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Risperdal

- General
  - Generic name is risperidone
  - Introduced 1994
- Evidence:
  - FDA-approval
    - Bipolar mania/mixed episodes (since 2003) in adults.
    - May soon be FDA-approved for as an augmentor to lithium and valproic acid in the treatment of mania.
    - Treatment of irritability associated with autism in children and adolescents (ages 5-16), including symptoms of aggression, deliberate self-injury, temper tantrums, and quickly changing (labile) moods (since 10/06)
  - General
    - Evidence in borderline personality disorder.
    - May augment efficacy of antidepressants in the treatment of depressive disorders
    - Well accepted for treatment of agitation and aggression in elderly clients with dementia; this has recently (2006) come into question.
  - Adult bipolar, mood instability and schizophrenia
    - Mania
      - Two 3 week placebo-controlled RCTs for adults with mania:
        - 43-48% response rate with Risperdal
        - 24-33% with placebo
        - 47% with Haldol
      - Gopal, 2005, safe and effective as monotherapy for mania in double-blind, placebo-controlled study:
        - 42% remission rate with Risperdal at 3 weeks
        - 13% with placebo
    - Treatment-resistant depression
      - 2007: 268 patients, Risperdal vs. placebo added to antidepressants when residual symptoms of depression remained after 4 weeks on an antidepressant; 0.25-2 mg/day
        - Efficacy
          - Response rate higher
          - Degree of reduction of symptoms higher at week 4 and week 6
          - Remission rate higher
      - 2006: 489 treatment-resistant depressed patients in a multicenter study; 4-6 weeks of open-label Celexa monotherapy followed by 4-6 weeks of Celexa plus Risperdal followed by 24-week, double-blind, placebo-controlled discontinuation phase
        - Efficacy
          - 11.2% response rate with Celexa monotherapy; remission rate not clear.
          - 63% of those in the Risperdal augmentation phase remitted.
        - Discontinuation phase (either Risperdal was continued or replaced with placebo)
          - Risperdal: median time to relapse 102 days; 53.3% relapse rate
          - Placebo: median time to relapse 85 days; 54.6% relapse rate
        - Post-hoc analysis of those who responded to Celexa monotherapy with less than a 25% reduction in symptoms
          - Risperdal: median time to relapse 97 days; 56.1% relapse rate
          - Placebo: median time to relapse 56 days; 64.1% relapse rate
      - 2006: 463 depressed patients received an optimized antidepressant trial; the 274 folks who did not respond sufficiently were randomly assigned to adjunctive Risperdal 1-2 mg/day vs placebo—in both cases, folks improved but Risperdal did statistically significantly more than placebo, but only by a little.
      - Shelton: adjunctive Risperdal vs. Wellbutrin—both effective but Risperdal produced results within 1 week
      - Rapaport et al, 2006: Risperdal 0.5-1 mg/day efficacious as adjuvant with Celexa in adults; continuing Risperdal beyond 6 weeks did not extended or improve benefits.
      - Brawman-Mintzer, 2005: adjunctive Risperdal safe and effective in generalized anxiety disorder

- Hirose and Ashby: 6 week, 36-patient, open-label study of fluvoxamine plus Risperdal as initial antidepressant treatment

