**Supplementary** **Table**: Comparison with other recent systematic reviews and meta-analyses.

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| Author & date | Main features of the previous meta-analysis | Main features of the current study |
| D’Alò et al., 2021 | * Children and adolescents only. * Both the old and new-generation antipsychotics. * Only placebo-controlled studies. * Included both efficacy and withdrawal RCTs within the same analysis. | * Participants of all ages. * All new-generation antipsychotics only. * Placebo-controlled as well as head-to-head and combination of intervention studies. * Included only prospective efficacy RCT and excluded withdrawal RCTs from the analysis. |
| Alfageh et al., 2019 | * Meta-analysis of only safety data based on medication-related adverse events. | * Meta-analysis of both efficacy and safety data based on medication-related adverse events. |
| Fallah et al., 2019 | * Network meta-analysis of only eight RCTs. * Included only three new-generation antipsychotics. * Excluded non-peer-reviewed publications. | * Meta-analysis of 21 RCTs * Included four new-generation antipsychotics. * Included four non-peer-reviewed publications (one a conference abstract and three publications on the Clinical trial site). |
| Linden et al., 2022 | * Both pharmacological and non-pharmacological interventions. * Included only one RCT on antipsychotics. * The outcomes are anxiety and depression only. | * All new-generation antipsychotics only. * Included 21 RCTs and 16 secondary papers. * Any outcome including agitation and irritability. |
| Park et al., 2016 | * Meta-analysis of antipsychotic use among primarily youths, a proportion of whom had autism and/or intellectual disabilities. * No separate data on autism. * Included prevalence studies of all types of antipsychotics. | * Only people with autism of all ages. * Included only RCTs on only new generation antipsychotics. * Did not include any prevalence studies. |
| Zhou et al., 2021 | * Meta-analysis of all psychotropic medications. * Included seven RCTs on three new-generation antipsychotics. | * Meta-analysis of new-generation antipsychotics only. * Included 21 RCTs on four new-generation antipsychotics. |

**References:**

1. Alfageh BH, Wang Z, Mongkhon P, et al: Safety and tolerability of antipsychotic medication in individuals with autism spectrum disorder: a systematic review and meta-analysis. Pediatric Drugs 2019: 21:153-167.
2. D’Alò GL, De Crescenzo F, Amato L, et al: Impact of antipsychotics in children and adolescents with autism spectrum disorder: A systematic review and meta-analysis. Health Quality Life Outcomes 2021; 19(1):1-19.
3. Fallah MS, Shaikh MR, Neupane B, et al: Atypical antipsychotics for irritability in pediatric autism: A systematic review and network meta-analysis. J Child Adolesc Psychopharmacol 2019;29(3):168-180.
4. Linden A, Best L, Elise F, et al: Benefits and harms of interventions to improve anxiety, depression, and other mental health outcomes for autistic people: A systematic review and network meta-analysis of randomised controlled trials. Autism 2022; 1-24. https://doi.org/10.1177/13623613221117931
5. Park SY, Cervesi C, Galling B, et al: Antipsychotic use trends in youth with Autism Spectrum Disorder and/or Intellectual Disability: A meta-analysis. J Am Acad Child Adolesc Psychiatry 2016; 55(6):456-468.
6. Zhou MS, Nasir M, Farhat LC, et al: Meta-analysis: Pharmacologic treatment of restricted and repetitive behaviors in Autism Spectrum Disorders. J Am Acad Child Adolesc Psychiatry 2021; 60(1):35-45.

**Supplementary Table 2**: Reasons for excluding studies.

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| Citation | Reasons for exclusion |
| Aman MG, Kasper W, Manos G, et al: Line-item analysis of the aberrant behavior checklist: Results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. J Child Adolesc Psychopharmacol 2010; 20(5):415-422. | This paper has included data from two aripiprazole papers (Owen 2009 + Marcus 2009), and we have already included these two papers separately in primary studies. |
| Anderson LT, Campbell M, Adams P, et al: The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. J Autism Dev Disord 1989; 19(2):227-239. | This study is on haloperidol, which is not a second-generation APT. We included new-generation antipsychotic RCTs only. |
| Anderson LT, Campbell M, Grega DM, et al: Haloperidol in the treatment of infantile autism: Effects on learning and behavioral symptoms. Am J Psychiatry 1984; 141(10):1195–1202. | This study is on haloperidol, which is not a second-generation APT. We included new-generation antipsychotic RCTs only. |
| Benton TD. Aripiprazole to treat irritability associated with autism: A placebo-controlled, fixed-dose trial. Curr Psychiatry Rep 2011; 13(2):77-79. | Same data as in Marcus’s 2009 aripiprazole study, which is already included. |
| Caicedo C, Williams SH. Risperidone improves behavior in children with autism. J Fam Pract 2002; 51(11):915. | It is a summary abstract of the McCracken (RUPP) 2002 RCT on risperidone, which is already included. |
| Campbell M, Anderson LT, Small AM, et al: The effects of haloperidol on learning and behavior in autistic children. J Autism Dev Disord 1982; 12(2):167-175. | This study is on haloperidol, which is not a second-generation APT. We included new-generation antipsychotic RCTs only. |
| Cohen IL, Campbell M, Posner D. A study of haloperidol in young autistic children: a within-subjects design using objective rating scales. Psychopharmacol Bull 1980; 16(3):63-65. | This study is on haloperidol, which is not a second-generation APT. We included new-generation antipsychotic RCTs only. |
| Cohen IL, Campbell M, Posner D. Behavioral effects of haloperidol in young autistic children. An objective analysis using a within-subjects reversal design. J Am Acad Child Psychiatry 1980; 19(4):665-677. | This study is on haloperidol, which is not a second-generation APT. We included new-generation antipsychotic RCTs only. |
| EUCTR2006-005346-37-NL. A randomized, double-Blind, placebo-controlled maintenance of effect study of olanzapine in the treatment of disruptive behavioral symptoms in children and adolescents with Pervasive Developmental Disorders 2006. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01892127/full> (last accessed on 01.12.22) | Results are not available on the Clinical Trial website. |
| EUCTR2015-001320-31-Outside-EU/EEA. A study to evaluate the efficacy and safety of risperidone (R064766) in children and adolescents with irritability associated with autistic disorder. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01870569/full> 2015 (last accessed on 01.12.22) | Results are not available on the Clinical Trial website. |
| Findling RL, Mankoski R, Timko K, et al: A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. J Clin Psychiatry 2014; 75(1):22-30. | It is a placebo-controlled withdrawal study. We excluded withdrawal studies. |
| Hellings JA, Zarcone JR, Crandall K, et al: Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism. J Child Adolesc Psychopharmacol 2001; 11(3):229-238. | This paper presented secondary data, but there is no reference to the primary study. |
| Hellings JA, Zarcone JR, Reese RM, et al: A crossover study of risperidone in children, adolescents and adults with mental retardation. J Autism Dev Disord 2006; 36(3):401-411. | This is a cross-over study, and no specific data for Phase I, are available, which is an inclusion criterion in our protocol. |
| Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Risperidone in the treatment of children and adolescents with autistic disorder: A double-blind, placebo-controlled study of efficacy and safety, followed by an open-label extension study of safety. clinicaltrials.gov; 2014. <https://clinicaltrials.gov/ct2/show/NCT00576732> (last accessed on 01.12.22) | The same data are presented in the Kent 2013 paper, which is already included. |
| Lamberti M, Siracusano R, Italiano D, et al : Head-to-head comparison of aripiprazole and risperidone in the treatment of ADHD symptoms in children with autistic spectrum disorder and ADHD: a pilot, open-label, randomized controlled study. Paediatr Drugs 2016; 18(4):319‐329. | The outcomes are more related to ADHD than ASD. Also, the study is not blinded. |
| Levine SZ, Kodesh A, Goldberg Y, et al: Initial severity and efficacy of risperidone in autism: Results from the RUPP trial. Eur Psychiatry 2016; 32:16-20. | The same data was presented in the RUPP/McCracken 2002 study. |
| Martsenkovsky I, Martsenkovska I, Martsenkovskyi D. Risperidon and atomoxetine in the treatment of several and challenging behaviors in children with PDD. Eur Psychiatry 2015; 30:195. | It is a conference abstract, and there are no data on the number of children included in the placebo, risperidone and atomoxetine groups. Also, the treatment is for ADHD rather than ASD. |
| McCracken. Risperidone treatment of autistic disorder: Longer-term benefits and blinded discontinuation after 6 months. Am J Psychiatry 2005; 162(7):1361-1369. | It is a placebo-controlled discontinuation study. |
| McCracken JT, McGough J, Shah B, et al: Risperidone was safe and effective for short term treatment of children with autism and serious behavioural disturbances. Evid Based Med 2003; 8(1):22. | It is a summary report of the McCracken/RUPP 2002 study. |
| NCT00005014. Treatment of autism in children and adolescents. 2000. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02024836/full> (last accessed on 01.12.22) | Same data as in other secondary RUPP 2002 papers; Aman et al., 2005, Anderson et al., 2007, Aman et al., 2008, Arnold et al., 2010, Levine et al., 2016, Lindsay et al., 2006, McCracken et al., 2002, which are already included in our review. |
| NCT00057408. A controlled study of olanzapine in children with autism. 2003. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01509239/full> (last accessed on 01.12.22) | Results are not available on the Clinical Trial website. |
| NCT00870727. Study of aripiprazole in the treatment of pervasive developmental disorders. 2009. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01596587/full> (last accessed on 01.12.22) | Results are not available on the Clinical Trial website. |
| NCT01171937. 2010 Risperidone treatment in children with autism spectrum disorder and high levels of repetitive behavior. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01530768/full> (last accessed on 01.12.22). | Results are not available on the Clinical Trial website. |
| NCT01333072. Biomarkers in Autism of Aripiprazole and Risperidone Treatment (BAART). https://clinicaltrials.gov/show/NCT01333072 2010; (last accessed on 01.12.22). | It is the same as the De Vane et al., 2019 paper, which is already included in our review. |
| NTR294. Risperidone in children and adolescents with severe disruptive behavior problems.  <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01826301/full>, 2005 (last accessed on 01.12.22) | No results were posted on the website. |
| CN138178/NCT00332241. A multicenter double-blind, randomized, placebo-controlled, flexible-dosed, parallel-group study of aripiprazole in the treatment of children and adolescents with autistic disorder. 2022. <https://clinical-trials.otsuka.com/postings/cn138178> (last accessed on 01.12.22) | It is the same as the Owen et al., 2009 aripiprazole RCT that we have already included in our review. |
| Remington G, Sloman L, Konstantareas M, et al: Clomipramine versus haloperidol in the treatment of autistic disorder: A double-blind, placebo-controlled, crossover study. J Clin Psychopharmacol 2001; 21(4):440-444. | This study is on haloperidol which is not a new-generation APT. We have included only the new-generation antipsychotic RCTs in our review. |
| Stigler K, Wang Y, McDonald B, et al: Effects of aripiprazole on brain circuitry in youth with pervasive developmental disorders. Neuropsychopharmacol 2010; 35:S367. | This is only a conference abstract on neuroimaging outcomes. |
| Sunovion. A 6-week, randomized, parallel, double-blind, placebo-controlled, fixed-dose, multicenter study to evaluate the efficacy and safety of lurasidone in children and adolescent subjects with irritability associated with autistic disorder. 2016. <https://clinicaltrials.gov/ct2/show/NCT01911442> (last accessed on 01.12.22) | This paper presented the same data as in the Loebel et al., 2016 paper, which is already included. |
| Troost PW, Lahuis BE, Steenhuis MP, et al: Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. J Am Acad Child Adolesc Psychiatry 2005; 44(11):1137-1144. | It is a discontinuation study. |
| Troost PW, Althaus M, Lahuis BE, et al: Neuropsychological effects of risperidone in children with pervasive developmental disorders: A blinded discontinuation study. J Child Adolesc Psychopharmacol 2006; 16(5):561-573. | It is a discontinuation study. |

