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Randomised controlled trials of antipsychotics for people with autism spectrum disorder: a systematic review and a meta-analysis

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Abstract

Background. Despite unclear evidence to support the long-term use of antipsychotics to treat challenging (problem) behaviours in people with autism in the absence of a psychiatric disorder, this practice is common.

Methods. We conducted a systematic review and meta-analysis of all randomised controlled trials (RCTs) involving antipsychotics for people with autism of all ages, irrespective of the outcomes assessed. We searched seven databases and hand-searched ten relevant journals. Two authors independently screened titles, abstracts and full papers and extracted data using the Cochrane Handbook template. We conducted meta-analyses of outcomes and the rate of adverse events.

Results. We included 39 papers based on 21 primary RCTs that recruited 1482 people with autism. No RCT assessed any psychiatric disorder outcome, such as psychoses or bipolar disorder. A meta-analysis of ten placebo-controlled RCTs showed a significantly improved Aberrant Behaviour Checklist-Irritability score in the antipsychotic group with an effect size of −6.45 [95% confidence interval (CI) −8.13 to −4.77] (low certainty). Pooled Clinical Global Impression data on 11 placebo-controlled RCTs showed an overall effect size of 0.84 (95% CI 0.48 to 1.21) (moderate certainty). There was a significantly higher risk of overall adverse effects ($p = 0.003$) and also weight gain ($p < 0.00001$), sedation ($p < 0.00001$) and increased appetite ($p = 0.001$) in the antipsychotic group.

Conclusions. There is some evidence for risperidone and preliminary evidence for aripiprazole to significantly improve scores on some outcome measures among children with autism but not adults or for any other antipsychotics. There is a definite increased risk of antipsychotic-related different adverse effects.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder (NDD) that starts in early childhood and often continues into adulthood (American Psychiatric Association, 2013). ASD is characterised by (a) persistent deficits in social communication and social interaction across multiple contexts and (b) restricted, repetitive patterns of behaviour, interests, or activities (American Psychiatric Association, 2013). The reported rate varies between 1 in 160 (American Psychiatric Association, 2013) to 44 (Maenner et al., 2021) children. Comorbidities (overall 55–70%) such as other NDDs like intellectual developmental disabilities (IDD) (38%) and attention deficit hyperactivity disorder (25–28%), and psychiatric disorders such as psychosis (4–12%), anxiety (18–20%), and depression (11–19%) and also problem (challenging) behaviours (10–15%) are more common in ASD compared with the general population who do not have ASD (Deb et al., 2022). Similarly, the use of psychotropic medications (41.9–61.5%), particularly antipsychotics (11.7%), psychostimulants (12.5%), and antidepressants (3.8%), is widespread in this population, which seems to have increased over time (57% in 1998 v. 64% in 2002; $p < 0.05$) (Bachmann, Manthey, Kamp-Becker, Glaeske, & Hoffmann, 2013; Coury et al., 2012; Deb, Roy, & Limbu, 2022; Jobski, Höfer, Hoffmann, & Bachmann, 2017). Antipsychotics are commonly used for challenging behaviour in people with ASD (Deb et al., 2022).

Recent meta-analyses showed no definitive evidence of antidepressants, anti-anxiety medication (Deb et al., 2021), and mood stabiliser medications' efficacy (Limbu et al., 2022) on the core (such as restrictive and repetitive behaviour, RRB and impaired communication skills) or

associated symptoms (such as aggression, irritability and agitation) of ASD. The evidence for the efficacy of antipsychotic medications for people with ASD without a psychiatric diagnosis is unclear (Deb et al., 2022; Unwin & Deb, 2011). The quality of evidence varies, and different methodologies were used to gather evidence in different studies. For example, a recent systematic review and meta-analysis of randomised controlled trials (RCTs) of antipsychotics for people with ASD (D'Alò et al., 2021) only included studies on children and combined withdrawal studies with efficacy studies in the same meta-analysis and did not include non-inferiority RCTs. Other studies included RCTs on a small number of new-generation antipsychotics (Fallah et al., 2019; Linden et al., 2023; Zhou et al., 2021) or excluded non-peer-reviewed publications (Fallah et al., 2019). One meta-analysis included RCTs only involving side effects, and no efficacy data were presented (Alfageh et al., 2019). One meta-analysis included youths, some of whom had autism, but no separate data were presented for youths with ASD (Park et al., 2016).

Therefore, we updated the previous meta-analysis by including RCTs of all antipsychotics involving children, adolescents and adults and non-inferiority head-to-head comparison RCTs. We have described how our systematic review and meta-analysis differ from other recent meta-analyses in this field (Alfageh et al., 2019; D'Alò et al., 2021; Fallah et al., 2019; Linden et al., 2023; Park et al., 2016; Zhou et al., 2021) (online Supplementary Appendix 1).

