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Lack of Effect of Risperidone on Core Autistic Symptoms: Data from a Longitudinal Study

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Abstract

Objective: The purpose of this study was to investigate the course of autistic symptoms, using a quantitative measure of core autistic traits, among risperidone-treated children who participated in a 10 year life course longitudinal study.

Methods: Parents completed surveys of intervention history, as well as serial symptom severity measurements using the Social Responsiveness Scale (SRS), on their autism spectrum disorder (ASD)-affected children. Fifty participants (out of a total of 184 with full intervention histories) were reported to have been treated with risperidone during the course of the study. Serial SRS scores during risperidone treatment were available for a majority of children whose parents reported a positive effect from risperidone.

Results: Two thirds of risperidone-treated children ($n=33$) were reported by parents to have improved by taking the medication, with the principal effects described being that children were calmer, better focused, and less aggressive. SRS scores of children reported to have responded positively to risperidone did not improve over time.

Conclusions: Risperidone's beneficial effect on aggression and other elements of adaptive functioning were not necessarily accompanied by reduction in core ASD symptoms, as serially assessed by the same caregivers who reported improvement in their children. These results reflect the distinction between reduction in core symptom burden and improvement in adaptive functioning. Given the cumulative risks of atypical neuroleptics, the findings underscore the importance of periodic re-evaluation of medication benefit for children with ASD receiving neuroleptic treatment.

Introduction

CHILDREN WITH AUTISM SPECTRUM DISORDER (ASD) experience impairment caused by core symptoms of social communicative impairment and restricted repetitive behaviors, as well as a high incidence of irritability, aggression, and hyperactivity. Optimal management of ASDs involves targeting primary neurodevelopmental deficits as well as associated maladaptive behaviors, generally via a comprehensive approach including pharmacotherapy and behavioral therapies, as well as developmental, educational, and social supports (Scahill et al. 2012).

Although the prevalence of ASD continues to rise, with the latest estimate at 1 in 68 children affected (Centers for Disease Control and Prevention 2012), United States Food and Drug Administration (FDA)-approved pharmacotherapies for ASD remain limited. Only risperidone and aripiprazole have FDA approval for irritability and aggression associated with ASDs, and neither is indicated for core ASD symptoms. Nonetheless, given the disability incurred by core ASD symptoms, several investigations have probed whether

these medications, in particular risperidone, may improve social-communicative function, repetitive behavior, or restriction in range of interests.

The literature describing risperidone's impact on core characteristics of ASDs has been mixed. Within the small number of randomized, placebo-controlled trials, several support improvements in overall ASD severity (Luby et al. 2006; Nagaraj et al. 2006), as well as specific primary ASD symptoms including socialization (Shea et al. 2004; Nagaraj et al. 2006; Pandina et al. 2007), language or communication (Shea et al. 2004; Nagaraj et al. 2006), and stereotyped, repetitive behaviors (Shea et al., 2004; Nagaraj et al. 2006). Open label trials (Zuddas et al. 2000; Williams et al. 2006; Gencer et al. 2008) and naturalistic studies (Masi et al. 2003; Capone et al., 2008) also support risperidone's ability to improve social functioning and autistic severity, and one controlled blinded study suggested that this effect was specific to risperidone versus the typical antipsychotic haloperidol (Miral et al. 2008). However, the largest randomized placebo-controlled trial of risperidone, Research Units on Pediatric Psychopharmacology

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Network, failed to show a benefit of risperidone on core ASD symptoms after 8 weeks (McDougle et al. 2005), and systematic reviews highlighting the more rigorously designed studies report the best evidence for improving irritability, rather than core ASD symptoms, with one review noting moderate evidence for amelioration of stereotyped behaviors but not social or communicative function (McPheeters et al. 2011).

Although the collective database continues to grow, treatment studies of risperidone in ASD share common limitations in their ability to address whether risperidone can promote sustained benefits in social-communicative competence and restricted, repetitive behaviors. These limitations include the brevity of the treatment trials, an important consideration given that some studies have noted slower improvement in social function versus disruptive behavior (Zuddas et al. 2000), and study designs in which core characteristics of ASD are secondary end-points. Because the largest trials selected for children with elevated irritability and aggression (McCracken et al. 2002), the findings related to risperidone's effects on core symptoms may be less generalizable to more heterogeneous clinical populations with ASD. In studies that have examined effects on social deficits, the instruments used often broadly characterized social function, rather than providing sensitive quantitative measurements of core ASD symptoms (Shea et al., 2004; Pandina et al. 2007; Scahill et al. 2013). Although the evidence of risperidone's efficacy for irritability in ASD is well established, knowing its impact on primary autistic impairment in children could be critical for treatment planning.