**Supplementary Table**: A narrative synthesis of extracted data from the included studies (Primary RCTs, n = 21)).

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| Study author and the publication date | Study type (methods used for ASD diagnosis) | Dose of medications | Participants (N, Age (mean ± SD, range), Gender, IQ (mean ± SD), Intervention, Follow Up) | Outcome measures used in the study | Findings | Our critique of the study |
|  | | | | | | |
| **Risperidone** |  |  |  |  |  |  |
| Kent et al., 2013 | Randomized, double-blind, placebo-controlled parallel-group study  (DSM-IV, ADI-R) | Risperidone low dose: fixed-dose 0.125 mg/day (<45kg) or 0.175 mg/day (>45kg)  Risperidone high dose: fixed-dose 1.25 mg/day (<45kg) or 1.75 mg/day (>45kg) | N = 96 (77 completed)  Age: 9 ± 3.1, 5-17 years  Male: 88%  IQ: not specified  Risperidone low dose = 30  Risperidone high dose = 31  Placebo: 35  FU: 33 weeks | ABC, CGI-S, C-YBOCS  Safety / Physical / Metabolic: adverse effects, EPS, SAS, BARS, AIMS, vital signs, physical examination, weight, ECG, blood tests | Mean baseline to endpoint change in ABC-I was significantly greater in the high-dose (p<0.001) but not the low-dose (p=0.164) group versus placebo.  CGI-S and C-YBOCS scores improved significantly only in the high-dose group.  Somnolence, sedation and increased appetite occurred more frequently in high-versus low-dose groups. | Short duration (6 weeks), and because of enrolment criteria for the RCT, the findings may not be generalizable to the clinical population. |
| Luby et al., 2006 | Randomized, double-blind, placebo-controlled parallel-group study  (DSM-IV) | Risperidone: maximum dose 1.5mg/day | N = 24 (one excluded as did not meet criteria)  Age: 4, 2.5-6 years  Male: 74%  IQ: Not specified  Risperidone: 11  Placebo: 12  FU: 6 months | CARS, GARS, VABS, CBCL, PLS-3  Safety / Physical / Metabolic: adverse effects, weight, height, blood tests (leptin and prolactin) | Controlling for baseline intergroup differences, pre-schoolers on risperidone demonstrated greater improvements in autism severity.  The change in autism severity scores from baseline to 6-month follow-up for the risperidone group was 8% compared to 3% for the placebo group. Notably, both groups significantly improved over the 6-month treatment period.  Preschool children tolerated low-dose risperidone well, with no serious adverse effects observed over a 6-month treatment period. Weight gain and hypersalivation were the most common side effects reported, and hyperprolactinemia without lactation or related signs was observed. | Small sample size risking Type II error.  Non-equivalence of groups at baseline (greater severity of ASD symptoms and greater developmental impairments in the risperidone group) |
| McCracken et al. (RUPP), 2002 | Randomized, double-blind, placebo-controlled parallel-group study  (DSM-IV, ADI-R) | Risperidone: maximum dose 2.5mg/day (<45kg) or 3.5mg/day (>45kg) | N = 101 (80 completed)  Age: 8.8 ± 2.7, 5-17 years  Male: 81%  IQ: 73% IDD  Risperidone: 49  Placebo: 52  FU: 2 months | ABC, CGI-I  Safety / Physical / Metabolic: adverse effects, weight, height, routine lab tests, vital signs, ECG | After eight weeks of treatment, the risperidone group had a significant decrease (improvement) in the mean ABC-I score compared with the placebo group (p<0.001).  The rate of a positive response (at least a 25% improvement in the score on the ABC-I and a rating of much improved or very much improved on the CGI-I scale) was significantly higher in the risperidone group (p<0.001).  Risperidone therapy was associated with higher weight gain compared with placebo (p<0.001). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group (p<0.05 for each comparison). | Short duration, and not clear how participants were recruited or the setting of the patients. |
| McDougle et al., 1998 | Randomized, double-blind, placebo-controlled parallel-group study  (DSM-IV) | Risperidone: maximum dose 10mg/day | N = 31 (24 completed)  Age: 28.1 ± 7.3, 18-43 years  Male: 71%  IQ: 77% IDD (IQ<70)  Risperidone: 15  Placebo: 16  FU: 12 weeks | CGI-I, Y-BOCS, SIB-Q, RF-RLRS, VAS  Safety / Physical / Metabolic: adverse effects, EPSEs, weight, vital signs | 57% of the patients treated with risperidone were categorized as responders compared with none of the placebo group (p<0.002).  Risperidone was superior to placebo in reducing repetitive behavior (p<0.001), aggression (p<0.001), anxiety or nervousness (p<0.02), depression (p<0.03), irritability (p<0.01), and overall behavioral symptoms of autism (p<0.02). Objective, measurable changes in social behavior and language did not occur.  Other than mild, transient sedation, risperidone was well tolerated, with no evidence of extrapyramidal, cardiac or seizure related symptoms. | The rating scales used to assess social relatedness were not sensitive enough to detect changes in the complex aspects of behavior. |
| Nagaraj et al., 2006 | Randomized, double-blind, placebo-controlled parallel-group study  (DSM-IV) | Risperidone: fixed-dose 1mg/day | N = 40 (39 completed)  Age: 5, 2-9 years  Male: 87%  IQ: 76% IDD  Risperidone: 20  Placebo: 20  FU: 6 months | CARS, CGAS, Global Impression of Parents, VSMS  Safety / Physical / Metabolic: adverse effects, AIMS, weight, height, blood tests (leptin and prolactin) | In the risperidone group, significantly more children showed improvement in the total CARS score and CGAS score compared with the placebo group (p<0.001 and p=0.035, respectively).  Risperidone significantly improved functioning in the domains of social responsiveness (p=0.014) and nonverbal communication (p=0.008) and decreased symptoms of hyperactivity (p=0.002) and aggression and irritability (p=0.016).  Risperidone was associated with increased appetite and mild weight gain, mild sedation in 20%, and transient dyskinesias in three children. | The duration of the RCT period is not clear. |
| NCT01624675, 2015 | Randomized, double-blind, placebo-controlled parallel-group study  (DSM-IV) | Risperidone: maximum dose 1mg/day (<20kg) or 2.5mg/day (20-45kg) or 3mg/day (>45kg) | N = 39 (29 completed)  Age: median 8/7, 5-17 years  Male: 77%  IQ: 100% FIQ > 35  Risperidone = 21  Placebo: 18  FU: 8 weeks | ABC-J, CGI-S, CGI-C, CGAS, PSQ  Safety / Physical / Metabolic: adverse effects, DIEPSS, vital signs, weight, ECG, blood tests | Statistically significant improvement in ABC-I score for the risperidone group compared with the placebo group (p=0.003).  No statistically significant between-group difference was found in the change of the lethargy/social withdrawal subscale score from baseline to the endpoint (ANCOVA, p=0.6409), while the other three subscale scores showed statistically significant improvements in the risperidone group compared with the placebo group (p=0.0353 on the stereotypic behavior, p=0.0042 on the hyperactivity/noncompliance, and p=0.0364 on the Inappropriate Speech)  No statistically significant difference between CGI-C and CGI-S.  Statistically significant improvement for CGAS in the risperidone group compared with the placebo group (p=0.0045). | Not all detail information is available from the Clinical trial website. |
| Shea et al., 2004 | Randomized, double-blind, placebo-controlled parallel-group study  (DSM-IV) | Risperidone: maximum dose 0.06mg/kg/day | N = 80 (72 completed)  Age: 7.5, 5-12 years  Male: 77%  IQ: 53% IDD (IQ < 70)  Risperidone: 41  Placebo: 39  FU: 8 weeks | ABC, N-CBRF, VAS, CGI-C  Safety / Physical / Metabolic: adverse effects, ESRS, vital signs, body weight | Participants taking risperidone showed a significantly greater mean decrease in the ABC-I score compared with those taking a placebo (p<0.001).    The risperidone-treated group also showed a significant decrease on  the other four subscales of the ABC (p<0.05) and on the conduct problem, insecure/anxious, hyperactive, and overly sensitive subscales of the N-CBRF (parent version); and on VAS of the most troublesome symptom.  More risperidone-treated participants showed global improvement in their condition compared with the placebo group.  Risperidone-treated participants showed more somnolence and statistically significantly greater increases in weight, pulse rate, and systolic blood pressure. Extrapyramidal symptom scores were comparable between groups. | Short study duration. |
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| **Risperidone vs Aripiprazole** |  |  |  |  |  |  |
| Devane et al., 2019 | Randomized, double-blind, parallel-group non-inferiority study  (DSM-IV, ADR-I, ADOS) | Aripiprazole: maximum dose 15mg/day  Risperidone: maximum dose 2.5 mg/day (<45kg) or 3mg/day (>45kg) | N = 61 (51 completed)  Age: median 8.5/8.3, 6-17.5 years  Male: 79%  IQ: not specified  Aripiprazole = 31  Risperidone = 30  FU: 10-week | ABC-I, CGI, Children’s Sleep Habits Questionnaire  Safety / Physical / Metabolic: adverse effects, SAS, AIMS, BARS, height, weight, blood pressure, hip and waist circumference, blood tests | Participants in both groups showed a significant improvement on the ABC-I subscale after one week and continued for the remaining nine weeks.  Improvement was greatest in the risperidone group at every assessment period and was statistically significantly better than that in the aripiprazole group at weeks 3 and 6 (p<0.05).  No dose-limiting adverse events occurred during the dose-titration period. Mean weight gain in the aripiprazole group was significantly less than that in the risperidone group at week 4 (p=0.033) and week 10 (p<0.001). | A large proportion of eligible participants were already being treated off-label with one of the study drugs or with alternative pharmacotherapy. |
| Ghanizadeh et al., 2014 | Randomized, double-blind parallel-group non-inferiority study  (DSM-IV, ADI-R) | Aripiprazole: maximum dose 10mg/day (<40kg) or 15mg/day (>40kg)  Risperidone: maximum dose 2 mg/day (<40kg) or 3mg/day (>40kg) | N = 59 (50 completed)  Age: 9.55, 4-18 years  Male: 81%  IQ: not specified  Aripiprazole = 29  Risperidone = 30  FU: 2 months | ABC, CGI-I  Safety / Physical / Metabolic: adverse effects, weight, height, BP | The risperidone and the aripiprazole groups both showed a statistically significant improvement in all ABC subscales scores at follow-up. There was no significant intergroup difference for any ABC subscale.  The rates of adverse effects were not significantly different between the two groups. | Short study duration.  Small sample size risking type II error. |
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| **Risperidone vs Haloperidol** |  |  |  |  |  |  |
| Miral et al., 2008 | Randomized, double-blind, parallel-group non-inferiority study  (DSM-IV) | Risperidone: maximum dose 0.08 mg/kg/day  Haloperidol: maximum dose 0.08 mg/kg/day | N = 30 (28 completed)  Age: 10.5, 7-17 years  Male: 80%  IQ: not specified  Risperidone: 15  Placebo: 15  FU: 12 weeks | RF-RLRS, ABC, CGI-I, CGI-S, Turgay DSM-IV PDD Rating Scale  Safety / Physical / Metabolic: adverse effects, ESRS, UKU Side-effect rating Scale, weight, height, vital signs, blood tests, ECG | The reduction from baseline in RF-RLRS, sensory-motor (subscale I) and language (subscale V) scores were significant in the risperidone group (p<0.05).  Compared with haloperidol, the risperidone group showed a significantly greater reduction (improvement) in the ABC and DSM-IV PDD scale scores (p<0.05 and p<0.01).  Sensory motor behaviors (subscale I) and language at the end of the 12th week, and RF-RLRS sensory motor and language subscale scores improved significantly in the risperidone than the haloperidol group (p<0.05).  There was a greater increase of serum prolactin level in the risperidone group, while liver function tests showed a poorer result in the haloperidol group. | Small sample size risking Type II error. |
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| **Risperidone vs Memantine** |  |  |  |  |  |  |
| Nikvarz et al., 2016 | Randomized, open-label parallel-group non-inferiority study  (DSM-IV) | Risperidone: maximum dose 3mg/day  Memantine: maximum dose 20mg/day | N = 34 (30 completed)  Age: 6.7 ± 3.2, 4-17 years  Male: 77%  IQ: not specified  Risperidone: 16  Memantine: 18  FU: 8 weeks | CARS, ABC, CGI-I, CGI-S  Safety / Physical / Metabolic: adverse effects | Both risperidone and memantine  reduced the scores of 4 ABC subscales as well as the 10-item and the total score of CARS significantly at follow-up. However, there was no statistically significant intergroup difference in any of these scores.  Relatively, a larger number of participants on risperidone showed “very much improvement” when assessed by the CGI-I scale compared with those on memantine. | Unblinded.  No placebo control.  Small sample size risking type II error.  Short follow-up period. |