Methods

We followed PROSPERO guidelines (crd.york.ac.uk/prospero) and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) checklist (Moher et al., 2015) for this review and search strategy. The study was registered with the PROSPERO database (registration number: CRD42022343669, 4th July 2022). We searched the following databases for English language publications EMBASE, MEDLINE, Cochrane database, clinicaltrials.gov, PsycINFO, ERIC, and CINAHL from their inception till 30th May 2022. We also hand-searched four relevant journals in the field of ASD (Autism, Journal of Autism and Developmental Disorders, Autism Research, Journal of Autism Spectrum Disorder) and six in psychopharmacology (Psychopharmacology, Neuropsychopharmacology, International Journal of Neuropsychopharmacology, Journal of Clinical Psychopharmacology, Human Psychopharmacology, Journal of Child and Adolescent Psychopharmacology) for relevant articles between 2000 and 30th May 2022. Search terms using descriptors for ASD, antipsychotics, outcomes (ASD core symptoms, associated symptoms such as challenging behaviour and psychiatric disorders such as psychoses, schizophrenia and mania) and RCTs (online Supplementary Appendix 2) were developed after a scoping search and based on our previous systematic reviews on psychotropic medications in ASD (Deb et al., 2021; Limbu et al., 2022). Two authors (MR and JS) independently screened titles, abstracts and full papers using the eligibility criteria (online Supplementary Appendix 2). Bibliographies of identified articles were also searched. Grey literature including conference abstracts and unpublished data available on clinicaltrials.gov site were included. Two authors (AR and MM) independently assessed the quality of papers using the Cochrane Risk of Bias scale (Higgins, Savović, Page, Elbers, & Sterne, 2020) (online Supplementary Appendix 2). Two authors (AR and MM) independently extracted data using a data extraction form based on the Cochrane Handbook template (Lefebvre et al., 2019) (online Supplementary Appendix 2). A third author (SD) arbitrated any disagreement between the authors. Where necessary, the authors of the original articles were contacted for more information.

Eligibility criteria included all RCTs on people with ASD (defined using a standardised method) of all ages involving any antipsychotics, irrespective of the outcome measures (any repeatable measure) used (e.g. psychiatric disorder, challenging behaviour and ASD core symptoms). The control arm included a placebo or another medication or non-pharmacological intervention. RCTs with both matched and unmatched control groups were included. Crossover trials were included only if data were available from Phase I, as it was impossible to exclude any bias caused by the carryover effect on Phase II.

Apart from presenting summary information through a narrative synthesis, where possible, we pooled data for meta-analysis using RevMan 5.4 for Windows software and created forest plots. We did meta-analysis only on the primary RCTs and not on data derived from secondary publications from the main RCTs. We used a random effects odds ratio (OR) for dichotomous or standardised mean difference (SMD) with a 95% confidence interval (CI) for continuous data. We conducted a sensitivity analysis where heterogeneity was high ($I^2 > 50\%$). We assessed each meta-analysis's certainty level as either high or moderate or low or very low based on the five domains using the Grading of Recommendations Assessment, Development and Assessment (GRADE) criteria (Guyatt et al., 2013*a*, 2013*b*). We assessed publication bias using a funnel plot and calculated Egger's test (Egger, Smith, Schneider, & Minder, 1997). We used AMSTAR2 scoring (Shea et al., 2017) to assess the overall quality of our systematic review.

We contacted the relevant authors for missing data but received no response from most. If the data were still missing, we either excluded those data or, using RevMan 5.4 calculator, converted CI or standard error (S.E.) data to standard deviation (S.D.) as per the Cochrane Handbook formulae (Li, Higgins, & Deeks, 2019). We used the mean endpoint score if data on mean change from baseline were unavailable. For consistency, as per the Cochrane Handbook guideline (Li et al., 2019), we converted pooled dichotomous data (OD) to continuous data (MSD), where most studies presented continuous data.

Results

Study characteristics

Our search identified 2340 citations from seven databases, from which 523 duplicates were removed. From the remaining 1817 citations, 1392 were excluded at the title and 355 and 31, respectively, at the abstract and full paper screening stage (see PRISMA flow chart in online Supplementary Appendix 3). We provided reasons for the exclusion in online Supplementary Appendix 1. We included 39 papers based on 21 primary RCTs and 18 secondary papers originating from these 21 primary RCTs. Altogether 1482 people with ASD were recruited in these primary studies, of whom 1262 completed the study (85.2%). Of the 21 primary RCTs, only one study included adults aged 18 or above ($n = 31$) and the rest were on children and adolescents (2–17.5 years). Of 1396 participants (one study of $n = 86$ did not state the gender ratio), 1177 were male (84.3%). Of the 21 primary RCTs, only five were on aripiprazole and one each on olanzapine and lurasidone. The rest were on risperidone ($n = 14$). All RCTs on aripiprazole, olanzapine and lurasidone were placebo-

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controlled. All these studies used a pure placebo (i.e. identical sugar pills not vitamins etc.) (Fent, Rosemann, Fässler, Senn, & Huber, 2011). Of the 14 RCTs involving risperidone, seven were placebo-controlled. Two RCTs compared risperidone with aripiprazole and one each haloperidol, divalproex sodium and memantine. One RCT compared the combination of risperidone with parent training and another behavioural intervention in the form of virtual reality respectively with the risperidone-only group. Nine studies included participants with IDD, and the rest did not specify the IQ of the participants. In one of the nine studies, all children had low to moderate IDD ($n = 45$), but the rest did not present separate data on participants with IDD. The dose of risperidone ranged between 0.125–10 mg/day, but most used 0.25–2.5 mg/day dose. The dose of aripiprazole varied between 5–20 mg/day. The dose of lurasidone was 20–60 mg/day, and olanzapine up to 20 mg/day. We excluded five crossover trials involving haloperidol because no data were available from Phase I.