To investigate whether core features of autism improve over time in children taking risperidone, we capitalized on the availability of data from a life course longitudinal study involving a relatively unselected sample of children affected by ASD, whose parents provided serial measures of autistic symptom severity and retrospective histories of the interventions their children had received. This naturalistic, longitudinal approach minimized the potential for detection bias, as parental reports were not contingent on treatment with risperidone, and facilitated observation of treatment responses over many months to years. We examined whether enduring use and parental report of a positive effect from risperidone over the course of the study was associated with a decline in symptom burden, as measured serially using the Social Responsiveness Scale (SRS), a quantitative measure of autistic symptoms.

Methods

Participants

A total of 235 families actively enrolled in the Autistic Traits Life Course and Genetic Structure study (Constantino et al. 2009), in which 184 parents provided retrospective summaries of interventions with their children. Participants were recruited from the psychiatry practice of the senior author (J.N.C.) and through public recruitment efforts starting in 2002. All ASD diagnoses ($n=184$) were made by a physician, and confirmed using the Autism Diagnostic Interview Revised and/or the Autism Diagnostic Observation Scale. Parents reported that 50 of the participants with ASD had undergone treatment with risperidone, and among those described as responding positively to risperidone, 23 had serial SRS measurements that were highly informative with respect to the effect of risperidone (see Data analysis section). Selected sample characteristics are provided in Table 1.

Measures

The SRS is an extensively validated quantitative trait measure of social-communicative and restricted/repetitive behavior deficits referable to core ASD symptoms, in which informants base their ratings on cumulative observations of the subject in the subject's natural social settings (Constantino et al. 2000, Constantino and Gruber 2012). Scores are continuously distributed across the entire population, exhibit a unitary factor structure in cross-sectional research (Constantino et al. 2004), and are largely independent of intelligence quotient (IQ) among verbal ASD subjects (Constantino et al. 2003), such that total scores index quantitative variations in the severity of autistic impairment. Higher scores correspond to greater impairment, and distinguish children with ASD from those with other psychiatric conditions. Subscale scores on the SRS 1) describe domains of core autistic symptoms (social awareness, social cognition, social communication, social motivation, and mannerisms) that may be differentially affected by a given treatment; and 2) relate to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) criterion domains for a diagnosis of ASD (American Psychiatric Association 2013; Frazier et al. 2014). Parents completed serial ratings using the SRS, typically annually, as a primary element of data collection for the longitudinal study. Serial teachers SRS

TABLE 1. PARTICIPANT CHARACTERISTICS ACCORDING TO MEDICATION USE

	Risperidone (n=23)	Other medication (n=78)	Medication-free (n=56)
Gender (% male)	95.7%	85.9%	94.6%
Age at initial SRS (years)	5.09 (2.87)*	7.08 (3.87)	5.59 (3.22)
Initial Parent SRS score	104.22 (19.79)	97.25 (30.82)	98.28 (30.03)
Initial Teacher SRS score	102.48 (31.55)	88.77 (33.00)	90.13 (33.05)
CBCL Internalizing T-Score	63.21 (9.00)	61.42 (10.21)	60.89 (10.20)
CBCL Externalizing T-Score	64.00 (10.52)* **	57.16 (11.07)	54.75 (12.33)
CBCL Total T-Score	67.47 (8.35)**	62.24 (10.28)	60.36 (10.61)
IQ Score	70.94 (21.37)	85.77 (25.26)	87.00 (31.53)
Risperidone dose (mg/day)	2.25 (1.62)	n/a	n/a
Risperidone duration (months)	52.84 (33.74)	n/a	n/a
Total number of psychotropic medication trials	3.87 (2.58)	3.50 (3.13)	n/a

Participants classified as "medication free" received no medication for a minimum of 3 years. All numbers with the exception of gender reported as means with standard deviations in parentheses. No trend-level or significant differences were observed between treatment groups based on either parent or teacher SRS scores. Asterisks indicate trend-level or significant differences for the risperidone group on *post-hoc* testing (* $p=0.053$ for age and $p=0.065$ for CBCL externalizing, risperidone vs. other-medicated group; ** $p\leq 0.05$, risperidone vs. unmedicated group). SRS, Social Responsiveness Scale; CBCL, Child Behavior Checklist; IQ, intelligence quotient.

scores, provided by different teachers over time, were also available for a subset of participants.

