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Original article

Initial severity and efficacy of risperidone in autism: Results from the RUPP trial

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ABSTRACT

Background: Risperidone is a common psychopharmacological treatment for irritability in autism spectrum disorder (ASD). It is not well-established how effective risperidone is across the initial symptom severity range. This study aims to examine the influence of baseline severity on the efficacy of risperidone in the treatment of ASD.
Methods: Participants were from the NIMH funded RUPP multisite, randomized, double-blind trial that compared risperidone to placebo to treat autistic disorder with severe tantrums, aggression, or self-injury. Participants were aged 5 to 17, and randomly assigned to risperidone ($n = 49$) or placebo ($n = 52$). Baseline and change scores were computed with the Aberrant Behavior Checklist (ABC) parent assessed scales with irritability as the primary outcome, as well as the clinician assessed ABC Irritability subscale, and Clinical Global Impression Scale.
Results: The relationship between baseline severity and change scores for the risperdone and placebo groups was examined with eight competing three-level mixed-effects models for repeated measure models. Significant ($P < 0.01$) interactions between treatment and baseline severity were observed for parent ABC ratings of irritability and lethargy only. Greater magnitudes of the differences between risperidone and placebo were observed from moderate to very severe baseline severity on irritability and lethargy. Initial severity values over approximately 30 had a strong effect on symptom change [irritability: effect size (ES) = 1.9, number needed to treat (NNT) = 2, lethargy ES = 0.9, NNT = 5].
Conclusions: Parents may expect benefits of risperidone on irritability and lethargy with moderate to severe symptoms of ASD.
Trial registration: Registry name: ClinicalTrials.gov, trial identifier: NCT00005014, URL: http://www.clinicaltrials.gov/ct2/show/NCT00005014?term=NCT00005014&rank=1, registered on March 31, 2000.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by a syndrome of social and linguistic impairments, as well as stereotyped and repetitive behaviors [1] in early childhood. It has an estimated prevalence rate of 1 in 88 [2] and is associated with a lifetime support cost of approximately $1.4 million both in the US and UK. Despite its burden to patients and their caregivers [3], no medication is currently available to treat the core symptoms of ASD. The Food and Drug Administration has approved two psychotropic agents (risperidone and aripiprazole) to treat comorbid irritability associated with ASD [4]. Based on registry data it is estimated that the prevalence of psychotropic medication use in ASD reaches 64% [5], with the most common antipsychotic being risperidone at 10.3% [6]. Despite its prevalent use, the role of initial severity in treatment response to pharmacotherapy for ASD is unclear.

Compared with ASD, in other disorders, such as depression and schizophrenia, the role of initial severity on symptom change has been systematically examined. For example, in the antidepressant psychopharmacological treatment of major depressive disorder,

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the results of some [7–9] but not all studies [10,11] report diminished efficacy at mild levels of depressive disorder. In schizophrenia, however, second generation antipsychotics (including risperidone) are reported to be efficacious across the entire baseline severity range, with greater benefit being expected for those with greater initial severity [12].

The role of initial severity has been examined in some clinical trials of ASD. Among children with high levels of repetitive behavior randomized to citalopram or placebo, greater baseline severity was significantly associated with increased placebo response on some factors (e.g., hyperactivity and not irritability) [13]. Baseline severity was found to moderate rather than mediate risperidone treatment effects on irritability [14]. The aforementioned study did not, however, differentiate rating sources (i.e., caregivers and clinicians) or utilize all available assessments to maximize statistical power. Research to date is yet to appropriately examine the association between initial severity and change with treatment in ASD. Specifically, initial severity (a) has not been analyzed following the initial severity literature [9,11,12]. That literature maximizes repeated assessments, compares competing models of initial severity, and identifies potential cut off points along the initial severity symptom spectrum. Also, the initial severity effects of clinical impressions, stereotypy and hyperactivity, while significant in the primary RUPP report are unknown [15]. Furthermore, differences between clinical and caregiver raters have not been examined to date. Accordingly, evidence of the efficacy of psychotropic agents in the treatment of ASD is not clearly established across the initial severity symptom spectrum.

In the current study, we aim to examine the association between baseline symptom severity and efficacy of risperidone over placebo in the treatment of ASD.