ASD was diagnosed either clinically or using standardised diagnostic criteria such as the Diagnostic and Statistical Manual (DSM) (American Psychiatric Association, 2013) or International Classification of Diseases (ICD) (World Health Organization, 2019), or standardised diagnostic tools such as Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989). Most studies assessed the effect of antipsychotics on associated behaviours such as irritability, aggression and agitation using measures like the Aberrant Behavior Checklist-Irritability subscale (ABC-I) (Aman, Burrow, & Wolford, 1995) and Clinical Global Intervention-Improvement (CGI-I) scale (National Institute of Mental Health, 1985) etc. A few studies assessed compulsive behaviour using Children-Yale Brown Obsessive Compulsive Scale (C-YBOCS) (Scahill et al., 1997). No RCT assessed the effect of medications on psychiatric disorders such as psychoses or bipolar disorder.

Narrative synthesis

A narrative synthesis of data is presented in online Supplementary Appendix 1. Most RCTs are on risperidone ($n = 14$), followed by aripiprazole ($n = 5$). There is only one large-scale RCT on lurasidone involving 150 children and a very small RCT on olanzapine involving only eight children. There are no published RCTs on other antipsychotics for people with autism apart from the crossover trials on haloperidol that we excluded.

Risperidone

Seven of the 14 RCTs compared risperidone with a placebo, all showing a statistically significant improvement in the risperidone over the placebo group according to the various outcome measures. However, different studies used different outcome measures. Therefore, it is difficult to point out one specific clinical symptom/behaviour that was improved by risperidone. Two RCTs compared risperidone with aripiprazole. Both studies showed post-intervention improvement in the primary outcome measures in both arms, but in one study, risperidone was better than aripiprazole when compared with the placebo, but the other did not show any statistically significant intergroup difference in the outcome. One non-inferiority RCT found a statistically significant better outcome from risperidone than haloperidol. Another non-inferiority RCT found no significant intergroup difference between risperidone and memantine. However, in another small head-to-head comparison, risperidone was found to be significantly better than divalproex sodium. One RCT compared risperidone with a combination of risperidone and parent training, and another a combination with a behavioural intervention using a virtual reality (VR) game. Both studies showed a statistically significant improvement in the combination than the risperidone alone group. Most RCTs were from the USA, and apart from one major RCT, most studies were supported by pharma companies. Two studies were not published in any peer-reviewed journal, but the data were collected from a conference presentation in one case and the Clinical Trial web page in the other.

Aripiprazole

Five RCTs compared the efficacy of aripiprazole with a placebo. Four found significantly better outcomes in the aripiprazole group, but one did not. The two large-scale RCTs were conducted by the pharma company that manufactures aripiprazole. Two of the five RCTs were not published in any peer-reviewed journal, but the data were obtained from the Clinical Trial website.

Lurasidone

Only one RCT has been published on the efficacy of lurasidone. This large-scale ($n = 150$) multi-centre placebo-controlled study showed no statistically significant intergroup difference in the outcome.

Olanzapine

Only one very small ($n = 8$) placebo-controlled RCT on the efficacy of olanzapine showed significantly better improvement in the intervention group.

Adverse effects

Most studies reported significant weight gain, increased appetite, and somnolence in the intervention group. Other adverse effects included raised prolactin levels with and without galactorrhoea, drooling, constipation, and extrapyramidal symptoms (online Supplementary Appendix 1).

Meta-analysis of efficacy

It was possible to pool data on ABC-I on ten placebo-controlled RCTs (five on aripiprazole, four on risperidone, and one on lurasidone) (see Fig. 1). The overall pooled data, including all three antipsychotics, showed a significant ABC-I score improvement in the intervention group (effect size: −6.45; 95% CI −1.83 to −4.77; $p < 0.00001$), with moderate heterogeneity, $I^2 = 58\%$, and low certainty. As for individual antipsychotics, lurasidone did not show any statistically significant intergroup difference (effect size: −1.9, 95% CI −5.92 to 2.12; $p = 0.35$; no heterogeneity, $I^2 = 0\%$). Both aripiprazole (effect size = −5.23, 95% CI −6.22 to −4.25; $p < 0.00001$; no heterogeneity, $I^2 = 0\%$) and risperidone (effect size = −8.25, 95% CI −10.93 to −5.56; $p < 0.00001$; moderate heterogeneity, $I^2 = 52\%$) showed a statistically significant improvement in ABC-I score in the intervention group.

Initially, we pooled CGI data on 11 placebo-controlled RCTs (four on aripiprazole, five on risperidone, and one each on lurasidone and olanzapine) (see Fig. 2). The overall effect size involving all antipsychotics was 0.84 (95% CI 0.48 to 1.21; $p < 0.00001$). As for the individual antipsychotics, aripiprazole