- Treatment of psychosis/schizophrenia in adults (since 1994)
  - Many studies, some of which are below
  - Abilify vs. Risperdal (12-week study) in first episode psychosis (Robinson et al, 2016)
    - Average dose of Abilify 15 mg/d vs. Risperdal 3.2 mg/d
    - Comparable overall efficacy
    - Comparable over all retention/discontinuation rates
    - Abilify more effective for negative symptoms, but more akathisia
    - Risperdal associated with more problems with lipids/cholesterol, elevated glucose, and elevated prolactin
  - Cariprazine 3 mg/day vs. Risperdal 4 mg/day (6-week study; Durgam et al, 2014)
    - Similar efficacy
    - Cariprazine with
      - less prolactin elevation
      - slightly less weight gain (1.5 kg vs. 2 kg)
      - slightly less tremor/EPS (4% vs. 7%)
  - Cariprazine vs. Risperdal and negative symptoms (461 subjects; Nemeth et al, 2017)
    - Cariprazine superior out through > 25 weeks
  - McEvoy et al, 2007: 52-week DB, RCT Zyprexa vs. Seroquel vs. Risperdal in early psychosis—comparable efficacy and overall tolerability
  - Zyprexa vs Geodon in a 28-week double-blind study in 277 patients with schizophrenia
    - Zyprexa was more effective
    - Geodon demonstrated less weight gain and less lipid profile difficulties
  - Harvey et al, 2006: treatment of Risperdal at the time of the first episode of schizophrenia is associated with wide-ranging improvements in cognitive functioning (as opposed to Haldol)
  - Zhong et al, 2006, comparison of Seroquel and Risperdal in the treatment of schizophrenia: both safe and equally effective.
  - Emsley et al, 2006: RCT comparing Risperdal and Haldol, 522 patients with schizophrenia; of the patients (77%) who achieved a response, the timing of the response to Risperdal was as follows:
    - **23% by 1st week**
    - **23% by 2nd week**
    - **18.5% by 3rd week**
    - **12.5% by 4th week**
    - 22.5% after 4 weeks
    - 11.2% after 8 weeks
  - Relapse prevention in schizophrenia (over 800 days)
    - 65% relapse-free on Risperdal 2-8 mg
    - 40-45% on Haldol 5-20 mg
- PTSD
  - 7 of 9 RCT's (Risperdal, Zyprexa) showed benefit (though small studies, other meds allowed)
  - Meta-analysis of 7 RCT, DB studies of Risperdal or Zyprexa either alone or as adjuvants positive (though only 192 patients involved in the studies)
  - Bartzokis et al 2005; Krystal et al 2011;
  - BUT, benefits from Risperdal were modest at best such that the risk-benefit ratio weighs towards recommendations against the use of Risperdal and atypical antipsychotic medications as monotherapy OR adjunctive treatment.
- OCD
  - Simpson et al, 2013: Risperdal not more effective than CBT for augmenting SRI's in OCD
  - Erzegovesi et al, 2006: positive
  - McDougle et al, 2000: positive
  - 4 open-label studies; negative statistically (but 40% response rate) in Hollander et al, 2003a

- Tic disorders
  - Efficacious and safe in youth with tic disorders in 2 open studies
- Youth

- Disruptive behavior disorders
  - Aman, et al, 2015: follow-up; helpful with decreasing anxiety avoidance and aggression
  - Aman, et al, 2014: follow-up, helpful
  - Aman, et al, 2013: Risperdal vs. placebo added to parent training + stimulant in severe aggression in children with ADHD; 168 youth aged 6-12 yo; 9 wks
    - Risperdal moderately helpful (though inconsistently)
    - Side effects "augmented" (with Risperdal) vs "basic" (with placebo)
      - Trouble falling asleep: 19.2% in augmented vs. 36.3% in basic
      - Cough: 19.2% in augmented vs. 25% in basic
      - Appetite decrease: 12.3% in augmented vs. 23.8% in basic
      - Appetite increase: 13.7% in augmented vs. 8.8% in basic
      - Gastointestinal upset: 16.4% in augmented vs. 5% in basic
      - Vomiting: 13.7% in augmented vs. 7.5% in basic
      - Sedation: 21.9% in augmented vs. 25% in basic
  - Krieger, et al, 2011: helpful in severe mood dysregulation disorder
  - Armenteros et al, 2007: ADHD and aggression; 25 youth, 7-12 yo; effective
  - Pandina et al, 2006: following up on Reyes 2006, found to be efficacious irrespective of intelligence (in 527 youth described below)
  - Reyes et al, 2006: long-term use of Risperdal in children with disruptive behavior disorders and subaverage intelligence; 355 patients 6-15 yo; 2 years of study; DB RCT; safe and effective throughout the 2 years.
  - Pandina et al, 2006: 527 youth treated 10-21 months, 0.75-1.5 mg: height, prolactin, testosterone, development and maturation all normal.
  - Croonenberghs et al, 2005: 504 youth with disruptive behavior disorders and subaverage IQ, aged 5-14 yo, 52 week: effective
  - Findling et al, 2004: 107 youth with severe conduct disorder; aged 5-12 yo; 48 weeks: effective
  - Biederman, 2004 controlled study demonstrated safety and efficacy in the treatment of disruptive behavior disorder
  - Aman et al, 2004: youth with both ADHD and disruptive behavior disorder; Risperdal added to stimulant treatment; effective; side effects (%):