2. Material and methods

2.1. Participants

The National Institute of Health Research Units on Pediatric Psychopharmacology (RUPP) Autism Network's first study [16] was a double-blind comparison of risperidone ($n = 49$) with placebo ($n = 52$) for 8 weeks, with flexible dosing in the first 4 weeks. The RUPP study centers were the University of California, Ohio State University, Indiana University, Yale University, and Johns Hopkins University. Each center approved the study protocol, and written informed consent was obtained prior to enrollment [15,16].

RUPP included children and adolescents aged 5 to 17 (mean 8.8 years) with autistic disorder with irritability, self-injurious behavior, and/or aggression. The study design [16] and results [15] have been reported. Results demonstrated that risperidone was superior to placebo on the primary outcomes: the Aberrant Behavior Checklist Irritability subscale, at eight weeks [effect size (ES) = 1.2] and the CGI-I (attaining ratings of "much improved" or "very much improved"; risperidone group: 69%, placebo group 12%). Statistically significant ($P < .05$) secondary outcomes were: stereotypy (ES = 0.8), and hyperactivity (ES = 1.0) but not social withdrawal (ES = 0.4) or inappropriate speech (ES = 0.3) [15].

2.2. Measures

The Aberrant Behavior Checklist (ABC) and the Clinical Global Impression (CGI; [17]) were the study outcomes. The ABC was developed as a measure of severity and treatment effects for patients with developmental disabilities. Each item of the 58 items of the ABC was rated from 0 ("not at all a problem") to 3 ("the problem is severe in degree"). The five ABC subscales were: Irritability (e.g., self-injurious behaviors; 15 items); Lethargy/Social Withdrawal (16 items); Stereotypic Behaviors (e.g., rituals; seven items); Hyperactivity (16 items); and Inappropriate Speech (e.g., excessive talking; 4 items). Also, the ABC item total was computed. Prior research confirmed the psychometric properties of validity and reliability of the ABC [18]. The ABC had similarly worded versions for clinicians and caregivers (i.e., parent) [18]. By design, in the RUPP study, parents rated the complete ABC biweekly to week 8, whereas clinicians rated only the ABC irritability subscale at baseline, and weeks 4 and 8.

In addition to the ABC, the CGI Severity (CGI-S) and Improvement (CGI-I) rating scales were used to estimate severity and change, each on a 7-point scale. CGI-S ratings were collected at baseline and range from 1 ("normal, not at all ill") to 7 ("among the most extremely ill patients"). CGI-I ratings were collected post-baseline to week 8 and range from 1 ("very much improved") to 4 ("no change"), to 7 ("very much worse").

2.3. Analyses

The primary statistical analysis investigated the relationship between baseline symptom severity and subsequent symptom change in the comparison of risperidone versus placebo. As the primary outcome, we used the parent-based ABC Irritability Change score [19], since it was the most frequently scheduled irritability assessment. Analyses were also computed for the ABC parent total and subscales, the ABC clinician-based Irritability scale, and CGI scales (with CGI-S at baseline and CGI-I as outcome).

First, we adopted the approach to study change following the initial severity literature [12]. This statistical analysis investigated the relationship between baseline symptom severity and subsequent symptom change in the comparisons of risperidone versus placebo. Differences in change scores between the risperidone and placebo were computed with mixed-effects model repeated measures analysis with maximum likelihood estimation [11,20]. The following models with increasing complexity were tested:

- time, treatment and the two-way time by treatment interaction;
- supplementing model I, baseline and all two-way interactions among time, treatment and baseline;
- supplementing model II, the three-way interaction of linear time by treatment by baseline;
- supplementing model III, the two-way and three-way interactions among quadratic time, treatment and baseline.

These models were tested unadjusted and adjusted for confounders (age, and sex). Across models, clustering was accounted for with random effects, such that: level 1 represented the week, level 2 the trial participant, and level 3 the site.

The model with the smallest Bayesian Information Criterion (BIC) was identified as the most parsimonious [21]. All statistical analyses were done in R [22] using the nlme package [23]. This analytic strategy closely resembles prior initial severity studies by using competing mixed-effects model repeated measures [9,11,12]. If the baseline treatment group interaction was statistically significant (i.e., $P < .05$) for the most parsimonious model, then that model was plotted, and predicted values were used to identify the number needed to treat and effect sizes based on established methods [24].

3. Results

For the primary outcome, the most parsimonious model to predict ABC irritability based on parent-ratings was model 2 that