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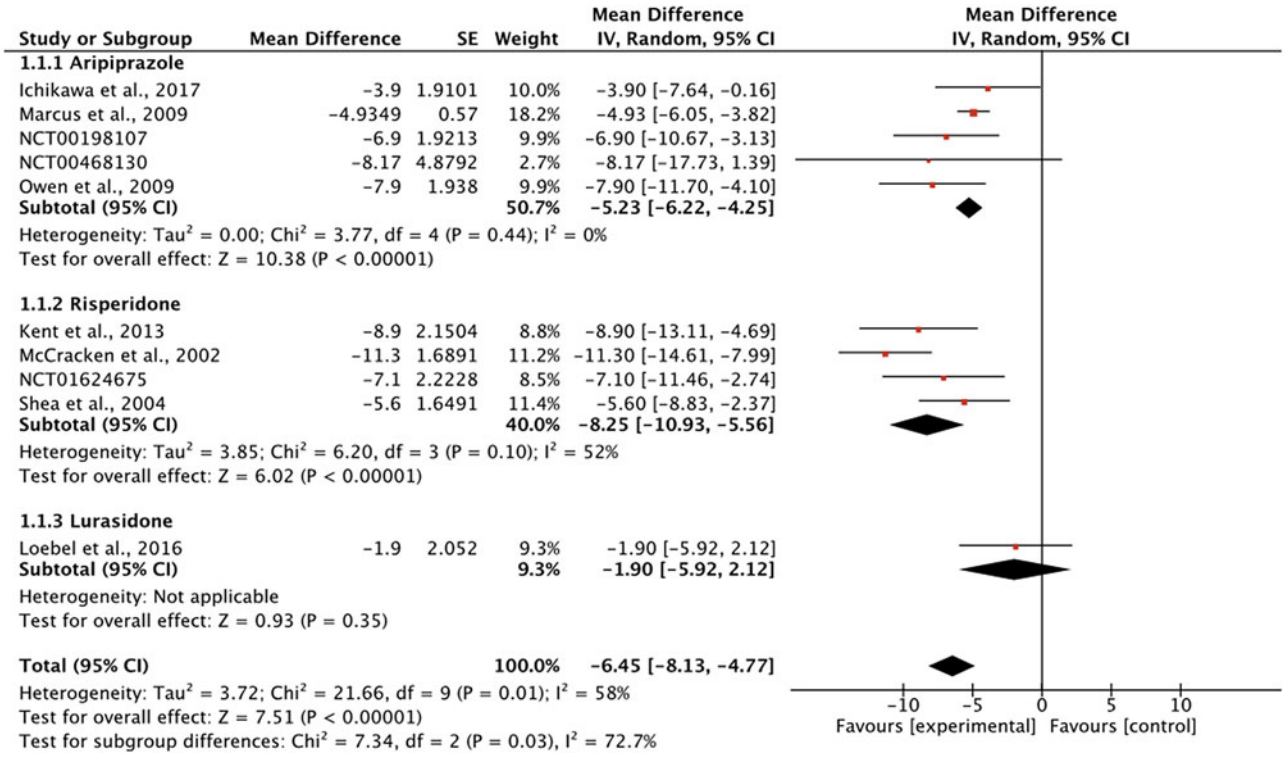

Figure 1. ABC-I forest plot.

showed an effect size of 0.83 (95% CI 0.14 to 1.51), risperidone 1.03 (95% CI 0.58 to 1.49), olanzapine 0.99 (95% CI −1.27 to 3.25), and lurasidone 0.31 (95% CI −0.03 to 0.65). However, the heterogeneity was high ($I^2 = 75\%$), and the certainty level was moderate as we combined the continuous variable, such as SMD, with dichotomous data, such as OR. After a sensitivity analysis and removing the dichotomous data, we pooled data from six RCTs (three on aripiprazole and one each on risperidone, olanzapine and lurasidone). This lowered the heterogeneity ($I^2 = 57\%$). After the sensitivity analysis, the overall effect size involving all antipsychotics was −0.77 (95% CI −1.14 to −0.04; $p < 0.00001$) (online Supplementary Appendix 3). A forest plot of C-YBOCS data is presented in online Supplementary Appendix 3.

Adverse effects

We pooled data on the overall rate of adverse effects for eight RCTs (four for aripiprazole, three for risperidone and one for lurasidone). Overall, the antipsychotic group showed a statistically significant ($p = 0.003$) increased odd (OR 2.25, 95% CI 1.33–3.83) with moderate heterogeneity (I^2: 41%) (moderate certainty) (see Fig. 3). We could pool data on weight gain for 12 RCTs (seven for risperidone, three for aripiprazole and one each for lurasidone and olanzapine). Weight gain was highly significantly worse ($p < 0.00001$) in the overall antipsychotic than the placebo group (OR 3.9; 95% CI 2.84–5.36), showing no heterogeneity (low certainty) (see Fig. 4). We pooled data on the sedation rate from 12 RCTs (six for risperidone, four for aripiprazole, and one each for lurasidone and olanzapine). Sedation was highly significantly worse ($p < 0.00001$) in the overall antipsychotic than the placebo group (OR 6.66; 95% CI 3.94–11.26), showing very low heterogeneity (I^2: 18%) (moderate certainty) (see Fig. 5). We pooled data on the rate of increased appetite for nine RCTs (six for risperidone, two for aripiprazole and one for olanzapine). Increased appetite was significantly worse ($p = 0.001$) in the overall antipsychotic than the placebo group (OR 4.15; 95% CI 1.75–9.87), showing moderate heterogeneity (I^2: 56) and low certainty (online Supplementary Appendix 3). There was no increased risk for the dropout rates due to any cause but an increased risk for dropouts for adverse effects only ($p = 0.003$) (low certainty) (online Supplementary Appendix 3).

Quality assessment

Funnel plot

Funnel plots (online Supplementary Appendix 3) did not reveal any publication bias (Egger's test: $z = 0.0886$, $p = 0.9294$).

Risk of bias

Six of the 21 (29%) included RCTs showed at least one high risk of bias according to the Cochrane risk of bias scores, but most showed uncertain risks in most assessment areas (online Supplementary Appendix 2).

AMSTAR2

AMSTAR 2 rating showed correct response to all areas (online Supplementary Appendix 2). We have presented a PRISMA-P checklist in online Supplementary Appendix 2.