Between years 8 and 9 of the study, parents completed a Summary of Life Course Interventions, (SLCI) (Supplementary Fig. 1) (Supplementary material is available in the online article at <http://www.liebertonline.com/cap>), a retrospective questionnaire regarding number, type, and duration of interventions, as well as the overall effect of the treatment. Parental descriptions of treatment effect of risperidone were reviewed (H.U.R.) and participants were classified as corresponding to either 1) an overall positive effect or 2) an overall negative effect (including no benefit) from risperidone. Additional information regarding medication history, including date and dosage, was obtained through either parent report or physician record.

Parents also completed the Child Behavior Checklist (CBCL) *at study baseline only*. The CBCL is an established parent report measure for rating children's behavior in a broad range of domains linked to psychopathology (Achenbach 1991). Scores on this measure include total severity, internalizing behavior, and externalizing behavior. T scores from 65 to 70 signify borderline clinical severity; scores >70 signify clinical severity.

Data analysis

Analyses of change in parent SRS score over the course of risperidone treatment were conducted for those participants whose parents reported a positive effect from risperidone. Twenty-three participants (within the original group of 33 reported to respond positively to risperidone) had SRS measurements whose timing occurred such that scores were informative with respect to response to risperidone. For 16 of these 23 subjects, a pretreatment SRS baseline score, followed by at least one SRS score on treatment (> 1 month time between scores, mean treatment duration 37.22 ± 24.79 months) was available. (We refer to these as "before-and-during treatment" [BDT] subjects.) For a partially overlapping set of 19 subjects (mean treatment duration 62.94 ± 27.72 months), time-rated changes in SRS score could be calculated from serial (on average, yearly) SRS measurements obtained during treatment with risperidone. (We hereafter refer to these as "serial measurement on treatment" [SMT] subjects.) A subset of BDT subjects ($n = 14$) and SMT subjects ($n = 14$) also had sufficient serial teacher SRS scores for these analyses.

All analyses, including arithmetical calculations, Student's *t* tests, linear regression, and ANOVAs were calculated in SPSS version 20.

Results

Characteristics of the "positive effect" subjects with longitudinal SRS data informative to risperidone treatment response, as well as subjects using other medications or no medications, are reported in Table 1. Children taking risperidone did not significantly differ in initial parent or teacher SRS score, IQ, internalizing T score on the CBCL, or total number of psychotropic medication trials, from other groups. Age at initial SRS was significantly different across groups ($F = 4.300$, $df = 2$, $p = 0.015$), and the risperidone-treated group was younger than the "other medication" group ($p = 0.053$). Significant and marginal group differences were observed for CBCL externalizing scores ($F = 3.943$, $df = 2$, $p = 0.023$) and total scores ($F = 2.963$, $df = 2$, $p = 0.056$), respectively. On *post-hoc* testing, CBCL externalizing scores were higher in the risperidone group than in the unmedicated group ($p = 0.019$) and the other-medicated group ($p = 0.065$), with the

latter difference at the level of a trend. The risperidone group's total CBCL scores were in the borderline range for a clinical level of severity, and significantly greater than those of the unmedicated group only ($p = 0.05$).

According to parental report on the SLCI, 33 of the 50 study subjects who had received risperidone experienced positive effects from the medication, whereas 17 experienced negative effects (Supplementary Table 1)(Supplementary material is available in the online article at <http://www.liebertonline.com/cap>). The most commonly reported positive effects were reduced irritability, aggression, and anxiety. Weight gain was by far the most common negative effect. Mean duration of treatment for the negative effect group was highly variable, but on average, it was lower than for the positive effect group: 27.84 ± 29.17 versus 45.22 ± 32.54 months ($t = 1.83$, $df = 46$, $p = 0.078$).