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| **Risperidone vs Divalproex sodium** |  |  |  |  |  |  |
| Martsenkovsky et al., 2014 | Parallel design RCT of risperidone vs. divalproex sodium  (DSM IV, ADI-R, ADOS-G) | Risperidone: mean dose 0.05-0.1mg/kg/day  Divalproex sodium: titrated up to effect and/or valproate level between 50 and 100 pg/ml | N = 86  Age: 3-6 years  Male: Not stated  IQ: not specified  Risperidone: Not stated  Divalproex: Not stated  FU: 16 weeks | ABC-I, CGI-I, OAS-M  aggression, impulsivity, hyperactivity, stereotypy, tics | Risperidone is significantly better than Divalproex in improving irritability measured by CGI-I (p=0.002, d=1.46); OAS-M aggression against objects (p=0.005); ABC-I (teacher rating) (p=0.05) | Much information is missing as published only as a conference abstract. |
|  |  |  |  |  |  |  |
| **Risperidone + Parent education** |  |  |  |  |  |  |
| Aman et al., 2009 | Parallel design RCT of a combination treatment of risperidone + parent training (COMB) vs risperidone alone (MED)  (DSM-IV, ADI-R) | Risperidone: maximum dose 3.5 mg/day (switch to aripiprazole if ineffective)  COMB: average 10.9 parental training sessions | N = 124 (95 completed)  Age: 6 -17.5 years  Male: 85%  IQ: 43% IQ<70  COMB (medication + training) = 75  Medication = 49  FU: 24 weeks | HSQ, ABC, C-YBOCS, CGI-I  Safety / Physical / Metabolic: adverse effects, weight, height, BMI | COMB was superior to MED on HSQ score (p=0.006).  Groups did not differ on CGI-I scores at the endpoint. Compared with MED, COMB group showed significant reductions (improvement) in ABC-I (p=0.01), Stereotypic Behavior (p=0.04), and Hyperactivity / Noncompliance subscales (p=0.04).  Both groups had significant gains in height and substantial gains in weight and BMI. As compared by analysis of covariance, the differences between groups were not significant in weight, height, or BMI on percentile-normed growth lines. | Unblinded. No placebo control.  No parent training group alone.  Non-equivalence of groups at baseline (with the MED group functioning at a lower level), although further statistical analysis, ruled out any effect of IQ on the HSQ or ABC-I scores. |
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| **Risperidone + VR** |  |  |  |  |  |  |
| Kouhbanani et al., 2021 | Randomized, control trial of a combination of risperidone + behavioral intervention (VR) vs. risperidone alone  (DSM-V, ADI-R, CARS) | Risperidone: maximum dose 1.75mg/day (<20kg) or 2.25mg/day (20-45kg) or 3.5mg/day (>45kg) | N = 45 (43 completed)  Age: 9, 6-12 years  Male: 67%  IQ: 100% low to moderate IQ  Risperidone: 15  Risperidone + VR: 15  Control: 15  FU: 6 months | CARS (behavioural symptoms), VABS | Risperidone + VR group showed a statistically significant improvement in social skills (p<0.001) and behavioral symptoms (p<0.001) at follow-up compared with the risperidone-only group. | Unblinded. Small sample size risking type II error. |
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| **Aripiprazole** |  |  |  |  |  |  |
| Ichikawa et al., 2017 | Parallel group placebo controlled RCT  (DSM-IV) | Aripiprazole: maximum dose 15mg/day | N = 92 (89 completed)  Age: 10.1, 6-17 years  Male: 82%  IQ: 63% IDD  Aripiprazole: 47  Placebo: 45  FU: 8 weeks | ABC, CGI-I, CGI-S, C-YBOCS (compulsion scale only), CGAS  Safety / Physical / Metabolic: adverse effects, DIEPSS, AIMS, BARS, C-SSRS, vital signs, weight, ECG | Aripiprazole was significantly more efficacious than placebo at treating irritability, as measured by the caregiver-rated ABC-I subscale score from week 3 through week 8 (p=0.044).  Aripiprazole produced significant improvements over the placebo on CGI-I score, mean ABC-hyperactivity subscale score, mean CGI-S score and CAS score. No significant difference between the groups in the mean ABC-stereotypy score.  Significantly more responders were in the aripiprazole group than in the placebo group (p=0.033).  No serious adverse event was reported in the aripiprazole group. | Short study duration. |
| Marcus et al., 2009 | Parallel group placebo-controlled fixed dose RCT  (DSM-IV) | Aripiprazole low dose: fixed-dose 5mg/day  Aripiprazole medium dose: fixed-dose 10mg/day  Aripiprazole high dose: fixed-dose 15mg/day | N = 218 (178 completed)  Age: 10, 6-17 years  Male: 89%  IQ: Not specified  Aripiprazole 5mg: 53  Aripiprazole 10mg: 59  Aripiprazole 15mg: 54  Placebo: 52  FU: 8 weeks | ABC, CGI-I, CGI-S, C-YBOCS (compulsion scale only), PedsQL, CGSQ),  Safety / Physical / Metabolic: adverse events, SAS, AIMS, BARS, vital  signs, ECG, weight, laboratory assessments. | At week 8, all aripiprazole doses produced significantly greater improvement than placebo in mean ABC-I subscale scores (p<0.05).  All aripiprazole doses demonstrated significantly greater improvements in mean CGI-I score than placebo at week 8.  The most common adverse event leading to discontinuation was sedation. There were two serious adverse events: presyncope (5 mg/day) and aggression (10 mg/day). There was significant weight gain in the aripiprazole groups (p<0.05 versus placebo). | Short study duration. |
| NCT00198107, 2019 | Parallel group placebo-controlled RCT  (DSM-IV) | Aripiprazole: maximum dose 10mg/day (<50kg) or 15mg/day (>50kg) | N = 81 (72 completed)  Age: 9.2 ± 3.2, 5-17 years  Male: 86%  IQ: not specified  Aripiprazole = 40  Placebo = 41  FU: 8 weeks | ABC, CGI-I, C-YBOCS (compulsion scale only), VABS, ADOS, SRS  Safety / Physical / Metabolic: adverse effects | Significant reduction in the ABC-I score in the aripiprazole group (post-intervention score: 18.6, 95% CI 15.8-21.4) compared with the placebo group (post-intervention score: 25.5, 95% CI 22.8-28.3) (p=0.0006).  Improvement in CGI-I score with aripiprazole (odds ratio 0.5, 95% CI 0.31-0.79) compared with placebo (odds ratio 0.1, 95% CI 0.05-0.23) | Short study duration. |
| NCT00468130, 2022 | Parallel group placebo-controlled RCT | Aripiprazole: maximum dose 10mg/day (<40 kg), 20mg/day (>40 kg) | N = 13 (9 completed)  Age: 12.4 ± 2 years  Male: 85%  IQ: Not stated  Aripiprazole: (N = 7; 5 completed)  Male: 86%  Placebo: (N = 6; 4 completed)  Male: 83%  FU: 8 weeks | CGI-I, ABC-I  Rate of adverse effects | CGI-I: Aripiprazole: baseline (3.83 ± 0.41) vs. FU (2.67 ± 1.21); placebo: baseline (4.25 ± 1.25) vs. FU (4.25 ± 1.5) (p=0.06).  ABC-I: Aripiprazole: baseline (15.67 ± 11.65) vs. FU (6.83 ± 6.7); placebo: baseline (8 ± 4.58) vs. FU (8.67 ± 10.69) (p=0.725).  Adverse event (worsening of depression): Aripiprazole: (1/7) (14.29%); placebo: 0% | Not all information is available on the Clinical Trial website. |
| Owen et al., 2009 | Parallel group placebo-controlled flexible dose RCT  (DSM-IV, ADI-R) | Aripiprazole: maximum dose 15mg/day | N = 98 (75 completed)  Age: 9.3, 6-17 years  Male: 82%  IQ: not specified  Aripiprazole: 47  Placebo: 51  FU: 8 weeks | ABC-I, CGI-I, C-YBOCS (compulsion scale only), PedsQL, CGSQ  Safety / Physical / Metabolic: adverse effects, SAS, BARS, AIMS, vital signs, weight, ECG, lab tests, | Mean improvement in ABC-I score was significantly greater in the aripiprazole than the placebo group from week 1 through week 8 (p<0.001).  Aripiprazole demonstrated significantly greater global improvements than placebo, as assessed by the mean CGI-I score from week 1 through week 8 (p<0.001). However, clinically significant residual symptoms may still persist for some patients.  Discontinuation rates as a result of adverse events and EPS-related adverse event rates were slightly higher for the aripiprazole group. No serious adverse events were reported. Aripiprazole treatment was associated with significantly greater mean weight change compared with placebo at the endpoint (p=0.005). | Short study duration. |
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| **Lurasidone** |  |  |  |  |  |  |
| Loebel et al., 2016 | Randomized, double-blind, placebo-controlled fixed dose parallel-group study  (DSM-IV, ADI-R) | Lurasidone low dose: fixed-dose 20mg  Lurasidone high dose: fixed-dose 60mg | N = 150 (128 completed)  Age: 10.7, 6-17 years  Male: 82%  IQ: not specified  Lurasidone low dose: 50  Lurasidone high dose: 49  Placebo: 51  FU: 6 weeks | ABC-I, CGI-I, C-YBOCS, CGSQ  Safety / Physical / Metabolic: adverse effects, AIMS, SAS, BARS), blood tests, urinalysis, vital signs, weight, height, ECG | The least squares (LS) mean improvement from baseline to week 6 in the ABC-I was not significantly different for lurasidone 20 mg/day and lurasidone 60 mg/day versus placebo.  CGI-I scores showed significantly greater LS mean improvement at week 6 for lurasidone 20 mg/day versus placebo (p = 0.035) but not for lurasidone 60 mg/day.  Discontinuation rates due to adverse events were no higher in lurasidone groups. Adverse events with an incidence >10% (lurasidone combined dose, placebo) included vomiting and somnolence.  Modest changes were observed in weight and selected metabolic parameters. | The original clinical research was sponsored by Sunovion Pharmaceuticals Inc. The sponsor was involved in the design, collection, and analysis of the data. |
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| **Olanzapine** |  |  |  |  |  |  |
| Hollander et al., 2006 | Randomized, double-blind, placebo-controlled parallel-group study  (DSM-IV, ADI-R, ADOS) | Olanzapine: maximum dose 20mg/day | N = 11 (8 completed)  Age: 9, 6-14.8 years  Male: 82%  IQ: 64% IDD  Olanzapine: 6  Placebo: 5  FU: 8 weeks | CGI-I, C-YBOCS, OASM,  Safety / Physical / Metabolic: adverse effects (Olanzapine Side Effect Checklist, AIMS, SAS, BARS), weight, height, BP, pulse | Olanzapine was superior to the placebo on the mean CGI-I score with a significant linear trend x group interaction (p=0.012). 50% on olanzapine versus 20% on placebo were responders.  No significant change (linear trend x condition interaction) on the C-YBOCS (p=0.777), the OAS-M irritability measure (p = 0.325), or the OAS-M aggression measure (p=0.671).  Participants in the olanzapine group gained more weight than participants in the control group. | Short study duration. Small sample size risking type II error. |

ABC: Aberrant Behavior Checklist; ABC-C, Aberrant Behavior Checklist-Community version; ABC-I, Aberrant Behavior Checklist-Irritability; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; AIMS, Abnormal Involuntary Movement Scale; ASD, Autistic Spectrum Disorder; BARS, Barnes Akathisia Rating Scale; BMI: Body Mass Index; CARS, Childhood Autism Rating Scale; CBCL, Childhood Behavior Checklist; CGAS: Children’s Global Assessment Scale; CGI, Clinical Global Impressions Scale; CGI-I, Clinical Global Impressions Scale-Improvement; CGI-S, CGI-Severity, CI, Confidence Interval; CGSQ, Caregiver Strain Questionnaire; CPRS, Conners’ Parents Rating Scale; C-YBOCS, Children’s Yale Brown Obsessive Compulsive Scale; df: degree of freedom; DIEPSS, Drug Induced Extra-Pyramidal Symptoms Scale; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision; ECG, Electrocardiogram; EL, expressive language; EPS, Extrapyramidal symptoms; ESRS, Extrapyramidal Symptom Rating Scale; FU, Follow-up; GARS, Gilliam Autism Rating Scale; ICD-10, International Classification of Diseases 10th Revision; HSQ, Home Situations Questionnaire; IDD, Intellectual Developmental Disorder; IQ, Intelligence Quotient; ITT: Intention to Treat; MR, Mental Retardation; N, number; N-CBRF, Nisonger Child Behavior Rating Form; OAS-M, Overt Aggression Scale-Modified; PAS-R: Preschool Anxiety Scale-Revised; PBO, Placebo; PL-ADOS, Pre-linguistic Autism Diagnostic Observation Schedule; PDD, Pervasive Developmental Disorder; PedsQL, Pediatric Quality of Life Inventory; PEP-3, Psychoeducational Profile third edition; PLS-3: Preschool Language Scales, 3rd Edition; PSQ, Parent Satisfaction Questionnaire; RF-RLRS, Ritvo-Freeman Real Life Rating Scale; RL, receptive language; RRB: Restrictive Repetitive Behaviors; SARS,SAS, Simpson-Angus Rating Scale; SD, Standard deviation; SE, Standard Error; SIB-Q, Self-injurious behavior-Questionnaire; SRS: Social Responsiveness Scale; UKUSERS, UKU Side-Effect Rating Scale; VABS-II : Vineland-Adaptive Behaviour Scale-II; VAS, Visual Analogue Scale; VR: Virtual Reality; VSMS, Vineland Social Maturity Scale; YBOCS: Yale-Brown Obsessive Compulsive Scale.