Discussion

In this systematic review, we included 21 primary RCTs and 18 secondary papers ($n = 39$ papers) involving 1482 participants with ASD of all ages compared with D'Alò et al. (2021) recent

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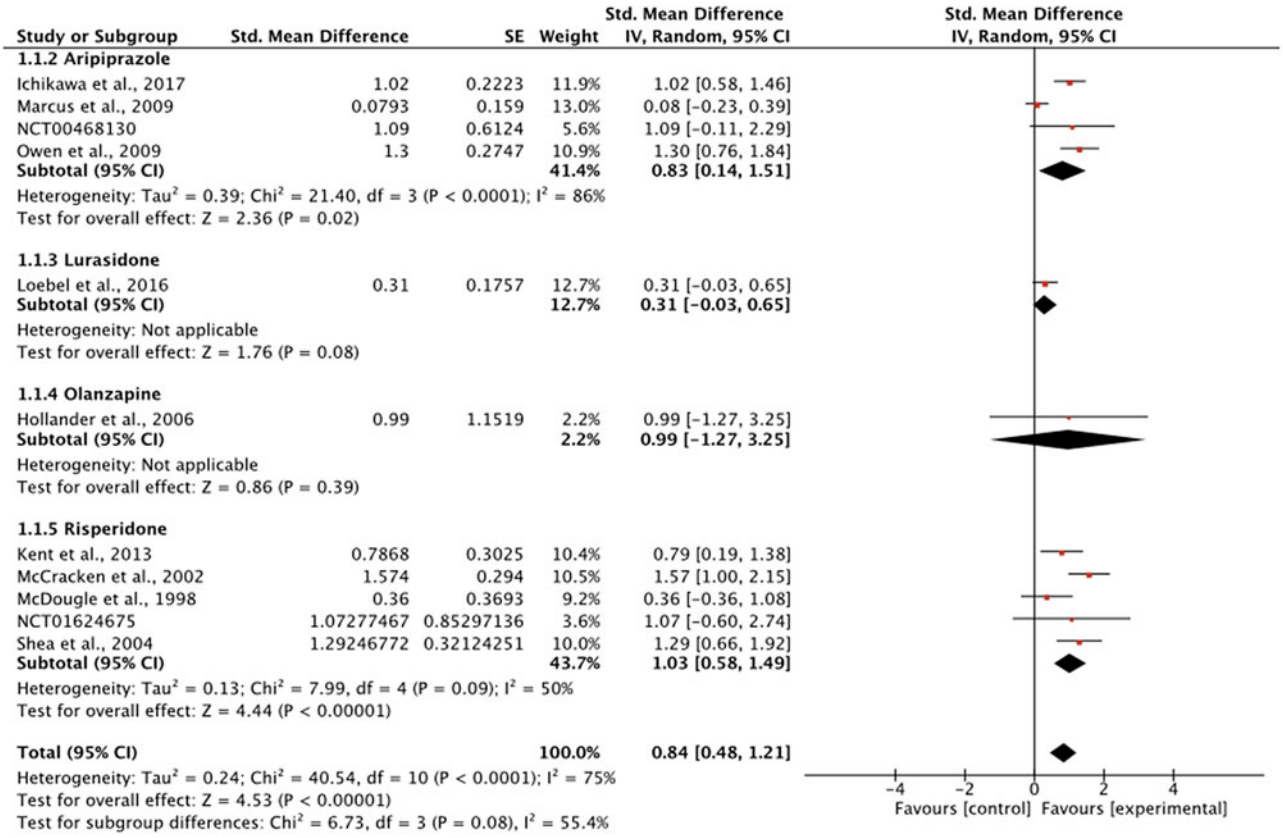

Figure 2. CGI-I forest plot.