Sixteen subjects reported to respond positively to risperidone had parent SRS scores before and during treatment (BDT) with risperidone, allowing calculation of the change in score from a pretreatment baseline. Parent SRS scores for this group increased (worsened) by 4.19 ± 7.98 points/year ($t = -3.266$, $df = 15$, $p = 0.005$) (Table 2). Similarly, for the 19 who had serial parent measurements on treatment (SMT) with risperidone, significant increases in SRS scores were observed, specifically during the period of treatment with risperidone, by 3.38 ± 6.01 points/year ($t = -3.112$, $df = 18$, $p = 0.006$). Both BDT and SMT groups also demonstrated increasing (worsening) scores on all five SRS subscales (Table 2).

Using linear regression, we examined whether baseline parent SRS score or CBCL externalizing score predicted differences in parent SRS scores during risperidone treatment, and neither had a significant effect ($F[2,15] = 0.189$, $p = 0.829$). We note also an absence of age effects on SRS scores within the age range studied in this clinical sample (Constantino and Gruber 2012).

To explore whether lack of improvement in parent SRS scores was unique to risperidone responders, we compared changes in SRS scores for groups on 1) other medications or 2) no medications

TABLE 2. CHANGES IN SRS SCORES AMONG CHILDREN WITH A REPORTED POSITIVE EFFECT FROM RISPERIDONE

	Children with SRS scores before and during treatment (BDT, n = 16)	Children with serial measurements on treatment (SMT, n = 19)
Mean change in total SRS score, points/year (SD)	4.19 (7.98)**	3.38 (6.01)**
Subscale score, mean change in points/year (SD)		
Social Awareness	2.19 (3.02)	1.11 (2.77)
Social Cognition	0.94 (4.89)	1.11 (3.38)
Social Communication	6.13 (6.89)	3.84 (5.45)
Social Motivation	1.75 (4.51)	1.47 (5.66)
Autistic Mannerisms	3.88 (6.03)	3.00 (4.97)

BDT refers to subjects with SRS scores available "before-and-during treatment" with risperidone. SMT refers to participants with SRS scores available during treatment with risperidone ("serial measurement on treatment"). Increases in scores signify worsening core symptoms. Means are shown with standard deviations (SD) in parentheses.

**Indicates significant differences at $p < 0.01$.

SRS, Social Responsiveness Scale.

over a 3 year time period. Unlike risperidone responders, these two groups demonstrated mean improvements in SRS scores over time, statistically significant for the latter group, with an effect size of ~ 0.56 (other medication: -0.46 ± 11.84 points/year [$t=0.899$, $df=70$, $p=0.372$]; no medication: -6.64 ± 8.72 points/year [$t=4.989$, $df=47$, $p=0.000$]).

We also repeated analyses of changes in SRS score using available teacher SRS scores for the risperidone-treated group. Baseline teacher and parent SRS scores were not significantly different (Table 1; $t=0.234$, $df=22$, $p=0.817$). Changes in serial teacher SRS scores relative to risperidone treatment confirmed a lack of significant improvement in core ASD symptoms for both the BDT group (-0.08 ± 13.20 points/year ($t=0.322$, $df=11$, $p=0.753$)) and the SMT group (1.20 ± 16.81 points/year [$t=0.528$, $df=13$, $p=0.607$]).

Discussion

We capitalized on a naturalistic, life course longitudinal study to provide a unique, unbiased observation regarding the course of autistic symptomatology in patients treated with risperidone over a number of years. The data strongly suggest that although a majority of parents of risperidone-treated children with ASD noted improvement in their children's condition when treated with risperidone, the children's core ASD symptoms, as serially measured by the SRS, failed to improve, and in fact subtly worsened over time. This finding was surprising for several reasons. First, because core features are so fundamental to ASD, parent-reported improvement (and concomitant decision making by physicians to incur risperidone-related risks over time), could be anticipated to be associated with improvement in core symptomatology. Second, other studies, including shorter-term randomized placebo-controlled trials, have suggested improvements in social function during treatment with risperidone. Third, our group previously observed a cohort effect within the larger sample from which this study's subjects were drawn, in the direction of subtle but measurable improvement over time in autistic impairment measured by the SRS, rather than decline (Constantino et al. 2009).

It is worth noting that many of the children examined in this study, which began recruitment in 2002, would have elicited a practitioner's recommendation for risperidone at a time when such use would have been off-label. Hence, the sample may be weighted toward relatively severe behaviors among children with ASDs, and study participants on risperidone did in fact display higher externalizing and total scores on the CBCL, in spite of comparable initial SRS scores. Here, in the context of a long-term longitudinal study, we observed a lack of response of core symptom burden in the setting of "real-world" clinical judgments about the risk-benefit ratio of continuing treatment with risperidone.