	Risp/stim	Risp/plac	Plac/stim	Plac/plac
Somnolence	37.1	51.2	13.2	10.3
Headache	17.1	27.9	20.5	5.3
Stomach upset	14.3	18.6	7.9	7.7
Vomiting	8.6	18.6	2.6	7.7
Weight increase	14.3	7	0	0
Appetite inc	17.1	7	2.6	2.6
Insomnia	0	9.3	7.9	10.3

  - Aman et al, 2002: 118 youth with disruptive behavior disorders and subaverage IQ; 5-12 yo, safe and effective; side effects:
    - Somnolence 51% vs. 10% placebo
    - Headache 29% vs. 14% placebo
    - Vomiting 20% vs. 6% placebo
    - Stomach upset 15% vs. 6% placebo
    - Inc weight 15% vs. 2% placebo
    - Elevated prolactin 13% vs. 2%
    - Inc appetite 11% vs. 6% placebo
  - Snyder et al, 2002: DBD, low IQ; 110 youth, 5-12 yo; DB RCT; effective
  - Turgay et al, 2002: DBD, low IQ; 77 youth, 5-12 yo; 48 weeks; benefit maintained
  - Van Bellighen et al, 2001: DBD low IQ, 13 youth, 6-14 yo; DB RCT; effective
  - Buitelaar et al, 2001: DBD, low IQ, 38 youth, ~14 yo; effective
  - Findling et al, 2000: conduct disorder; DB RCT; 20 youth; 5-15 yo; effective
- Mania/maintenance, mono and combination therapy
  - Geller et al, TEAM Study, 2012; Risperdal vs. Lithium Vs. Depakote in mania
    - Risperdal (avg dose 2.57): 68%
    - Lithium (avg bld level 1.09): 35%
    - Depakote (avg bld level 113): 24%
  - Pavuluri et al, 2010: Risperdal vs. Depakote in 6-17 yo youth with mania

        - Risperdal 65-78% response rate and 65% remission rate
        - Depakote 42-45% response rate and 33% remission rate
    - Saxena, 2006: safe and effective in the treatment of aggression in kids with bipolar disorder whose symptoms were not fully controlled by mood stabilizers.
    - Biederman et al, 2006: youth aged 6-11 with bipolar disorder and ADHD, 59 youth, 12 month open label study: 74% response rate
    - Reyes et al, 2006: relapse prevention of disruptive behavior disorders, 527 youth, aged 5-17 yo; effective
    - Biederman et al, 2006: youth aged 4-6 with bipolar disorder, 8 week, open-label trial of Risperdal (16 youth) and Zyprexa (15 youth); results:
        - Drop-out rates:
            - 6% with Risperdal
            - 40% with Zyprexa
        - Response rates:
            - 69% with Risperdal
            - 53% with Zyprexa
        - Reduction in symptoms greater with Risperdal
        - Reduction in symptoms was within one week of starting Risperdal and within two weeks
        - Depressive symptoms reduced with Risperdal but not Zyprexa
    - Pavuluri et al, 2006: one-year open-label trial of Risperdal augmentation in lithium nonresponder youth with preschool-onset bipolar disorder: 38 youth ages 4-17 (mean age 11); all received lithium monotherapy initially; patients who failed lithium after 8 weeks and those who relapsed after an initial response were given Risperdal augmentation for up to 11 months; results:
        - 17/38 on lithium monotherapy responded
        - 21/38 did not:
        - Risperdal augmentation→ 86% response
    - Biederman, 2003: 30 children 6-17 yo with bipolar disorder (mixed, hypomanic, or manic episode); open label; 8 weeks; safe and effective
    - An open-label study in pediatric bipolar disorder showed evidence of efficacy in the treatment of bipolar disorder (but not in co-morbid ADHD symptoms).
    - Frazier, 1999: chart review of adjunctive Risperdal in 28 youths with bipolar disorder; rapid, robust and sustained responses for manic (82%), psychotic (69%) and aggressive (82%) symptoms. Average dose 1.7 mg.
- Schizophrenia
    - Sikich, 2006: 50 youth aged 8-19 with psychotic disorders randomly assigned to Zyprexa, Risperdal or Haldol, 8 weeks; at week 8, 27/50 responded and continued for an additional 12 weeks; few patients gained additional benefits in the latter 12 weeks (though the early benefit was maintained)
    - Zalsman, 2003—11 adolescents with schizophrenia, open-label, safe and effective
    - Armenteros, 1997—10 adolescents with schizophrenia, open-label study, safe and efficacious
- Autism, PDD
    - Scahill et al, 2012: 24-week, three-site, RCT, 124 children (4-13): med alone (0.5-3.5 mg/day with switch to Abilify if ineffective allowed), or combination of med plus parent training; results: both groups showed benefit, with modestly more improvement in the combo group
    - Troost et al, 2006; Luby et al, 2006 (pre-school youth; beneficial but small difference with placebo); McDougle et al, 2005; RUPP Autism Network, 2005 and 2002; Shea et al, 2004; McCracken et al, 2002; Masi et al, 2001
    - RUPP 2009, 124 subjects, 4-13, PDD's and significant irritability, 24 week, three-site, randomized, trial, med vs. med+therapy
        - Response rates better for med+ther than med alone
    - RUPP 2002, 101 subjects, autism, irritability, 8 wks, double-blind, placebo controlled, 5-17 yo, 1.8 mg/day (0.5-3.5 mg/day); 2.26 mg/day for med alone vs. 1.98 mg/day for med+ther
        - Response rates
            - 69% Risperdal
            - 12% placebo
        - Side effects
            - Weight gain 2.7 kg avg (0-6 kg) vs 0.8 kg avg (0-3 kg) with placebo
            - Increased appetite
            - Fatigue
            - Drowsiness