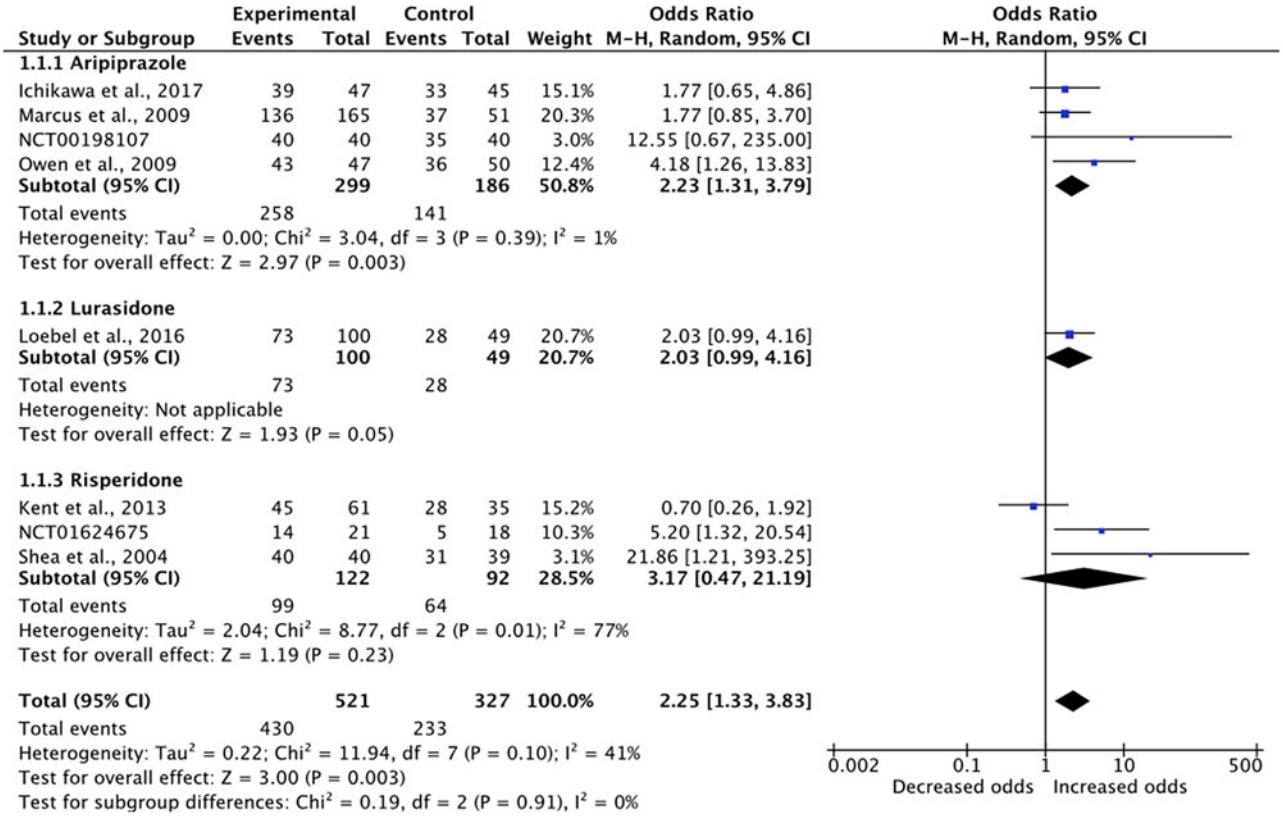

Figure 3. Overall rate of the adverse events forest plot.

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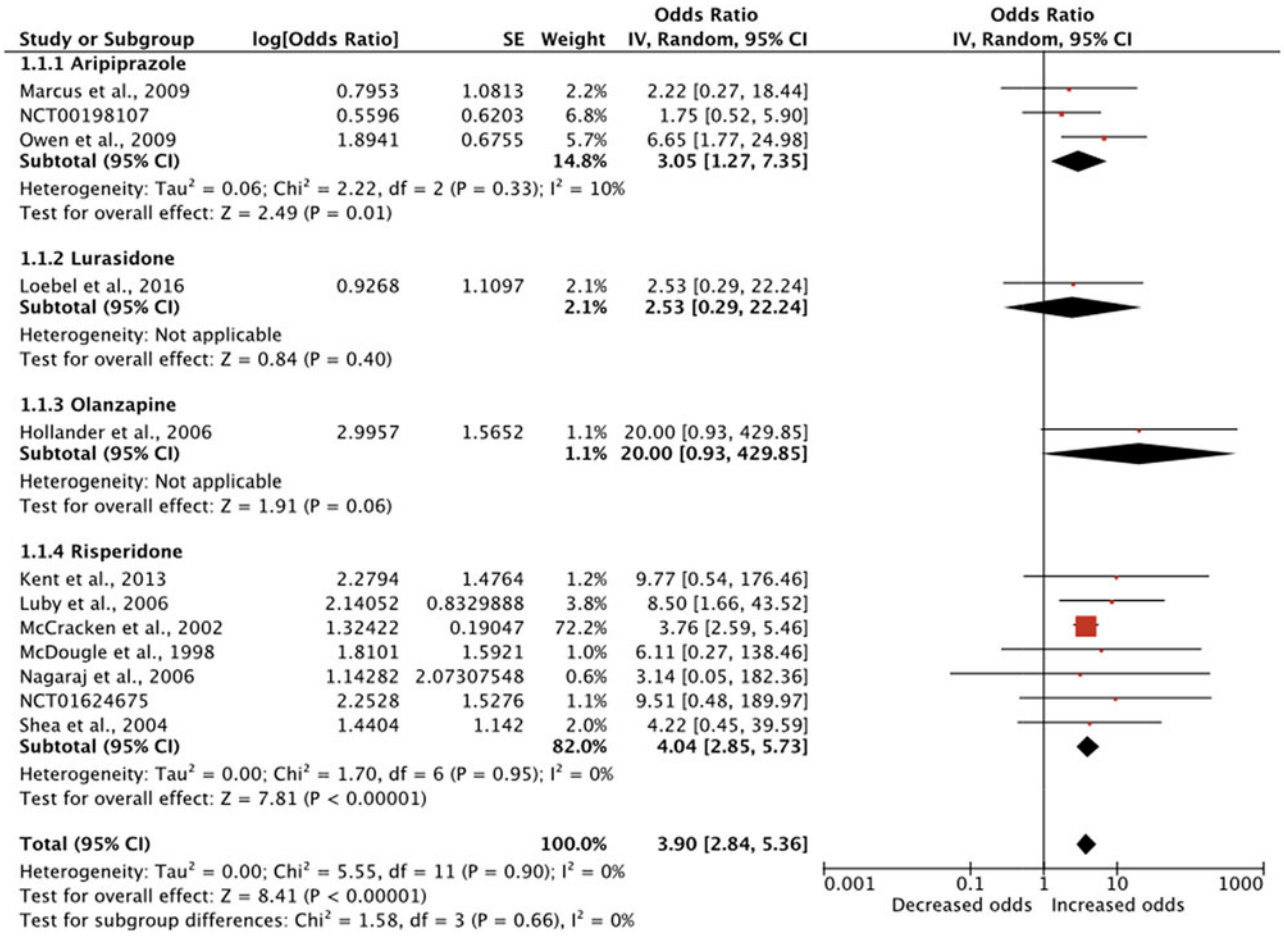

Figure 4. Weight gain adverse effect forest plot.

meta-analysis that included 21 RCTs involving overall 1309 children only. We excluded nine of the 21 RCTs in D'Alò et al. (2021) review for the following reasons. Five were on haloperidol which we excluded as they were all crossover trials. Another RCT on risperidone used a crossover design which we excluded as data were unavailable from Phase I. We excluded three more studies as they were placebo-controlled withdrawal RCTs which may bias analysis if mixed with prospective efficacy studies. Instead, we added one RCT on adults with ASD and five head-to-head comparison RCTs with risperidone not included in the D'Alò et al. (2021) review. Additionally, we included two RCTs that combined risperidone and non-pharmacological interventions and another placebo-controlled study involving aripiprazole, not included in D'Alò et al. (2021) study.