Although the SLCI was retrospective, introducing possible recall bias, the benefits and side effects reported by parents conform well to what is documented in the literature (Troost et al., 2005; Jesner et al. 2007; Lemmon et al. 2011; McPheeters et al. 2011), supporting the validity of parent report for this purpose. Only a minority of parents reported improvements in symptoms related to core features, with decreased rigidity/perseveration being more commonly reported than improved social competency, a finding also supported in reviews of current literature (McPheeters et al. 2011). We documented long treatment courses, on average nearly 28 months, for children whose parents reported predominantly negative effects or no effect from risperidone. This observation suggests that 1) improvement in either comorbid symptomatology

or adaptive functioning may be driving decision making regarding duration of treatment; and 2) lack of a medication effect on core symptoms may not always be well integrated in treatment decisions for this challenging clinical population.

Our study has several unique strengths, including a naturalistic, longitudinal design featuring a much longer time course (several years) than standard clinical trials, and, therefore, occupying a unique vantage point of observation on the effects of risperidone in ASD. This lengthier period allows investigation of long-term outcomes under circumstances that are generalizable to routine clinical practice. The fact that the study is more highly representative of families who viewed their children as benefiting from risperidone presents an important opportunity to clarify the nature of perception of improvement by parent report.

A limitation of the study is that participants were not randomized. Unmeasured differences within the risperidone-treated group, in addition to the higher levels of externalizing measured on the CBCL, could therefore have contributed to the lack of improvement in core autistic symptoms. Therefore, although our findings illustrate that risperidone treatment fails to reduce core symptom burden, we cannot conclude that risperidone caused this outcome. Lack of blinded ratings is another limitation, as treatment-related expectations could have altered parents' perceptions of their children's core symptoms. It is also possible that parents, particularly those with children on risperidone, may have been less attentive to core symptoms because of prioritizing management of disruptive behaviors, in line with a prior treatment study (Arnold et al. 2003). However, SRS scores from teachers corroborated the accuracy of parental report for the risperidone-treated group, as baseline parent and teacher SRS scores did not significantly differ and teacher SRS scores similarly failed to improve over time. Further, given the gradual improvement in SRS scores previously reported for the larger longitudinal study sample (Constantino et al. 2009), parental bias would have been expected to promote lower SRS scores, the opposite of what we observed.

A separate issue is that the SRS, by virtue of being a trait-based, heritable index of ASD severity, admittedly poses a stringent criterion for detecting change in ASD symptomatology. Nevertheless, core symptoms have been reported to improve in other treatment studies using the SRS, which was able to ascertain nuanced incremental changes in response to intervention (Klaiman et al. 2013; Laugeson et al. 2014). Additional limitations of the study include a relatively small sample size and the likelihood of children's exposure to other interventions while on risperidone. Replication in a larger prospective cohort would be key for ascertaining whether treatment with risperidone is a risk factor for sustained (albeit subtle) worsening of core autistic symptomatology over time, and how such worsening should weigh into cost-benefit ratios for the initiation and continuation of treatment with risperidone in ASD-affected children with aggression and/or irritability. Such considerations should occur within the context of comprehensive appraisal of the intervention options for children with ASD, including combined treatments with medication and behavioral therapies, which may better address core ASD symptoms, while minimizing medication doses and potential side effects (Scahill et al. 2012).

Conclusions

We conclude that risperidone's beneficial effect on aggression and other elements of adaptive functioning in this longitudinal study sample were not generally accompanied by reduction in core ASD symptoms, as serially assessed by the same caregivers who

reported improvement in their children. These results reflect the important clinical distinction between reduction in core symptom burden and improvement in adaptive functioning in the management of ASD.

Clinical Significance

Given the lengthy course of risperidone treatment shown in this life-course longitudinal study, periodic re-evaluation of medication benefit for children with ASD receiving atypical neuroleptics is essential for balancing the positive effects on adaptive functioning with the cumulative risk of side effects. Clinicians should remain mindful that improvement in core ASD symptoms, a goal of effective treatment in ASD, is likely to require interventions beyond what can be achieved by current FDA-approved pharmacotherapies.

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