        - Dizziness
        - Drooling
        - No muscle side effects
    - Risperdal was safe and effective when used in the treatment of pediatric autism and pervasive developmental disorder (in the latter case, children were treated up to three years)
- Some of the side effects and risks include:
    - Lassitude (physically run down) in 28%
    - Abdominal pain 25% vs. 7.7% in placebo
    - Sedation/sleepiness in 8-27% vs. 15.4% in placebo
    - Appetite increase/weight gain in 8.3-23% vs. 0 in placebo; 4 pounds over 1 year
        - Safer et al, 2004
            - 5-11 yo's
                - At 4-8 wks: 5.5% increase
                - At 9-16 wks: 7.5% increase
                - At 17-56 wks: 16% increase
            - 12-17 yo's
                - At 4-8 wks: 4% increase
                - At 9-16 wks: 6% increase
                - At 17-56 wks: 8% increase
            - 33-44 yo's
                - At 4-8 wks: 2% increase
                - At 9-16 wks: 3% increase
                - At 17-56 wks: 3.5% increase
            - 71-83 yo's
                - At 4-8 wks: <1% increase
                - At 9-16 wks: <1% increase
                - At 17-56 wks: <1% increase
    - Increased prolactin
        - 95-97% of boys with increased prolactin will NOT develop breast enlargement (3-5% will)
    - Headache 15.2%
    - Increased salivation in 15%
    - Dry mouth 14%
    - Ejaculatory dysfunction in 13%
    - Rigid muscles OR slowed motor movements in 12%
    - Dizziness 11%
    - Akathisia (muscle restlessness) in 10.4-15%
    - Agitation 8.3%
    - Lack of menstrual period in 9%
    - Muscle/motor side effects
    - Increase in prolactin (usually transient but in youth may be persistent)
    - Blurred vision
    - Hypersalivation
    - Glucose intolerance/diabetes
    - Cholesterol and lipid abnormalities
    - Liver abnormalities (case reports)
    - Slight increase in risk of seizures (0.3% rate)
    - To date, not associated with congenital anomalies
    - A number of other side effects and risks in multiple organ systems.
    - Manufacturer-sponsored review of 5 multicenter studies of the use of Risperdal in children over 11-12 months; no abnormalities in growth or sexual maturation were seen despite transient increases in prolactin (2004)
    - Pregnancy
        - Case studies and drug registries (Coppola et al, 2007; McKenna, 2005) have not shown increased malformations
        - In post-market drug registry, there were 68 prospective cases, with 3.8% of cases reporting a major malformation and 16.9% rates of miscarriage, which was not significantly than the normal population (Coppola et al, 2007)
        - Case reports of self-limiting extra-pyramidal side effects in infants exist
- Pharmacodynamics
    - Blocks D2, 5HT2a/7, alpha-1/2 receptors
    - Metabolized by 2D6
    - Half-life is 3 hours (20 hours in poor metabolizers), but that of active metabolite is ~24 hours
    - Peak within 1-2 hours