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**Supplementary Table**: A narrative synthesis of extracted data from the included studies (Secondary papers; n = 18).

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| Study | Study Type | Dose of medication | Participants (N, Age (mean ± SD, range), Gender, IQ (mean ± SD), Intervention, Follow Up) | Outcome measures used in the study | Finding |
| **SECONDARY to McCracken /RUPP 2002 Risperidone RCT** | | | | | |
| Aman et al., 2005 | Acute 8-week, Double-blind, placebo-controlled trial of risperidone.  DSM-IV based clinical evaluation and ADI-R. | Risperidone up to 2.5 mg/day below 44.9 kg body weight.  3.5 mg/day in divided doses above that.  Control on placebo | Mean age 8.8 years  5-17 years  Male: 82 (81%)  Female: 19 (19%)  Control Group-  Mean age8.8 years  5-17 years  Male: 82 (81%)  Female: 19 (19%)  8 week follow up | SARS, AIMS, Sleep in minutes  Blood cell counts, Liver and kidney function tests,  Height and weight  Vital signs | Laboratory: Statistically (but not clinically) significant group-by-drug interaction changes were found for red blood cells, neutrophil, and lymphocyte counts, and for SGPT/SGOT.  Side effects: Significantly more common with risperidone: tired during the day (p<0.0001), excessive appetite (p< 0.0001), difficulty waking (p=0.05), excessive saliva or drooling (p=0.04), and dizziness or loss of balance (p=0.04). Significantly less common with risperidone: difficulty falling asleep (p=0.02) and anxiety (p=0.05). |
| Aman et al.,2008 | Acute, double blind, placebo controlled, parallel groups design  DSM- IV based clinical evaluation and ADI-R | Risperidone up to 2.5 mg/day below 44.9 kg body weight.  3.5 mg/day in divided doses above that.  Control on placebo | Overall, for intervention and control group:  Range: 5 to 17 years  Mean (SD): 9.42 (2.96)  Male: 29 (76.3%)  Female: 9 (23.7%) Average/low average ability 8 (21.05%)  Mild intellectual disability 18 (47.36%)  Moderate intellectual disability 8 (21.05%)  Severe intellectual disability 1 (2.63%)  Profound intellectual disability 2 (5.26%) | Cancellation Task, Analogue Classroom Task, and the Verbal Memory Test  Purdue Pegboard Test and the Visuospatial  Memory Test | Risperidone: more correct detections than placebo on the Cancellation Task [F (1, 17)=3.18, p=0.05, np 2=0.16] and more correct recognitions than placebo on the Verbal Learning Task, [F (1, 13)=4.42, p=0.05, np 2=0.20]. Immediate recall on the Verbal Learning Task in both drug conditions; a significant effect of Time (suggests a significant practice effect).  On the Purdue Pegboard, dominant hand insertions shows a significant effect over time for both treatments (i.e., a practice effect). Results indicate no significant effect attributed to drug (i.e., the Time by Drug interaction).  The Visuospatial Task (Dot Test) appeared to favour risperidone but this disappeared on analysing this variable by analysis of covariance (ANCOVA). |
| Anderson et al., 2007 | Multi-center trial with three phases: 8-week double-blind trial of parallel groups:  4-month open-label extension, a blinded 8-week  discontinuation phase.  DSM- IV based clinical evaluation and ADI-R | Mean risperidone doses at 8 weeks 1.80 and 1.96 mg/day for all participants and responders, respectively; mean dose at 6 months 2.08 mg/day  Placebo | Risperidone:  Range 5-17 years  Males: 8 years SD (2.8)  Females: 8.5 years SD (2.3)  Male: 33 (79%)  Female: 9 (21%)  Control:  Range (overall): 5-17 years  Mean age (SD) males: 8.9 years (2.5)  Mean age (SD) females: 10.0 years (3.0)  22 months follow | Mean prolactin level | Mean prolactin after 8 weeks of risperidone treatment increased to 39.0±19.2 ng/ml compared with 10.1±8.8 ng/ml for placebo (F1,76=74.9, p<.0001).  At 6 months the levels were significantly lower than at 8 weeks for the 43 participants (paired t=2.7, p=0.009).  For 30 subjects, long term follow up at 22+2 months, the levels were significantly higher than baseline (25.3±15.6 versus 10.4±10.1 ng/ml; paired T=4.5; p< .0001).  There were no prolactin related side effects noted.  The baseline and 8 week prolactin levels were similar across the genotype distributions of DRD2 polymorphisms. |
| Arnold et al., 2010 | Double blind placebo controlled parallel design  DSM-IV based evaluation | Risperidone: maximum dose 2.5mg/day (<45kg) or 3.5mg/day (>45kg) | Overall (separate data not provided for each group):  Age (in years): 5.1–16.9  Mean (SD): 8.8 (2.7) | ABC Irritability subscale score | High baseline ABC Irritability subscale score severity was associated with greater improvement in the risperidone group compared to placebo.  Weight gain was the only significant negative mediator of response to risperidone; main effect on outcome (x2=19.34, P=0.0001) and correlated with treatment (point-biserial R=0.57, p=0.0001). Those who gained more weight improved less with risperidone and more with placebo.  Dose had a strong and significant point-biserial correlation with treatment (r=0.47, p=0.0009); children taking risperidone were likely to receive lower doses than children randomized to placebo. Compliance was also significantly (weakly) correlated with treatment (r=0.22, p=0.028).  Of nonspecific predictors, parent education, family income, and low baseline prolactin positively predicted outcomes. Anxiety, bipolar symptoms, oppositional-defiant symptoms, stereotypy, and hyperactivity negatively predicted outcomes.  Risperidone moderated the effect of change in 50-nucleotidase, a marker of zinc status, for which decrease was associated with improvement only with risperidone, not with placebo. |
| Levine et al., 2016 | Double blind placebo-controlled trial for 8 weeks  RUPP study  DSM- IV based clinical evaluation and ADI-R | Risperidone-flexible dosing in the first 4 weeks | Overall (not specified per group)  Range: 5 to 17 years  Mean: 8.8 years  Risperidone n=49  Placebo n=52 | Parent bases ABC-I Change Score, ABC parent total, and subscales, the ABC clinician Irritability scales and CGI scales | Significant interactions between treatment and baseline severity were only seen for parent ABC ratings of irritability and lethargy and baseline severity (p<0.01). There was a strong effect on symptom change when the initial severity value was approximately 30 [irritability: effect size(ES)=1.9, number needed to treat (NNT)=2), lethargy, ES=0.9, NNT=5)] |
| Lindsay et al., 2006 | Randomised placebo-controlled trial of risperidone for disturbed behaviour  [RUPP] Autism Network 2002 | Risperidone | Overall (not specified per group)  Range: 5-13 years  Mean: 8.38 years (2.21)  Overall (not specified per group)  Male: 19 (95%)  Female: 1 (5%)  8 weeks follow up | Height, weight, Body mass index and nutritional intake | The risperidone group had significant weight increase compared with the placebo group (3.7 kg±2.1 vs. 1.6 kg±1.5, p=0.03) and height z scores (0.23±0.35 vs. 20.40±1.17, p=0.01).  During the double-blind phase, a dose of 1.8 mg of risperidone was significantly associated with an increase in BMI z score. With no significant effect of age, baseline BMI, or caloric intake.  Children in the risperidone group took in more vitamin K (19 mcg ±30) as compared with the placebo group (216 mcg ±37) (p<0.05).  Risperidone group had more vitamin K intake (19 mcg ±30) compared with the placebo group (216 mcg ±37) (p<0.05).  Participants in the risperidone group at the end of the double-blind phase had a greater mean intake of 16 of 20 nutrients, while that of 15 of 20 nutrients in the placebo group was smaller. |
| McDougle et al., 2005 | Double-blind, placebo-controlled trial followed by open label continuation, Risperidone, children and adolescents with autism.  DSM- IV based clinical evaluation and ADI-R | Risperidone 0.5-3.5mg/day | Overall:  N=101  Age 5-17 mean 8.8 years SD 2.7 years  Male 82% | ABC  CGI-I  RFS  C-YBOS,  Maladaptive domain of Vineland Adaptive Behaviour Scales. | Risperidone significantly decreased the overall score on  the Ritvo-Freeman scale and the scores on the subscales  for sensory motor behaviors (subscale I), affectual reactions  (subscale III), and sensory responses (subscale IV),  but it had no statistically significant effect on the scores on  the subscale for social relatedness (subscale II) or language  (Subscale V). The mean score changed from 15.51 (SD=2.73) to 11.65 (SD=4.02) in the risperidone group compared with 15.18 (SD=3.88) to 14.21 (SD=4.81) in the placebo group according to the Yale-Brown Obsessive Compulsive Scale. |
| Scahill et al., 2013 | Secondary analysis of data from two multi-center Randomized controlled trials on risperidone  DSM- IV based clinical evaluation and ADI-R | Risperidone titrated to a maximum dose of 2.5mg a day | Trial One  Risperidone n=49 Males 39 (80%)  Placebo n=52 Males 43(83%)  IQ>70  Trial Two  Risperidone n=11(23.9%)  Placebo n=6(13.3%)  IQ<70 Risperidone  N=35(76.1%)  Placebo n=39 (86.7%)  Age 5-17 years | Vineland Adaptive Behaviour Scale.  ABC.  CSI.  CGI-S | Of particular interest was Social Withdrawal Subscale of ABC which declined in all four groups.  Post hoc pair wise comparison showed significant differences between the placebo group and the three treatment groups; there were no significant differences between the three treatment groups. |
| Vo et al., 2016 | Multisite, 8-week, double-blind randomized trial RUPP, 2002  DSM- IV based clinical evaluation and ADI-R | Risperidone | 101 children (82 males and 19 females; age 5-17 years)  65 had completed ECG for study  35 out 49 on risperidone had ECG Range 5-17  Mean 8.3 SD 2.6  Male 27/35 (77.1%)  ID 18 (51.4%)  30 out of 52 on placebo had ECG Range 5-17  Mean 9.2 (SD 2.7)  Males 25/30 (83.3%)  ID 19 (63.3%) | ECG readings | There was no significant difference in the percentage of new cases of prolonged QTc across treatment groups (p=1.00).  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.  Using conventional doses during acute treatment in children with ASD and serious behavioural problems, there was no difference in the mean change in QTc between the risperidone and the placebo groups. Compared with the electrophysiologist, the machine readings may miss elevated QTc measurements |
| **SECONDARY to Aman et al. 2009 Risperidone vs combination of risperidone and parent training** | | | | | |
| Arnold et al., 2012 | Randomized parallel group clinical trial to compare medications alone (MED) with medications and parent training (PT) (COMB).  DSM- IV based clinical evaluation and ADI-R | Risperidone 0.5mg to 3.5mg/day with a switch to aripiprazole if ineffective, started at 2mg, adjusted to 15mg/day | 124 children  4 to 13 years  Randomized 3:2 to COMB group n= 75 or  MED n=49 for 24 weeks  Parents in COMB group also received PT  Families were contacted 18 moths after the study baseline. | HSQ, ABC, Irritability and Hyperactivity/Noncompliance subscales. | The improvement difference between treatments attenuated from after-treatment to follow-up for noncompliance (d=0.32 to 0.12) and irritability (d=0.46 to 0.03). The follow-up differences were nonsignificant (the noncompliance difference also was nonsignificant after treatment for these 87 families).  67% of the COMB group and 53% of the MED group were still taking risperidone, the original study medication. Most needed dose adjustments or additional medication, and the COMB group no longer had a significantly lower dose.  All COMB families but only 39% of MED families reported wanting parent training after treatment (p<0.0001).  At follow-up, 94% of those originally on COMB treatment were implementing behavior management techniques compared with 53% of those on MED treatment group (p=0.0001). |