In our review, according to the ABC-I and the CGI-I scores, the antipsychotic group showed a statistically significant improvement compared with the placebo. It is difficult to compare our findings directly with D'Alò et al. (2021) as they conducted meta-analyses based on symptoms and behaviours rather than a specific outcome measure. D'Alò et al. (2021) may have combined scores from different outcome measures for the same meta-analysis, which we did not do. This is problematic because the outcome measures used in the RCTs are not directly equivalent to specific symptoms or behaviours.

For example, the most commonly used outcome measure in these studies, ABC-I, although often presented as a measure of irritability and agitation, combines 15 symptoms and behaviour measures. These items include very different symptoms, such as aggression toward others, property and self, irritability, depressed mood, crying, immediate meeting of demands, temper tantrums, labile mood, agitation, shouting and inappropriate screaming etc. Therefore, it is difficult to know which of these symptoms or a combination of symptoms showed improvement when the total score of ABC-I improved. It is unclear which outcome measure or measures D'Alò et al. (2021) used for data analysis on 'hyperactivity, inattention, oppositeness, disruptive behaviour.' However, their findings in this meta-analysis are similar to our findings of the analysis of ABC-I data. Similarly, D'Alò et al. (2021) did not state which measures were used in their meta-analysis of the 'global functioning, global improvement', but their finding is similar to our findings based on the CGI-I score.

We have not presented the forest plot on the C-YBOCS scale score in the main text for the following reasons. First, it appears that in most studies, this scale was not used to measure obsessive-compulsive symptoms *per se* but was used as a proxy rather than a direct measure of ASD core symptoms, such as restrictive and repetitive behaviour. Second, C-YBOCS data were available on only a few RCTs and none involving risperidone. Also, autistic people do not like to receive intervention to change their core symptoms, such as repetitive behaviour, unless that improves their mental health or quality of life (Linden et al., 2023).

No RCT has presented any measure for a psychiatric disorder such as psychoses or bipolar disorder, or quality of life. Measuring

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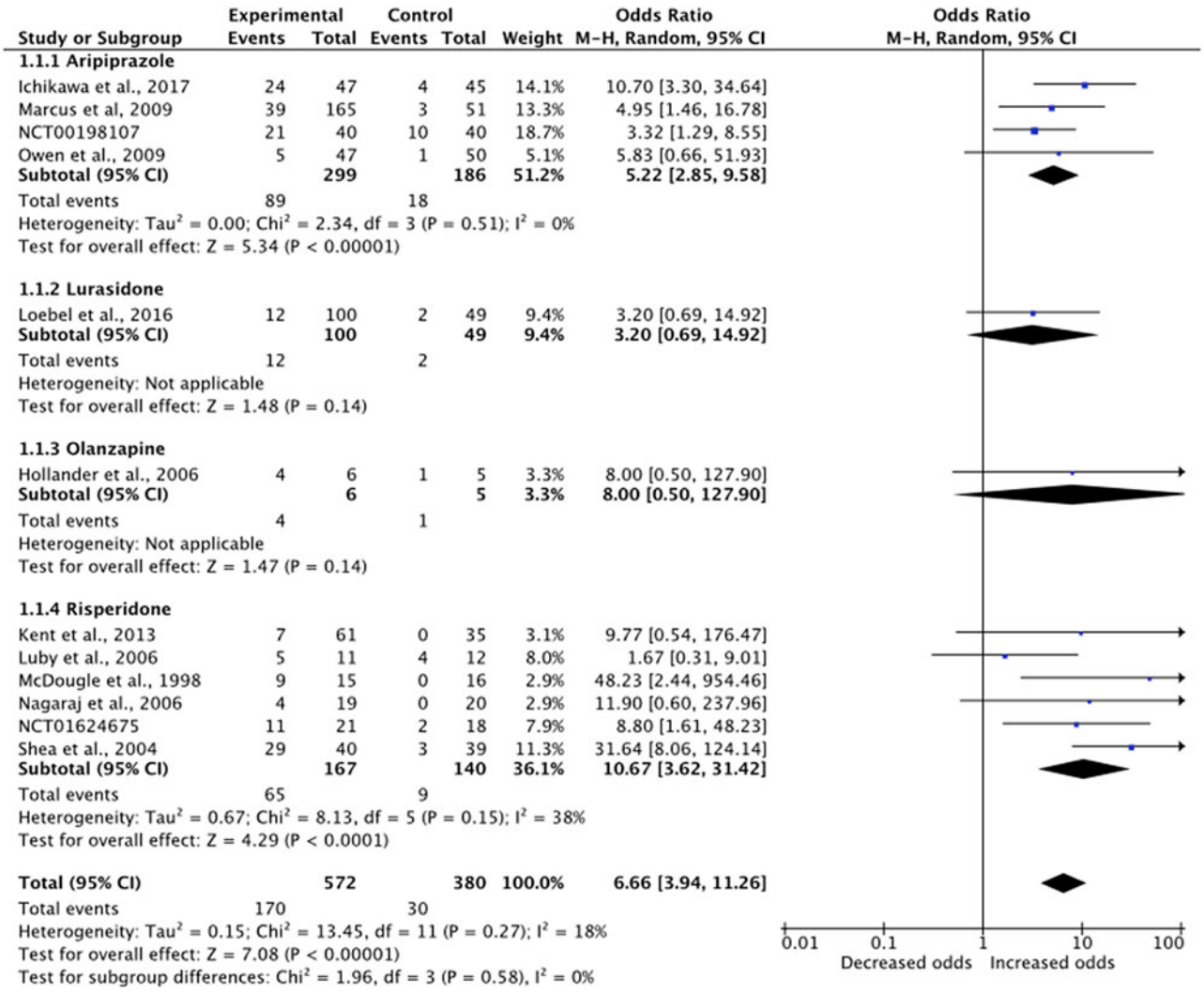