- Comes in
  - 0.25, 0.5, 1, 2, 3 and 4 mg tabs
  - M-Tabs: 0.5, 1, 2, 3, and 4 mg tabs
  - liquid (1 mg/ml; compatible with water, coffee, orange juice and low-fat milk but NOT cola or tea);
  - Risperdal Consta (intramuscular; 25 mg, 37.5 mg, or 50 mg every two weeks); effective dose range 0.25 mg to 6 mg/D

- **Invega (Paliperone Extended Release)**
  - General
    - metabolite of Risperdal
    - effective dose may be ?6 mg/day
    - half-life 23 hours
    - 3-15 mg/day no more likely to cause EPS than Zyprexa 10 mg or placebo
    - September, 2006—received FDA approvable letter
    - Uses OROS pill technology, providing steady 24-hour release
    - ?less risk of drug-drug interactions than Risperdal
    - Blocks D2 and 5HT2 receptors, but may function as a dopamine partial agonist like Abilify
  - Studied only in schizophrenia where it is safe and effective
  - Side effects
    - increased prolactin: 4-fold to 5-fold (vs. placebo)
    - EPS: 5% at 6 mg/d; 10-26% at 12 mg/d vs. 11% placebo;
    - somnolence: 13% (vs. 25% on Zyprexa 10 mg/day)
    - tachycardia: 12-20% (similar to Zyprexa; vs. 0% in placebo)
    - QTc prolongation
    - headache: 10-20% (similar to Zyprexa and placebo)
    - weight changes after 6 weeks
      - paliperone, 6 mg/day: 0.2 +/- 2.4 kg
      - paliperone, 9 mg/day: 0.6 +/- 2.7 kg
      - paliperone, 12 mg/day: 0.6 +/- 2.6 kg
      - Zyprexa, 10 mg/day: 1.3 +/- 2.8 kg
      - placebo: -0.7 +/- 2.4 kg

Risperidone Added to Psychostimulant in Children with Severe Aggression and Attention-Deficit/Hyperactivity Disorder: Lack of Effect on Attention and Short-Term Memory

Cristan A Farmer, Jeffery N Epstein, Robert L Findling, Kenneth D Gadow, L Eugene Arnold, Heidi Kipp, David J Kolko, Eric Butter, Jayne Schneider, Oscar G Bukstein, Nora K McNamara, Brooke S G Molina, Michael G Aman

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OBJECTIVE: Professionals have periodically expressed concern that atypical antipsychotics may cause cognitive blunting in treated patients. In this study, we report data from a double-blind, randomized, controlled study of stimulant plus placebo versus combined stimulant and risperidone to evaluate the effects of the atypical antipsychotic on attention and short-term memory.

METHODS: A total of 165 (n=83 combined treatment; n=82 stimulant plus placebo) children with attention-deficit/hyperactivity disorder and severe physical aggression, aged 6-12 years, were evaluated with Conners' Continuous Performance Test (CPT-II) and the Wechsler Intelligence Scale for Children-III (WISC) Digit Span subscale at baseline, after 3 weeks of stimulant-only treatment, and after six additional weeks of randomized treatment (stimulant+placebo vs. stimulant+risperidone).

RESULTS: At 3 weeks, improvement on CPT-II performance (Commissions and Reaction Time Standard Error; $p<0.001$) and on Digit Span memory performance ($p<0.006$) was noted for the full sample. At study week 9, no difference in CPT-II or Digit Span performance was observed between the randomized groups (ps=0.41 to 0.83).

CONCLUSIONS: Similar to other studies, we found no deleterious effects on attention and short-term memory associated with short-term use of risperidone. NCT00796302.

Tolerability, Safety, and Benefits of Risperidone in Children and Adolescents with Autism: 21-Month Follow-up After 8-Week Placebo-Controlled Trial

Michael Aman, Mallikarjuna Rettiganti, Haikady N Nagaraja, Jill A Hollway, James McCracken, Christopher J McDougle, Elaine Tierney, Lawrence Scahill, L Eugene Arnold, Jessica Hellings, David J Posey, Naomi B Swiezy, Jaswinder Ghuman, Marco Grados, Bhavik Shah, Benedetto Vitiello

Journal of Child and Adolescent Psychopharmacology 2015, 25 (6): 482-93

OBJECTIVE: Risperidone has demonstrated efficacy for acute (8 week) and intermediate length (6 month) management of severe irritability and aggression in children and adolescents with autism. Less is known about the long-term effects of risperidone exposure in this population. We examined the tolerability, safety, and therapeutic benefit of risperidone exposure over a 1-2 year follow-up period.