| Handen et al., 2013 | Double blind  parallel groups design to compare risperidone alone (MED) versus risperidone plus parent training (COMB).  DSM- IV based clinical evaluation and ADI-R | Risperidone to 1.75 mg/day for subjects weighing  14-20 kg, 2.5 mg/day for subjects weighing >20 and ≤45 kg and 3.5 mg/day for those weighing >45 kg. Participants who failed to respond to risperidone (or who had significant side effects, even if the medication dose was decreased) at week 8 were switched to aripiprazole. | Range (overall): 4-13 years  Male: 40 (81.6%)  Female: 9 (18.4)  Follow up -24 weeks | SOAP, HSQ, and ABC Irritability subscale. | At 24-weeks, there was 28% reduction in child inappropriate behavior during a Demand Condition (p=0.0002) and 12% increase in compliance to parental requests (p=0.004) for the two treatment conditions combined. Parents displayed 64% greater use of positive reinforcement (p=0.001) and fewer repeated requests for compliance (p<0.0001). In the analysis of covariance (ANCOVA), COMB parents used significantly more positive reinforcement (p=0.01) and fewer restrictive statements (p<0.05) than MED parents.  There was no statistically significant correlation between HSQ, ABC-Irritability scores, and SOAP measure changes. |
| Scahill et al., 2012 | 24-week, three-site, randomized controlled clinical trial  DSM- IV based clinical evaluation and ADI-R | Risperidone up to 2.5 mg/day < 45 kg  3.5mg/day>45 kg  Cross titrate to aripiprazole if response to Risperidone unsatisfactory | Intervention Group  COMB – Medication and PT  Range : 4-13 years  Mean : 7.38  SD : 2.21  Average 28 (38.4) .02  Borderline 18 (24.7)  Mild ID 14 (19.2)  Moderate ID 13 (17.8)  PDD diagnosis  Autistic disorder 49 (65.3) .83  PDD-NOS 22 (29.3)  Asperger’s disorder 4 (5.3)  Control Group  Medication  Range: 4-13 years  Mean: 7.5  SD: 2.8  Average IQ, 11 (22.5)  Borderline IQ, 12 (24.5)  Mild ID 9 (18.4)  Moderate ID 17 (34.7)  PDD diagnosis  Autistic disorder 32 (65.3)  PDD-NOS 13 (26.5) 22  Asperger’s disorder 4 (8.2)  Follow up 24 weeks | Vineland Standard and Age equivalent Scores | Both groups showed improvement over the 24-week trial on all Vineland domains.  Compared with MED, Vineland Socialization and Adaptive Composite Standard scores showed greater improvement in the COMB group (p=0.01 and 0.05, and effect sizes=0.35 and 0.22, respectively).  On Age Equivalent scores, Socialization and Communication domains showed greater improvement in COMB versus MED (p=0.03 and 0.05, and effect sizes=0.33 and 0.14, respectively). Using logistic regression, children in the COMB group were twice as likely to make at least 6 months’ gain (equal to the passage of time) in the Vineland Communication Age Equivalent score compared with MED (p=0.02). After controlling for IQ, this difference was no longer significant. |
| Scahill et al., 2016 | Multisite, randomized trial of risperidone only versus risperidone plus parent training  DSM-IV based clinical evaluation and ADI-R | Risperidone up to 2.5 mg/day < 45 kg  3.5mg/day>45 kg  Cross titrate to Aripiprazole if response to risperidone was unsatisfactory | N=124 (both groups)  Range: 4-13 years  Mean: 6.9  SD: 2.35  Across both groups:  IQ  <70: 43 (44.3)  >70: 54 (55.7)  PDD diagnosis  Autistic disorder 64 (66)  PDD-NOS 26 (26.8)  Asperger’s disorder 7 (7.2)  24 weeks | Weight, Waist Circumference, and Body Mass Index | In 97 patients with a mean of 22.9±2.8 weeks risperidone exposure, there was a 5.4 ± 3.4 kg weight gain over 24 weeks (p<0.0001); waist circumference increased from 60.7±10.4 cm to 66.8±11.3 cm (p<0.0001). At baseline, 60.8% (59 of 97) patients were classified as having normal weight; by week 24, only 29.4% (25 of 85) remained in that group.  Growth curve analysis showed a significant change in body mass index (BMI) z-scores from pre-treatment to week 24 (p<0.0001). This effect was significantly greater for patients with reported increased appetite in the first 8 weeks.  From pre-treatment to week 16, there were significant increases in glucose (p=0.02), haemoglobin A1c (p=0.01), insulin (p<0.0001), homeostatic model assessment–insulin resistance (HOMA-IR; p<0.001), alanine aminotransferase (p=0.01), and leptin (p<0.0001). Adiponectin declined (p =0.003). At baseline, seven participants met conventional criteria for metabolic syndrome; by week 16, 12 others also had this classification. |
| **SECONDARY to HELLINGS et al. paper, primary study is not described in the paper** | | | | | |
| Hellings et al 2005 | Prospective larger crossover study of risperidone for aggression and self-injury in children, adolescents, and adults with ID and PDD  DSM -IV criteria were used | Acute phase, mean risperidone dose 0.92 mg/day (range, 0.25–1.36 mg/day) for children and adolescents, and 2.0 mg/day for adults.  Maintenance dose: children and adolescents 1.25 mg/day (range, 0.25–2 mg/day), and for adults 1.36 mg/day (range, 1.0–1.5 mg/day). | Overall (data not specified for each group):  10 children and adolescents:  Range: 8–16 years  Mean: 12.5 years  11 adults:  Range: 24–56 years  Mean: 35.3 years  Overall (data not specified for each group):  Male: 20 (95%)  Female: 1 (5%)  46 weeks | Prolactin level | Children and Adolescents-mean serum prolactin increased significantly from 13.2±8.6 at baseline (n=10) to 31.0 ± 11.6 acutely (n=9, p=0.01) and 37.9 ± 10.4 in maintenance (n=7, p=0.02) after a minimum of 26 weeks (range, 26-38 weeks).  Adults- the increase was more marked; 11.6 ± 7.4 at baseline (n = 11) to 93.3 ± 54.2 acutely (n = 11, p = 0.001), but then decreased to 67.8 ± 62.9 in maintenance (n = 7, p = 0.02) after at least 33 weeks (range, 33–44 weeks)  Adult women had significantly more prolonged elevation and one Caucasian adult woman with the greatest elevation later developed dyskinesia. |
| **SECONDARY to Owen et al. 2009 and Marcus et al. 2009 RCTs on aripiprazole** | | | | | |
| Mankoski et al., 2013 | Two 8-week, double-blind, randomized, placebo-controlled studies of aripiprazole for the treatment of irritability –  Post-hoc analysis of pooled data  DSM- IV based clinical evaluation and ADI-R | Aripiprazole  Two trials: one was flexibly dosed (2-15 mg/day; target dose of 5, 10, or 15 mg/day), and the other had a fixed-dose schedule. | Overall (not specified per group)  Range: 77.2–79.2% were between the ages of 6 and 12 years  Mean: 9.4 to 10.0 years | Treatment emergent adverse events and weight gain | 259 (82%) were antipsychotic naïve (AN), 57 (18%) had previous antipsychotic exposure (PAE).  AN participants more likely to have somnolence (11.9% vs. 2.8%), sedation (22.7% vs. 11.1%), or fatigue (17.0% vs. 13.9%). They also had marginally higher rates of extrapyramidal disorder and drooling. 10.8% of AN on aripiprazole had at least one AE which led to discontinuation, this was 8.3% for PAE group.  AN group had a larger weight change from baseline compared with the placebo group (1.9 vs. 0.7 kg; treatment difference 1.2 kg, 95% CI: 0.5, 1.9) compared to PAE group and placebo group (0.4 vs. –0.4 kg; treatment difference 0.9 kg, 95% CI: -0.6, 2.4).  Younger people with higher baseline weight z scores were more at risk for weight gain.  Metabolic measures were not significantly different in the three groups. |
| Robb et al., 2011 | Two 8-week, randomized, double-blind, multi center, parallel-group trials on aripiprazole-pooled results analyses to study efficacy  ADI-R | Trial one – Aripiprazole was flexibly dosed (2-15mg/day)  Trial 2- Aripiprazole was on a fixed dose schedule 5, 1o, or 15mg/day | Aripiprazole  6-12 years n= 167(78.8%)  13-17years n=45(21.2%)  S.D 9.6(3.1)  Male: 188 (88.7%)  Female: 24 (11.3%)  Control  6-12 years n=79(78.2%)  13-17 years n=22(21.8%)  S.D 9.5(2.9)  Male: 91 (90.1%)  Female: 10 (9.9%) | Treatment-Emergent Adverse Events | Discontinuations due to adverse events with aripiprazole versus placebo were, overall, 10.4% versus 6.9%; participants 6-12 years: 10.8% versus 5.1%; and subjects 13-17 years: 8.9%versus 13.6%.  The frequent AEs in the aripiprazole-treated group compared with placebo were sedation (20.8% vs 4.0%), fatigue (16.5% vs 2.0%), vomiting (13.7% vs 6.9%), increased appetite (12.7% vs 6.9%), somnolence (10.4% vs 4.0%), and tremor (9.9% vs 0.0%).  Most adverse events were mild or moderate and occurred early. Only fatigue showed a dose-response relationship (P<0.05).  Mean body weight change (last observation carried forward, 1.6 vs 0.4 kg) was higher with aripiprazole than placebo (P < .001). There were no between-treatment differences in metabolic changes.  The extrapyramidal symptom-related adverse event incidence with aripiprazole versus placebo was, overall, 20.8% vs 9.9%; the incidence of akathisia-related events was 3.3% vs 8.9%. |
| Varni et al., 2012 | Post hoc analysis data from two 8-week, double-blind, randomized, placebo-controlled studies that compared the efficacy of aripiprazole  DSM- IV based clinical evaluation and ADI-R | Trial one – aripiprazole was flexibly dosed (2-15mg/day)  Trial 2- aripiprazole was on a fixed dose schedule 5, 1o, or 15mg/day | Aripiprazole  Range (overall): 6-17 years  Mean (SD): 9.5 (3.1)  Male: 147 (88.0%)  Female: 20 (12.0%)  Placebo  Range (overall): 6-17 years  Mean (SD): 9.4(3.0)  Male: 68 (89.5%)  Female: 8 (10.5%) | Paediatric Quality of Life Inventory -PedsQL | Aripiprazole was associated with significantly greater improvement than placebo in PedsQL combined-scales total score (difference, 7.8; 95% CI, 3.8 -11.8; p<0.001) and in 3 PedsQL scale scores (differences [95%CI]: Emotional Functioning, 7.8 [3.4-12.2]; Social Functioning, 6.2 [0.7-11.8]; Cognitive Functioning,9.3 [3.8-14.9]; all, P<0.05).  Patients who received aripiprazole were significantly more likely than those who received a placebo to have a clinically meaningful improvement on the combined-scales total score (odds ratio [OR]=1.9; 95% CI, 1.0-3.3; p<0.05), Emotional Functioning scale (OR=2.2; 95% CI, 1.2-4.0; p<0.05) and Social Functioning scale (OR=2.2; 95% CI, 1.2-4.1; P<0.05), and were significantly less likely to experience deterioration (OR: 0.3, 95% CI: 0.1-0.8; p<0.05) when “Stable” was used as the reference group. |
| **SECONDARY TO Shea et al RCT on risperidone** | | | | | |
| Pandina et al., 2007 | Randomised double blind placebo-controlled trial-  Sub group analysis  DSM-IV | Risperidone oral solution increased to a maximum of 0.06 mg/kg/day- adjustment weekly by same investigator | Range (overall): 5-12 years  Mean (SD): 7.4 years (2.4)  Male: 19 (70.4%)  Female: 8 (29.6%)  IQ < 84: 19 (100)  IQ > 84: 0 (0)  Mean IQ (SD): 50.8 (19.8)  Control Group:  Range (overall): 5-12 years  Mean (SD): 7.1 years (2.1)  Male: 24 (85.7%)  Female: 4 (14.3%)  IQ < 84: 18 (75)  IQ > 84: 6 (25)  Mean IQ (SD): 60.1 (26.9) | ABC-I, N-CBRF, VAS-MS, CGI-C | There was a significantly greater reduction in ABC-I subscale score with risperidone compared with placebo at week 2 and at each subsequent evaluation point (p=0.05)  The reduction in ABC-I from baseline to end point was 20.6(8.1) to 7.2(5.9) compared to placebo 21.6 910.2) to 14.1(11.3), ES -0.7 |

ADI, Autism Diagnostic Interview- Revised; DSM -IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; SARS, Simpson Angus Rating Scale; AIMS, Abnormal Involuntary Movement Scale; ABC-I, Aberrant Behavior Checklist-Irritability; COMB, Combined; MED, medication; PT, Parent Training; HSQ, Home Situations Questionnaire; SOAP, Standardized Observation Analogue Procedure; HSQ, Home Situation Questionnaire; PDD, Pervasive Developmental Disorders; CGI, Clinical Global Improvement; AE, Adverse Effect; N-CBRF, Nisonger-Child Behaviour Rating Form; VAS-MS, Visual Analog Scale for the most troublesome symptom; CGI-C, Clinical Global Impression-Change; CGI-S, Clinical Global Inventory-Severity; CSI, Child Symptom Inventory; ES, Effect size; RFS, Ritvo Freeman Scale; c-YBOCS, Children’s Yale Brown Obsessive Compulsive Scale; ID, Intellectual Disability.

