taking to examine both primary outcomes simultaneously by controlling the family-wise error rate.

6.2 Multiple Informants

An additional problem was the multiple informants for the primary analyses. While all parents provided ratings of ADHD symptoms and noncompliance, some teacher data were missing (due to summer vacations, etc.). Rather than attempt to composite the informants prior to analysis, we decided to use the method of O'Brien (1984) and Lehmacher et al. (1991) to combine multiple test statistics into a single hypothesis test. Our intent was to estimate the effect of PT on noncompliance (measured by two primary outcome variables) relative to no PT, with random coefficient mixed models applied to these multivariate longitudinal data (Gao et al., 2006). We planned to standardize each outcome variable into z -scores (based on sample baseline mean and SD) to ensure the same measuring scale (O'Brien, 1984). Each outcome measure, we assumed, would reveal random slopes for different subjects. The model proposed would consider the associations of different measures from the same individual. The same procedure will be used for parent and teacher ratings of ADHD symptoms.

6.3 Different Time Points to Optimal Effects

A third problem was the different times – to optimal effect for the two treatments. We expected ATX to show optimal effect by 10 weeks. However, we knew from the RUPP-PI study (Aman et al, 2009) that PT might not show its full effect until week 20, well after the double-blind ATX-placebo comparison of this study. Therefore, although we had proposed to do a secondary test for PT at 10 weeks (at the end of the 2×2 blinded phase), the primary analysis for noncompliance was intended for analysis at 22 weeks. Another complex issue was that the medical treatment would no longer be strictly controlled by protocol after week 10; alternative medications could be introduced as clinically indicated. Thus, we planned to compare the PT vs. no-PT groups on medication type and dose during the extension (after week 10). We determined that if they did not differ, we could assume that alternative medication and dose variations did not interfere with the noncompliance comparison between PT and no PT. If a medication difference *was* found, we would examine the pattern of the medication difference (number of drugs, dose), and then could consider the medication profile as covariate(s) for the primary analysis.

7. DISCUSSION

The CHARTS study is similar to previous studies in that it was designed to incorporate both a pharmacological treatment and a psychosocial intervention (Abikoff et al. 2004; Aman et al., 2009; March et al., 2004; POTS, 2004; The MTA Cooperative Group, 1999). However, it contained some unique features designed to address the complexities of treating children with ASD and to reconcile the need for placebo with the need for enough time for PT to show an effect. The study design made maintaining the blind more difficult than in a study of monotherapy. Consequently, we gave special consideration to preserving the independence of study evaluators. Also, the treatments were hypothesized to have complementary effects, with ATX primarily modifying ADHD symptoms and PT primarily modifying noncompliance. Further, because the effects of ATX were expected to emerge more quickly than the effects for PT, our primary analyses for ATX effects were based on data from the Week 10 visit. Conversely, our primary analyses for PT were based on Week 22 data. In order to enhance the generalizability of our findings, our primary outcome measures are composites of parent and teacher ratings. Because we were dealing with multiple informants, we proposed a model that would consider the associations of different measures from the different individuals. We also included secondary measures that consisted of blinded clinician ratings, standardized behavior observations scored by blinded observers and computerized tests of attention. The decision to use dual outcomes and multiple measures made data analyses more difficult as well, and we were obliged to address the problem of multiple tests for related domains. The design of CHARTS may be informative for researchers planning other RCTs.

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Highlights

This paper reviews the rationale for a double-blind, placebo-controlled RCT.

It tests whether ATX and Parent Training is superior to single treatment /placebo.

Challenges include: study design, blindness, outcome measures and data analysis.

Our goal is to assist researchers planning multimodal RCTs for children with ASD.

Figure 1.

Study flow chart. Note: ATX = Atomoxetine (Strattera); PT= Parent Management Training (in behavior intervention); ASD = Autism Spectrum Disorders. Study 1 is a 10-Week, double-blind, placebo-controlled comparison of effects of (a) ATX (ATX/No PT), (b) PBO (PBO/No PT, (c) ATX + PT, (d) PBO + PT.

Table 1**CHARTS Design Decisions and Rationale**

Design Decisions	Rationale
Study Design Decisions (see section 3)	
Use of four treatment arms (ATX alone, ATX + PT; PBO alone, PBO + PT)	PT only group important to establish PT efficacy; Placebo group important to establish ATX efficacy
Selection of 10-week randomized, double-blind, placebo-controlled study	Ensure sufficient time for positive effects of ATX
Selection of 24-Week Extension	Ensure sufficient time for positive effects of PT
Blinded Raters: Therapeutic effects blind to side effects	To minimize treatment bias
Selection of Treatment Options (see section 4)	
Use of atomoxetine (Strattera)	New FDA indication for ADHD
Use of manualized Parent Training: Clinician Fidelity	To decrease noncompliance and increase adaptive skills
Use of alternative medication treatments after the failure of ATX	Prevent attrition in the 24-week extension
Selection of Two Study Primary Study Outcomes (see section 5)	
ADHD and Noncompliance Measures ^a	Evaluate improved ADHD symptoms with medication. Evaluate increased compliance and adaptive behavior with Parent Training
Data Analytic Plan (see section 6)	
Two Outcome Domains Multiple Informants	Hochsberg's Procedure Model considered the associations of different measures for the same individual
Different Time Points to Optimal Effects	Primary analyses for ATX at Week 10; Primary analyses for PT at Week 22

^aParent and Teacher SNAP IV, Home and School Situations Questionnaires, Parent and Teacher SER, Standard Observation Analogue Procedure (SOAP), CGI-S and CGI-I for both ADHD symptoms and noncompliance.