METHODS: In a naturalistic study, 84 children and adolescents 5-17 years of age (from an original sample of 101) were assessed an average of 21.4 months after initial entry into a placebo-controlled 8 week trial of risperidone for children and adolescents with autism and severe irritability. They were assessed at baseline and at follow-up on safety and tolerability measures (blood, urinalysis, electrocardiogram [ECG], medical history, vital signs, neurological symptoms, other adverse events), developmental measures (adaptive behavior, intelligence quotient [IQ]), and standardized rating instruments. Treatment over the follow-up period, after completion of protocol participation, was uncontrolled. Statistical analyses assessed outcome over time with or without prolonged risperidone therapy.

RESULTS: Two-thirds of the 84 subjects continued to receive risperidone (mean 2.47mg/day, S.D. 1.29mg). At follow-up, risperidone was associated with more enuresis, more excessive appetite, and more weight gain, but not more adverse neurological effects. No clinically

significant events were noted on blood counts, chemistries, urinalysis, ECG, or interim medical history. Regardless of drug condition at follow-up, there was considerable improvement in maladaptive behavior compared with baseline, including core symptoms associated with autism. Height and weight gains were elevated with risperidone. Social skills on Vineland Adaptive Behavior Scale (VABS) improved with risperidone. Parent-rated Aberrant Behavior Checklist (ABC) Irritability subscale scores were reduced in those taking risperidone at follow-up. Several other measures of maladaptive behavior (some related to socialization) also showed improved functioning in association with risperidone on the ABC or on the Modified Real Life Rating Scale.
CONCLUSIONS: Increased appetite, weight gain, and enuresis are risks associated with long-term risperidone. Our data suggest that these risks were balanced by longer-term behavioral and social benefits for many children over 1.8 years of ongoing treatment.

Lack of effect of risperidone on core autistic symptoms: data from a longitudinal study
Natasha Marrus, Heather Underwood-Riordan, Fellana Randall, Yi Zhang, John N Constantino
Journal of Child and Adolescent Psychopharmacology 2014, 24 (9): 513-8
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.

No Apparent Cardiac Conduction Effects of Acute Treatment with Risperidone in Children with Autism Spectrum Disorder
Lan Chi Vo, Christopher Snyder, Courtney McCracken, Christopher J McDougle, James T McCracken, Michael G Aman, Elaine Tierney, L Eugene Arnold, Daniel Levi, Michael Kelleman, Deirdre Carroll, John Morrissey, Benedetto Vitiello, Lawrence Scahill
Journal of Child and Adolescent Psychopharmacology 2016 October 11
OBJECTIVES: Risperidone is approved for the treatment of serious behavioral problems in children with autism spectrum disorder (ASD). This study examined the effects of risperidone on cardiac conduction in children with ASD.
METHODS: Data were collected from an 8-week, five-site trial conducted by the Research Units on Pediatric Psychopharmacology Autism Network. Children (age 5-17 years) were randomly assigned to risperidone (n=49) or placebo (n=52) under double-blind conditions. Risperidone was superior to placebo in reducing serious behavioral problems. A standard 12-lead, electrocardiogram (ECG) was obtained in most subjects at screening and week 8. A pediatric electrophysiologist blind to treatment assignment reviewed all available ECGs for readability, abnormalities, and cardiac conduction parameters, including QTc. The electrophysiologist measurements were compared to machine readings. A second blinded electrophysiologist examined all available ECGs for abnormalities and a 20% random sample for QTc.
RESULTS: Of the 101 randomized subjects in the trial, complete pretreatment and week 8 data were available on 65 subjects (placebo n=30; risperidone n=35). The electrophysiologist did not identify any cardiac conduction adverse effects of risperidone and there was no difference in mean change on the QTc compared to placebo. The Bland-Altman plot showed a systematic bias in QTc measurements by the electrophysiologist and machine. Machine readings produced higher values than the electrophysiologist for shorter QTc intervals and machine scoring was lower than electrophysiologist readings for longer QTc values (p=0.001). Two electrophysiologists had overall percent agreements of 82.9% (95% CI: 76.3 to 89.6) on qualitative assessment and 88.6% (95% CI: 79.3 to 98.0) on QTc interval.
CONCLUSION: Using conventional doses during acute treatment in children with ASD and serious behavioral problems, there was no difference in the mean change in QTc between risperidone and placebo. Compared to the electrophysiologist, the machine readings may miss elevated QTc measurements.