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**Supplementary Table**: Narrative synthesis of adverse events data.

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| --- | --- | --- |
| Study | Adverse Events (AE) | Adverse Events (AE) |
| Aman et al., 2009 | MED Group n=49  Weight increase n=40 (81.6%)  Insomnia n=24 (49.0%)  Somnolence n=24 (49.0%)  Epistaxis n=7 (14.3%)  Rhinitis n=39 79.8%  Cough n=39 (79.6%)  Appetite increase n=38 (77.6%)  Fatigue n=33 (67.4%)  Vomiting n=19 (38.8%)  Excess saliva n=16 (32.7%)  Enuresis n=16 (32.7%)  Headache n=18 (36.7%)  Diarrhoea n=17 (34.7%)  Constipation n=18 (36.7%)  Skin rash n=12 (24.5%)  Anxiety n=14 (28.6%)  Dyspepsia n=9 (18.4%)  Polydipsia n=11 (22.5%)  Nausea n=12 24.5%)  Pyrexia n=8 (16.3%)  Dry mouth n=14 (28.6%)  Pharyngitis n=9 (18.4%)  Tachycardia n=7 (14.3%)  Abdominal pain n=6 (12.2%)  Dyskinesia n=7 (14.3%)  Nasal congestion n=7 (14.3%)  Tremor n=4 (8.2%)  Dizziness n=2 (4.1%)  Epistaxis n=7 (14.3%)  Polyuria n=3 (6.1%)  Ear infection n=2 (4.1%) | COMB Group n=75  Weight increase n=53 (70.7%)  Insomnia n= 23 (30.7%) p .04  Somnolence n= 32 (42.7%)  Epistaxis n=3 (4.0%)  Rhinitis n=60 (80%)  Cough n=55 (73.3%)  Appetite increase n=55 (73.3%)  Fatigue n=60 (80%)  Vomiting n= 34 (45.3%)  Excess saliva n=36 (48%)  Enuresis n=32 (42.7%)  Headache n=25 (33.3%)  Diarrhoea n=24 (32%)  Constipation n=21 (28%)  Skin rash n=24 (32%)  Anxiety n=22 (29.3%)  Dyspepsia n=21 (28%)  Polydipsia 17 (22.7%)  Nausea 15 (20%)  Pyrexia n=18 (24%)  Dry mouth n=11 (14.7%)  Pharyngitis n=14 (18.7%)  Tachycardia n=11 (14.7%)  Abdominal pain n=11(14.7%)  Dyskinesia 7(9.3%)  Dyskinesia n=7 (9.3%)  Tremor n=9 (12%)  Dizziness n=9 (12%)  Epistaxis n=3 (4%)  Polyuria n=7 (9.3%)  Ear infection n=6 (8%) |
| De Vane et al., 2019 | Risperidone n=30  With at least 1 AE=23 (77%)  Sedation n= 2 (23%)  Somnolence n=0 (0%)  Difficulty sleeping n=0(0%)  Nausea n=0 (0%)  Constipation n=2 (7%)  Increased appetite n=3(10%)  Enuresis n=0(0%)  Agitation n= 0(0%)  Headache n=1 (3%)  Decreased appetite n=0 (0%)  Vomiting n=0 (0%)  Drooling n=4 (13%)  Dizziness n=0 (0%)  Tachycardia n= 1 (3%)  Muscle rigidity n=0 (0%)  Restlessness n=0 (0%)  Weight gain >7% n=21 (70%)  Dropouts  2 dropouts (weight gain) | Aripiprazole n=31  With at least 1AE=19 (61%)  Sedation n=7 (23%)  Somnolence n=4 (13%)  Difficulty sleeping n=3 (10%)  Nausea n=0 (0%)  Constipation n=1 (3%)  Increased appetite n=0 (0%)  Enuresis n=4 (13%)  Agitation n=2 (6%)  Headache n=1 (3%)  Decreased appetite n=1 (3%)  Vomiting n=1 (3%)  Drooling n=2 (6%)  Dizziness n=1 (3%)  Tachycardia n=0 (0%)  Muscle rigidity n=1 (3%)  Restlessness n=1 (3%)  Weight gain>7% n=8 (26%)  Dropouts  4 dropouts (bedwetting 1, weight gain 1, stomach aches 1, tremors 1) |
| Ghanizadeh et al., 2014 | Risperidone (n=30)  Increased appetite n=12 (40%)  Drooling n=12 (40%)  Day drowsiness n=5 (16.7%)  Decreased appetite n=4 (13.3%)  Fatigue n=4 (13.3%)  Constipation n=2 (6.7%)  Slowness n=4 (13.3%)  Tremor n=2 (6.7%)  Dystonia n=1 (3.3%)  Itches n=0 (0%)  Abdominal pain n=1 (3.3%)  Nervousness n=1 (3.3%)  Dry mouth n=0 (0%)  Tachycardia n=1 (3.3%)  Restlessness n=2 (6.7%)  Dyskinesia n=2 (6.7%)  Dizziness n=3 (10%)  Skin rash n=1 (3.3%)  Walking problem n=1 (3.3%)  Diarrhoea n=0 (0%)  Nausea n=2 (6.7%)  Vomiting n=2 (6.7%)  Insomnia 0 (0%)  Seizures n=1 (3.3%)  Diurnal enuresis 2 (6.7%)  Depression n=1 (3.3%)  Dropouts  Dropout 3 (lack of efficacy 1, declined to return 1, severe agitation and crying after taking medication) | Aripiprazole (n=29)  Increased appetite n=12 (34.5%)  Drooling n=9 (31%)  Day drowsiness n=6 (20.7%)  Decreased appetite n=6 (20.7%)  Fatigue n=4 (13.8%)  Constipation n=4 (13.8%)  Slowness n=4 (13.8%)  Tremor n=3 (10.3%)  Dystonia n=3 (10.3%)  Itches n=3 (10.3%)  Abdominal pain n=3 (10.3%)  Nervousness n=2 (6.9&)  Dry mouth n=2 (6.9%)  Tachycardia n=2 (6.9)  Restlessness n=1 (3.4%)  Dyskinesia n=1 (3.4%  Dizziness n=1 (3.4%)  Skin rash n=1 (3.4%)  Walking problem n=1 (3.4%)  Diarrhoea n=1 (3.4%)  Nausea n=1 (3.4%)  Nausea n=1 (3.4%)  Insomnia n=1 (3.4%)  Seizure n=0(0%)  Diurnal enuresis n=0 (0%)  Depression n=0 (0%)  Dropouts  Dropout 3 (hospitalised due to severity of symptoms 1, exacerbation of epilepsy 1, severe sedation after taking medication 1) |
| Hollander et al., 2006 | Olanzapine n=6  Insomnia (mild) n=1  Sedation (mild) n=4  Nervousness (mild) n=0  Rhinitis (mild) n=1  Decreased appetite (mild) n=1  Constipation (mild) n=3  Glazed eyes (mild) n=1  Thirst (mild) n=0  Increased appetite (mild) n=3  Moderate headache (mild) n=1  Weight gain (mild) n=2  Weight gain (moderate) n=1  Weight gain (severe) n=2  Dropout n=2  Parents non-compliant with follow-up arrangements | Placebo n=5  Insomnia (mild) n=0  Sedation (mild) n=1  Nervousness (mild) n=1  Rhinitis (mild) n=0  Decreased appetite (mild) n=0  Constipation (mild)n=0  Glazed eyes (mild) n=0  Thirst (mild) n=1  Increased appetite (mild) n=2  Moderate headache (mild) n=1  Weight gain (mild) n=0  Weight gain (moderate) n=1  Weight gain (severe) n=0  Dropout n-1  Parental disagreement regarding study participation |
| Ichikawa et al., 2017 | Aripiprazole n=47  Adverse event n=39 (83%)  Somnolence n=24 (51.1%)  Nasopharyngitis n=10 (21.3%)  Decreased appetite n=6 (12.8%)  Nausea n=3 (6.4%)  Vomiting n=3 (6.4%)  Fatigue n=3 (6.4%)  Gastroenteritis n=1 (2.1%)  Bruise n=1 (2.1%)  Dropout n=0 | Placebo n=45  Adverse event n==33 (73.3%)  Somnolence n=4 (8.9%)  Nasopharyngitis n=11 (24.4%)  Decreased appetite n=1 (2.2%)  Nausea n=1 (2.2%)  Fatigue n=0 (0%)  Gastroenteritis n=4 (8.9%)  Bruise n=3 (6.7%)  Dropout n=3 (exacerbations of the disease 1, Other 2) |
| Kent et al., 2013 | Risperidone Low dose n=30  Risperidone High dose n=31 [COMBINE]  Incidence of treatment-emergent adverse events (TEAE) 87% in the high-dose risperidone group  Incident of TEAE 60% in low dose risperidone group [COMBINE & AVERAGE]  The most common events in the combined risperidone groups included: increased appetite (26 %),  sedation (15 %),  somnolence (11 %),  weight increase (11 %).  *(Headache, abdominal discomfort, aggression, insomnia-information not provided)*  Dropout risperidone high dose n=6 (adverse event 1, lost on follow-up 1, withdrawal of consent 3, other 1)  Dropout risperidone low dose n=5 (lost on follow-up 1, withdrawal of consent 1, insufficient response 1, other 2) [COMBINE] | Placebo n=35  Incidence of TEAE 80% in placebo group  Adverse events more common in placebo group than either risperidone groups  Headache 11%  Abdominal discomfort 9%  Aggression 9%  Insomnia 6%  *(Increased appetite, sedation, somnolence, weight increase-information not provided)*  Dropout rate placebo n=8 (withdrawal of consent 1, insufficient response 6, study mediation non-compliance 1) |
| Kouhbanani et al., 2021 | None of the participants showed any adverse effects in the two experimental groups with risperidone use. |  |
| Loebel et al., 2016 | Lurasidone n=100 (low dose 20mg/day n=49; higher dose 60 mg/day n=51) [COMBINE]  Total emergent adverse event (TEAE) incidence n=73 (73%)  Vomiting n=18 (18%)  Somnolence n=12 (12%)  Nasopharyngitis n=8 (8%)  Akathisia n=6 (6%)  Fatigue n=5 (5%)  Weight increase n=5 (5%)  Cough n=5 (5%)  Sedation n=4 (4%)  Constipation n=3 (3%)  Dropout n=10 (Lack of efficacy 2, Adverse events n=4, lost to follow up 2, Withdrew consent 1, Miscellaneous 1)  Adverse events nausea 1, irritability 1, vomiting 1, suicidal ideation 1  Serious TEAE n=5 (arm fracture 3, increased irritability 1, appendicitis 1) | Placebo n=49  Total TEAE = 28 (57%)  Vomiting N=2 (4%)  Somnolence n=2 (4%)  Nasopharyngitis n=0 (0%)  Akathisia n=0 (0%)  Fatigue n=1 (2%)  Weight increase n=1 (2%)  Cough n=2 (4%)  Sedation n=1 (2%)  Constipation n= 1 (2%)  Dropout n=12 (lack of efficacy 1, adverse effects 4, lost on follow up 1, withdrew consent 6)  Adverse events irritability 1, decreased appetite 1, disturbance in attention 1, psychomotor hyperactivity 1, affective lability 1  Serious TEAEs n=0 |