Figure 5. Sedation adverse effect forest plot.

the quality of life of people with ASD or IDD could be problematic as these are mostly patient-rated, and many autistic people may find communicating their feelings and views difficult or express them differently than non-autistic people (Bertelli et al., 2022). This may affect the validity of these measures. Most quality-of-life measures are not health-related (Unwin & Deb, 2014). In that respect, CGI-I may be the closest measure to an overall improvement in functioning as a proxy for the quality of life.

Our findings of the increased risk of the overall rate of adverse events and specific medication-related adverse effects, such as increased appetite, weight gain and sedation, contrast D'Alò et al. (2021) findings but are consistent with findings from another meta-analysis (Fallah et al., 2019). However, not much data were available to analyse the adverse metabolic effects of the new-generation antipsychotics. Aripiprazole does not raise serum prolactin levels to the same extent as risperidone and can even decrease the prolactin level raised by other medications such as risperidone (Deb et al., 2014). Therefore, our findings showed a definite increased risk of adverse events associated with antipsychotics when used for people with ASD of any age in the context of a significant improvement in scores according to two measures.

Although the funnel plots did not show any significant publication bias, it is noteworthy that most RCTs were from the USA and were supported by pharma companies. In the case of aripiprazole RCTs, the pharma company that manufactures the medication conducted two main large studies. In other studies, it is difficult to determine any unconscious cognitive bias caused by pharma company support.

Several cofounders may have produced bias in the outcome of the RCTs. For example, most studies did not present separate data on participants with IDD, a common comorbidity of ASD (Bertelli et al., 2022; Deb et al., 2022). Most RCTs showed a strong placebo effect, and both placebo and medication effects were most pronounced within the first 1–3 weeks of the trial. After that, the effect tended to plateau from 5–7 weeks onward, risking an increase in the dose in real-life practice (McCracken et al., 2002; Owen et al., 2009; Shea et al., 2004). As most studies were add-on trials of antipsychotics, the confounding effect of concomitant medication use is unknown. Similarly, the bias caused by the confounding effect of concomitant non-pharmacological psychosocial and behavioural interventions is unknown. Given that associated behaviours like irritability and agitation are often long-standing, the short follow-up period of around eight weeks

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may not provide enough time to assess the long-term effects of these medications. Although some post-RCT open-label data are available for long-term efficacy and tolerability (Deb et al., 2022), without an RCT design, the long-term effects of placebo could not be assessed. Most studies did not consider the participants' baseline level of challenging behaviour, thus difficult to determine the optimum severity of challenging behaviour for which the medication may be effective. Similarly, a different baseline severity level of challenging behaviour in the intervention and the placebo arm may affect the outcome at follow-up in each arm. Apart from one small study, all other studies are on children thus, the effect of antipsychotics on adults with ASD remains unknown.

Also, it is not easy to configure the optimum dose of medication for treating challenging behaviour on which the outcomes of the included RCTs are primarily based. A low dose may not be effective, whereas a high dose may cause adverse effects. Most studies included a small number of participants risking a Type II error, and a high proportion of studies showed either high or uncertain risk according to the Cochrane risk of bias score. Psychiatric disorders such as psychoses, common in ASD (Bertelli et al., 2015, 2022), may lead to challenging behaviour. Therefore, without assessing the medication's effect on them, which is the case in the included RCTs, it is impossible to ascertain their confounding effect on the outcome of challenging behaviour, which is the common outcome measure used in the included studies.

Apart from risperidone and aripiprazole (and one large study of lurasidone with a negative finding), very little RCT-based evidence is available for other antipsychotics. In the future, RCTs involving antipsychotics should specify specific mental health or behavioural outcomes, include a valid quality-of-life measure, and consider the impact of relevant confounding factors in their design.

Strengths

Our study included the highest number of RCTs involving the highest number of participants among all the published meta-analyses of new-generation antipsychotics among people with ASD of all ages. We followed stringent criteria for the systematic review and meta-analysis, such as PROSPERO and Cochrane guidelines, and also the risk of bias assessment. We conducted funnel plot analysis and Egger's test to assess publication bias. We included papers published in peer-reviewed journals, conference abstracts, and web-based data. The overall quality of our systematic review, assessed by AMSTAR 2 criteria, is very high.

Limitations

We have included only English literature publications. To conduct a meta-analysis, it was only possible to pool data from 71.4–78.6% of 14 placebo-controlled RCTs. The heterogeneity of the meta-analysis was mostly moderate but sometimes high before the sensitivity analysis. According to the GRADE assessment, the certainty levels were low to moderate.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172300212X.

Data. Data availability does not apply to this article as no new data were created or analysed in this study.

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