Risperidone Treatment for Irritability in Fragile X Syndrome
Kelli C Dominick, Logan K Wink, Ernest V Pedapati, Rebecca Shaffer, John A Sweeney, Craig A Erickson
Journal of Child and Adolescent Psychopharmacology 2018 February 2
OBJECTIVE: The goal of this study was to assess the effectiveness of risperidone monoantipsychotic therapy targeting irritability in patients with Fragile X syndrome (FXS) in a naturalistic outpatient clinical setting.
METHODS: We examined the use of risperidone, predominantly in combination with other nonantipsychotic psychotropic agents, targeting irritability in 21 male patients with FXS with a retrospective analysis of a prospectively collected large developmental disabilities-specific treatment database. Mean age at start of treatment, treatment duration, final dose, body mass index (BMI), and Clinical Global Impressions-Improvement (CGI-I) Scale score at final visit were determined, and changes with treatment were analyzed using paired t-tests.
RESULTS: Mean age at start of treatment was 14.0 years. The final mean dose of risperidone was 2.5 mg/day. The mean duration of treatment was 22 months. Seven (33.33%) participants were considered treatment responders based on the CGI-I. Change in BMI between initiation and cessation of treatment episode was not significant, however, these data were only available for a subset (n=11) of patients.

CONCLUSIONS: Risperidone may be effective in the treatment of irritability in males with FXS. The overall effectiveness of monoantipsychotic treatment with risperidone was limited in this study compared with previous published reports; however, this may be the result of differences in outcome measures as well as a reflection of the level of functioning and severity of irritability in this sample.

Olanzapine Versus Risperidone in Children and Adolescents with Psychosis: A Meta-Analysis of Randomized Controlled Trials
Lei Xia, Wen-Zheng Li, Huan-Zhong Liu, Rui Hao, Xiang-Yang Zhang
Journal of Child and Adolescent Psychopharmacology 2018 January 22

OBJECTIVE: To compare the efficacy and safety of olanzapine and risperidone in children and adolescents (aged ≤18 years) with psychosis by conducting a meta-analysis of randomized controlled trials (RCTs).
METHODS: Several English and Chinese databases were searched for studies published before February 8th, 2017. Two independent investigators screened the studies according to prespecified criteria and extracted the data. Review Manager 5.3 was used to conduct the data synthesis.
RESULTS: Eight RCTs involving 457 participants (225 participants in the olanzapine group and 232 participants in the risperidone group) were included. No significant differences were observed in the mean scores on the Positive and Negative Syndrome Scale/Brief Psychiatric Rating Scale (standard mean difference [SMD] = -0.06, 95% confidence intervals [CI] = [-0.31, 0.19], p = 0.63), the positive symptom scores (SMD = -0.09, 95% CI = [-0.32, 0.15], p = 0.48), or the negative symptom scores (SMD = -0.11 95% CI = [-0.34, 0.13], p = 0.38) between the two groups. Regarding adverse effects, the mean increases in weight (MD = 2.90, 95% CI = [1.41, 4.39], p = 0.0001), body mass index (MD = 0.90, 95% CI = [0.42, 1.38], p = 0.0003), and incidence of hypersomnia (risk ratios [RR] = 1.98, 95% CI = [1.15, 3.43], p = 0.01) were higher in the olanzapine group, while the incidence of insomnia (RR = 0.31, 95% CI = [0.11, 0.85], p = 0.02), prolactin elevation (RR = 0.11, 95% CI = [0.01, 0.85], p = 0.03), myotonia (RR = 0.12, 95% CI = [0.03, 0.49], p = 0.003), tremor (RR = 0.22, 95% CI = [0.08, 0.63], p = 0.005), and akathisia (RR = 0.27, 95% CI = [0.12, 0.57], p = 0.0007) was higher in the risperidone group.
CONCLUSIONS: There is no significant difference in efficacy between olanzapine and risperidone for the treatment of children and adolescents with psychosis, but the side effect profiles of these two medications differ. High-quality RCTs are needed before recommending clinical treatment in children and adolescents.