| Luby et al., 2006 | Risperidone n=11  Transient sedation n=5  Increased appetite n=2  Hypersalivation n=2  Constipation n=1  *Hyperactivity information not provided* | Placebo n=12  Transient sedation n=4  Increased appetite n=3  Severe hyperactivity n=1  *Hypersalivation /constipation information not provided* |
| Marcus et al., 2009 | Aripiprazole n=165  TEAE n=136 (82.4%)  Sedation n=39 (23.7%)  Tremor n=17 (10.3%)  Somnolence n=14 (8.5%)  Drooling n=15 (9.1%)  Headache n=13 (7.9%)  Extrapyramidal disorder n=11 (6.7%)  Lethargy n=10 (6.1%)  Hypersomnia n=5 (3%)  Vomiting n=22 (13.3%)  Salivary hypersecretion n=11 (6.7%)  Nausea n=8 (4.8%)  Abdominal pain n=7 (4.2%)  Fatigue n=25 (15.2%)  Pyrexia n=15 (9.1%)  Thirst n=5 (3%)  Cough n=12 (7.3%)  Rhinorrhoea n=8 (4.8%)  Nasal congestion n=6 (3.6%)  Epistaxis n=5 (3%)  Nasopharyngitis n=16 (9.7%)  Gastroenteritis viral n=5 (3%)  Upper respiratory tract infection n=5 (3%)  Increased appetite n=20 (12.1%)  Decreased appetite n=13 7.9%)  Rash n=4 (2.4%)  Weight increased n=7 (4.2%)  Enuresis n=4 (2.4%)  Dropout 26 (adverse event 17, withdrawal of consent 3, lost to follow-up poor compliance 3, other 1, lack of efficacy 0) | Placebo n=51  TEAE n=37 (72.5%)  Sedation n=3 (5.9%)  Tremor n=0 (0%)  Somnolence n=2 (3.9%)  Drooling n=0 (0%)  Headache n=2 (3.9%)  Extrapyramidal disorder n=0 (0%)  Lethargy n=0 (0%)  Hypersomnia n=0 (0%)  Vomiting n=4 (7.8%)  Salivary hypersecretion n=1 (2%)  Nausea n=1 (2%)  Abdominal pain n=1 (2%)  Fatigue n=0 (0%)  Pyrexia n=0 (0%)  Thirst n-1 (2%)  Cough n=2 (3.9%)  Rhinorrhoea n=1 (2%)  Nasal congestion n=1 (2%)  Epistaxis n=0 (0%)  Nasopharyngitis n=2 (3.9%)  Gastroenteritis viral n= 0 (0%)  Upper respiratory tract infection n=0(0%)  Increased appetite n=2 (3.9%)  Decreased appetite n=1 (2%)  Rash n=1 (2%)  Weight increased n=1 (2%)  Enuresis n=1 (2%)  Dropout 14 (adverse event 4, lack of efficacy 3, lost to follow-up 3, withdrawal of consent 2, poor compliance 1, subject no longer meeting criteria 1 |
| Martsenkovsky, 2014 | Risperidone  Weight gain n=2  EPS n=2  Autonomic symptoms n= 6  Sedation n=5  Symptoms due to hyperprolactinemia n= 1 | Divalproex  Weight gain n=3  EPS n=0  Autonomic symptoms n=4 Sedation n=8  Symptoms due to hyperprolactinemia n=0 |
| McCracken et al., 2002 | Risperidone n=49  Increased appetite n=36 (73%) - 24 mild 12 moderate  Nasal congestion n=25 (51%)  Fatigue n=29 (59%),  Enuresis n=15 (31%)  Drowsiness n=24 (49%)  Vomiting n=16 (33%)  Insomnia n=7 (14%)  Anxiety n=12 (24%)  Diarrhoea n=9 (18%)  Constipation n=14 (29%)  Sleep problems n=11 (22%)  Skin irritation n=11 (22%)  Drooling n=13 (27%)  Headache n=9 (18)  Stomach ache n= 5 (10%)  Dry mouth n=9 (18%)  Increased thirst n=6 (12%)  Dizziness n=8 (16%)  Dyskinesia n= 6 (12%)  Nausea n=4 (8%)  Decreased appetite n=3 (6%)  Tremor n=7 (14%)  Tachycardia n=6 (12%)  Upper respiratory tract infection n=5 (10%)  Earache n=2(4%)  Muscle rigidity n=5 (10%)  Sore throat n= 5 (10%)  Restlessness n=3 (6%)  Weight gain 2.7±2.9kg  p < 0.001 compared with placebo  Dropout n=3 (treatment not effective) | Placebo n=51  Increased appetite n=15 (29%)-13 mild 2 moderate)  Nasal congestion n=20 (39%)  Fatigue n=14 (27%) p=0.003  Enuresis n=15 (29%)  Drowsiness n=6 (12%) p=<001  Vomiting n=12 (24%)  Insomnia n=15 (29%)  Anxiety n=10 (20%)  Diarrhoea n=11 (22%)  Constipation n=6 (12%)  Sleep problems n=9 (18%)  Skin irritation n=7 (14%)  Drooling n=3 (6%) p=0.02  Headache n=6 (12%)  Stomach ache n=9 (18%)  Dry mouth n=5 (10%)  Increased thirst n=5 (10%)  Dizziness n=2 (4%) p=0.05  Dyskinesia n=3 (6%)  Nausea n=5 (10%)  Decreased appetite n=5 (10%)  Tremor n=1 (2%)  Tachycardia n=1 (2%)  Upper respiratory tract infection n=2 (4%)  Earache n=4 (8%)  Muscle rigidity n=1 (2%)  Sore throat n=1 (2%)  Restlessness n=3 (6%)  Weight gain 0.8±2  Dropout n=1 Headache and seizure from the failure of VA shunt  17 withdrawn from the study (withdrawal of consent 1, non-adherence 1, loss to follow-up 3, lack of efficacy 12) |
| McDougle et al., 1998 | Risperidone n=15  Sedation n= 9 (60%)  Dry mouth n= 1 (7%)  Agitation n= 1 (7%)  Weight gain n= 2 (13%)  Enuresis n= 2 (13%)  Dyspepsia n= 1 (7%)  Diarrhoea n= 1 (7%)  Abnormal gait n= 1 (7%)  Sialorrhea: 1 (7%)  Constipation: 1 (7%)  Dropout n= 3 (agitation 1, abnormal gait 1, lack of improvement of symptoms 1) | Placebo n=16  Sedation n=0 (0%)  Dry mouth n=0 (0%)  Agitation n=5 (31%)  Weight gain n=0  Enuresis n=0  Dyspepsia n=0  Diarrhoea n=0  Abnormal gait n=0  Sialorrhea n=0  Constipation n=0  Dropout n=4 (agitation) |
| Miral et al., 2008 | Risperidone n=13  Constipation n=3 (23.1%)  Nocturnal enuresis n=3 (23.1%)  Upper Respiratory Tract Infection n=7 (53.8%).  Male breast enlargement n=1 (7.7%) | Haloperidol n=15  Constipation n=3 (20%), Nocturnal enuresis n=3 (20%), Blunted affect n=4 (26.7%) Rigidity n=3 (20%)  Difficulty sleeping n=3 (20%) Increased appetite n=4 (26.7%) Upper respiratory tract infection n=8 (53.3%). |
| Nagaraj et al., 2006 | Risperidone n=19  Increased appetite n=17  Mild sedation n=4  Transient dyskinesia n=3  Transient drooling n=1.  Mean weight gain in the risperidone group - 2.81 kg (SD = 2.04 kg), an increase of 17% | Placebo n=20  Weight gain in the control group was 1.71 kg (SD = 1.3), an increase of 9.3%. not significant  Dropout n=1 (did not report for follow-up) |
| NCT00198107, 2019 | Aripiprazole n=40  Vomiting n=15(37.5%)  Abdominal discomfort n=7(17.5%)  Diarrhoea n=7(17.5%)  Nausea n= 2(5%)  Tiredness n=21(52.5%)  Increased appetite n=16(40%) Decreased appetite n=12 (30%) Hypersalivation n=3 (7.5%)  Fever n=3 (7.5%)  Dry mouth n=2(5%).  Nasal Congestion n=16(40%)  Upper Respiratory problems n=3 (7.5%)  Weight gain n=8(20%)  Weight loss n=4 (10%)  Sleep interrupted n=4 (10%)  Dizziness n=4(10%)  Headache n=3 (7.5%)  Muscle rigidity n=3 (7.5%)  Tremor n=3 (7.5%)  Anxiety n=3 (7.5%)  Change in speech n=3 (7.5%)  Difficulty falling asleep n=3 (7.5%) Increased motor activity n=3 (7.5%)  Repetitive speech n=3 (7.5%)  Irritability n=3 (7.5%)  Restlessness n=3 (7.5%)  Sadness n=3 (7.5%)  Self-Injury n=3 (7.5%)  Stereotypy n=3 (7.5%)  Enuresis n=3 (7.5%)  Cough n=3 (7.5%)  Intermittent nosebleed n=3 (7.5%)  Localised rash n=3 (7.5%) | Placebo n=40  Vomiting n=8 (20%)  Abdominal discomfort n=3 (7.5%)  Diarrhoea n=3 (7.5%)  Nausea n=0 (0%)  Tiredness n=10 (25%)  Increased appetite n=11 (27.5%)  Decreased appetite n=6 (15%)  Hypersalivation n=3 (7.5%)  Fever n=2 (5%)  Dry mouth n=2 (5%)  Nasal congestion n=16 (40%)  Upper respiratory problems n=3 (7.5%)  Weight gain n=5 (12.5%)  Weight loss n=5 (12.5%)  Sleep interrupted n=8 (20%)  Dizziness n=0 (0%)  Headache n=8 (20%)  Muscle rigidity n=0 (0%)  Tremor n=0 (0%)  Anxiety n=0 (0%)  Change in sleep n=7 (17.5%)  Difficulty falling asleep n=6 (15%)  Increased motor activity n=5 (12.5%)  Repetitive speech n=2 (5%)  Irritability n=7 (17.5%)  Restlessness n=2 (5%)  Sadness n=0 (0%)  Self-injury n=1 (2.5%)  Stereotypy n=8 (20%)  Enuresis n=2 (5%)  Cough n=4 (10%)  Intermittent nosebleed n=0 (0%)  Localised rash n=3 (7.5%) |
| NCT01624675, 2015 | Risperidone n=21  TEAEs 14 (66.6%)  Increased appetite n=5(23.8%), Somnolence n=11(52.4%)  Weight gain n=4(19.0%)  Change in mean body weight from baseline 2.5kg in RIS group  Change in Prolactin level  41.423ng/ml in the risperidone group  Dropout 3 (lack of efficacy 1, withdrawal of consent 2) | Placebo n=18  TEAEs 5 (27.8%)  Increased appetite n=0 (0%)  Somnolence n=2 (11.1%)  Weight gain n=0 (0%)  Change in mean body weight from baseline 0.51kg in the placebo group.  Change in prolactin level 6.321ng/ml placebo group.  Dropout 7 due to lack of efficacy |
| NCT 00468130, 2022 | Aripiprazole n=7  Dropout n=2 (adverse event) One participant withdrew after worsening depression after the antidepressant was withdrawn. | Placebo n=6  Dropout n=2 (1 adverse event  1 reason not given) |
| Nikvarz et al., 2017 | Risperidone n=16  Increase in appetite n= 8 (53 %)  Somnolence n= 5 (33.3 %)  Fever n= 4 (26.7 %)  Indifference to self-defence n= 3 (20%) Enuresis n=2 (13.3 %)  Drooling, Nasal Congestion and Fatigue in n=1 each (6.7%)  Dropout n=1 (change of psychiatrist) | Memantine n=18  Somnolence n=2(13.3%)  Apnoea at the beginning of speaking n=2 (13.3%)  Worsening of stuttering n=1 (6.7%)  Decrease in appetite n=1 (6.7%) Nausea n=1 (6.7%)  Aggravation of throwing n=2 (13.3%)  Worsening of impulsive behaviour n=2 (13.3%) worsening in hyperactivity n=1 (6.7%)  Worsening of agitation n=1 (6.7%)  Worsening of pertinacity n=1 (6.7%)  Dropout n=3 (lack of efficacy) |
| Owen et al., 2009 | Aripiprazole n=47  TEAE n= 43 (91.5%)  Fatigue n=10 (21.3%)  Somnolence n=8 (17.0%)  Any EPS n=7 (14.95%)  Vomiting n=7 (14.9%)  Increased appetite n=7 (14.9%)  Sedation n=5 (10.6%)  Drooling n=4 (8.5%)  Tremor n=4 (8.5%)  Diarrhoea n=4 (8.5%)  Pyrexia n=4 (8.5%),  Headache n=3 (6.4%)  Insomnia n=3 (6.4%)  Enuresis n=3 (6.4%)  Nasal Congestion n=3 (6.4%)  Nasopharyngitis n=2 (4.3%)  Aggression n=1 (2.1%)  Urinary tract infection n=1 (2.1%)  Aripiprazole treatment was associated with clinically significant weight gain than placebo.  Dropout n=5 (1 fatigue, 1weight and appetite increase, 1 self-injury, 1 vomiting, 1 hyperactivity and aggression) | Placebo n=50  TEAE n=36 (72%)  Fatigue n=2 (4%)  Somnolence n=2 (4%)  Any EPS n=4 (8%)  Vomiting n=2 (4%)  Increased appetite n=5 (10%)  Sedation n=1 (2%)  Drooling n=0 (0%)  Tremor n=0 (0%)  Diarrhoea n=5 (10%)  Pyrexia n=1 (2%)  Headache n=8 (16%)  Insomnia n=4 (8%)  Enuresis n=4 (8%)  Nasal congestion n=1 (2%)  Nasopharyngitis n= 3 (6%)  Aggression n=4 (8%)  Urinary tract infection n=5 (10%)  Dropout n=3 (1 mania, negativism, and psychomotor hyperactivity, 1 case of aggression, 1 case of insomnia) |
| Shea et al., 2004 | Risperidone n=40  All experienced side effects n=40 (100%).  Somnolence n= 29 (72.5%)  Urinary tract infection n= 15(37.5%)  Rhinitis n=27.5%)  Increased appetite n=9 (22.5%)  Abdominal pain n=8 (20%)  Fever n=8 (20.0%)  Insomnia n=6 (15%)  Vomiting n=6 (15%)  Coughing n=6 (15.0%).  Headache n=5 (12.5%)  Apathy n=5 (12.5%)  Constipation n=5 (12.5%)  Tachycardia n=5 (12.5%)  Flu like symptoms n=4 (10%)  Anorexia n=4 (10%)  Fatigue n=4 (10%)  Increased salivation n=4 (10%)  Weight gain n=4 (10%) 2.7kg  Tremor n=4 (10%) | Placebo 39  All experienced side effects n=31 (79.5%)  Somnolence n=3 (7.7%)  Urinary tract infection n=6 (15.4%)  Rhinitis n=4 (10.3%)  Increased appetite n=4 (10.3%)  Abdominal pain n=3 (7.7%)  Fever n=7 (17.9%)  Insomnia n=6 (15.4%)  Vomiting n=6 (15.4%)  Coughing n=4 (10.3%)  Headache n= n=2 (5.1%)  Apathy n=0 (0%)  Constipation n=1 (2.6%)  Tachycardia n=0 (0%)  Flu like symptoms n=2 (5.1%)  Anorexia n=1 (2.6%)  Fatigue n=2 (2.6%)  Increased salivation n=4 (10%)  Weight gain n=1 (2.6%)  Tremor n=0 (0%) |
| Aman et al., 2005  Secondary to RUPP 2002 paper | Risperidone n=49  Figures are percentages  Difficulty falling asleep – Baseline 32.7, Mild 24.5, Mod to Severe 22.4 (p = 0.02) significantly less than placebo  Anxiety- Mild 18.1 Mod/S14.2  (p = 0.05) significantly less than the placebo  Tired during the day- Baseline 14.3, Mild 24.5, Mod/severe 22.4 (p <0.0001),  Excessive appetite - Baseline 12.2, Mild 49.0, Mod/S 32.6 (p < 0.0001)  Difficulty waking - Baseline 14.3 M=mild 34.7 Mod/Severe 12.2 (p = 0.05)  Excessive saliva - Baseline 8.2 Mild 24.5 Mod/Severe 4.0 (p = 0.04) Dizziness/loss of balance – Baseline 0.0 Mild 16.3 Mod/Severe 6.1 (p = 0.04)    Enuresis, dry mouth, nausea/vomiting, constipation, dyspepsia - no significant difference between two groups  Rhinitis, Coughing, Diarrhoea, skin rash, headaches, muscles appearing stuck, tongue movements – no information provided about difference between groups | Placebo n=52  Figures are percentages  Difficulty falling asleep – Baseline 50, Mild 30.8, Mod to severe 34.6  Anxiety – Baseline 32.7, mild 32.7, mod to severe 15.4  Tired during the day – Baseline 23.1, mild 42.3, mod to severe 11.5  Excessive appetite – baseline 11.5, mild 28.8 moderate to severe 9.6  Difficulty waking- Baseline 19.2, mild 19.2, mod to severe 7.7  Excessive saliva – baseline 7.7, mild 9.6, mod/severe 1.9  Dizziness/loss of balance – Baseline 1.9, mild 7.7, mod/severe 0.0 |
| Anderson et al., 2007 | Risperidone n=49  Mean prolactin after 8 weeks treatment increased to 39.0 ± 19.2 ng/ml compared with 10.1 ± 8.8 ng/ml for placebo (p <.0001).  At 6 months the levels were significantly lower than at 8 weeks for the 43 subjects (paired t = 2.7, p = .009).  For 30 subjects, long term follow up at 22+2 months, the levels were significantly higher than baseline (25.3 ± 15.6 versus 10.4 ± 10.1 ng/ml; paired T = 4.5;  p < .0001).  There were no prolactin related side effects noted | Placebo n=52 |
| Hellings et al., 2005 | Prolactin levels for children and adolescents (n=10) rose from 13.2±8.6 to 31±11.6 acutely and 37.9 in maintenance  Prolactin levels for adults (n=11) rose from 11.6±7.4 to 93.3±54.2 acutely and 67.8±62.9 in maintenance  Galactorrhoea, gynecomastia, and amenorrhoea not observed.  One Caucasian adult female with the greatest prolactin elevation later developed tardive dyskinesia. |  |
| Mankoski et al., 2013 | Antipsychotic Naïve n=256  Akathisia 1 (0.6%), Constipation 9 (5.1%)  Cough 9 (5.1%)  Decreased appetite 13 (7.4%)  Diarrhoea 14 (8.0)  Drooling 17 (9.7%)  Dry mouth 1 (0.6)  Extrapyramidal disorder 12 (6.8%)  Fatigue 30 (17.0)  Gastroenteritis, viral 4 (2.3%)  Headache 13 (7.4%)  Increased appetite 23 (13.1%)  Insomnia 6 (3.4%)  Lethargy 10 (5.7%)  Nasal congestion 2 (9.5%)  Nasopharyngitis 13 (7.4%)  Pyrexia 18 (10.2%)  Restlessness 3 (1.7%)  Rhinorrhoea 5 (2.8%)  Salivary hypersecretion 12 (6.8%)  Sedation 40 (22.7%)  Somnolence 21 (11.9%)  Tremor 17 (9.7%)  Vomiting 27 (15.3%) | Prior antipsychotic exposure n=57  Akathisia 2 (5.6%)  Constipation 2 (5.6%)  Cough 4 (11.1%)  Decreased appetite 1 (2.8%)  Diarrhoea 2 (5.6%)  Drooling2 (5.6%)  Dry mouth 2 (5.6%)  Extrapyramidal disorder 1 (2.8%)  Fatigue 5 (13.9%)  Gastroenteritis, viral 2 (5.6%)  Headache 3 (8.3%)  Increased appetite 4 (11.1%)  Insomnia 5 (13.9%)  Lethargy 0  Nasal congestion 2 (5.6%)  Nasopharyngitis 5 (13.9%)  Pyrexia 1 (2.8%)  Restlessness 2 (5.6%)  Rhinorrhoea 3 (8.3%)  Salivary hypersecretion 0  Sedation 4 (11.1%)  Somnolence 1 (2.8%)  Tremor 4 (11.1%)  Vomiting 2 (5.6%) |
| Pandina et al., 2007 | Risperidone n=27  Adverse events in 100% of subjects.  Somnolence 74%  Upper respiratory infection 41% Rhinitis 26%  Fever 26% vs. 18%  Increased saliva 15%  Coughing 15%  Vomiting 11%  Increased appetite 11%  Anorexia 11%  Influenza-like symptoms 11%  Most AEs were mild in severity.  Dropout n=2 (extrapyramidal disorder 1, lack of efficacy 1)  Weight increase in two risperidone and no placebo subjects. Mean change in  weight was greater but not statistically significant, for participants treated with risperidone (P = 0.276).  Movement disorders in risperidone group n=3  EPS n=1  Hyperkinesia n=1 | Placebo n=28  Adverse events in 71% of subjects  Somnolence 7%  Upper respiratory infection 18%  Rhinitis 7%  Fever 18%  Increasing saliva 4%  Coughing 11%  Vomiting 21%  Increased appetite 4%  Anorexia 4%  Influenza-like symptoms 4%  Dropout n=4 (overdose 1, insufficient response 2, withdrawal of consent 1) |
|  |  |  |
| Robb et al., 2011 | Aripiprazole n=213  Sedation 20%  Fatigue 16.5%  Vomiting 13.7%  Increased appetite 12.7%  Somnolence 10.4%  Tremor 9.9%  Weight gain 1.6kg    Dropout rate 10.4 | Placebo n=103  Sedation 4%  Fatigue 2% dose-response relationship p<0.05  Vomiting 6.9%  Increased appetite 6.9%  Somnolence 4%  Tremor 0%  Weight gain 0.4kg p<0.001  Dropout rate 6.9% |
| Vo et al., 2016 | At week 8 three subjects on Risperidone had QTC > 450 milliseconds not observed during screening (range 450- 484 milliseconds).  Change for the group on QTC was not statistically significant. | In the placebo group, the participant with prolonged QTC at screening and 3 additional participants exceeded 450 milliseconds threshold. |