4015 words excluding the title & references

Safety and Tolerability of Antipsychotic Medication in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis

1. INTRODUCTION

Autism spectrum disorder (ASD) is a persistent neurodevelopmental condition characterised by social communication impairment and stereotyped repetitive pattern of behaviours. The five diagnostic criteria used by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for the diagnosis of ASD, include 1) persistent deficits in social communication and social interaction across multiple contexts; 2) restricted, repetitive patterns of behaviour, interests, or activities; 3) presentation of symptoms in the early developmental period; 4) symptoms cause clinically significant impairment in important areas of current functioning; and 5) these disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Furthermore, Individuals who met the DSM-IV diagnosis criteria of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of ASD [1].

A systematic review conducted of worldwide prevalence studies of ASD from 1990 to 2010 estimated the global burden of ASD to be 52 million cases, equal to 7.6 per 1000 persons in 2010 [2]. Recent figures from the Center for Diseases Control (CDC) in US suggest an even higher prevalence of one in 59 of the population at 8 years of age [3]. The prevalence rate also differs through diverse ethnic groups, the estimated prevalence of ASD among white children was greater than among black children by almost 30% and greater than among Hispanic children by approximately 50% [4]. ASD appears to affect males more than females with an estimated male to female ratio of 4.62 [5]. In 2011, the lifetime cost of supporting an individual with ASD with intellectual disability was estimated to be £1.5 million in the UK and $2.4 million in the US [6].

ASD presents in childhood, although often diagnosis is delayed. Currently there is no treatment to cure ASD. Symptom management is required to improve the quality of life of affected individuals. Both pharmacological and non-pharmacological interventions are available for people with ASD. Non-pharmacological therapy includes educational, behavioural and psychological therapies. Pharmacotherapy is reserved to treat some of the more challenging issues such as irritability, aggression and self-injury [7].

Individuals with ASD may have other comorbid conditions such as attention deficit hyperactivity disorder, depression, epilepsy and schizophrenia. Psychotropic medication such as antipsychotics, antidepressants,

antiepileptic drugs and stimulants have been used for ASD patients with associated comorbidities [8]. There is limited evidence to guide psychotropic medication use in the ASD population; however, a study conducted on the UK population identified that psychotropic drugs were prescribed to 29% of the ASD individuals [9]. International studies have reported that the most prescribed drugs identified were sleep medication, psychostimulants and antipsychotics [10, 11]. Antipsychotics have been prescribed for 7% of people with ASD in the UK [9]. Risperidone is the only antipsychotic that has been approved in the UK for the managements of the behavioural issues in people with ASD. In US, aripiprazole and risperidone were approved by the Food and Drug Administration (FDA) for the treatment of irritability associated with autistic disorder in children [12, 13].

Antipsychotic medication (first-generation and second-generation) is used for the treatment of behavioural problems in individuals with ASD [7]. Several randomised controlled trials (RCTs) have evaluated the efficacy of antipsychotics in improving some of the issues associated with ASD [14-18]. However, evidence of antipsychotic safety in patients with autism is limited.. There is extensive information on the adverse effects of antipsychotic medication used in the treatment of adult mental illness such as psychosis and mood disorders. However, the population of people with ASD treated with antipsychotic medication is very different: treatment typically starts in childhood or adolescence, there is a high proportion of intellectual disability and there is also a high proportion of other comorbidity such as attention deficit hyperactivity disorder, epilepsy and sleep problems. Against this background, it was considered important to examine the evidence for AEs specifically in people with ASD treated with antipsychotic medication.

Adverse events (AEs) associated with antipsychotic use regardless the indication are common and include, but are not limited to, metabolic adverse events such as weight gain, diabetes mellitus and hyperprolactinaemia [19, 20], and movement disorders such as tardive dyskinesia, tremor and dystonia [20, 21]. Potentially serious AEs such as seizures are rare and potentially fatal AEs such as rhabdomyolysis or neuroleptic malignant syndrome (NMS) have been reported [22-24]. The overall aim was to provide a comprehensive review of the published evidence of the adverse events associated with antipsychotic use in patients with ASD in different age groups. The main objective was to conduct a meta-analysis of the RCTs and observational studies focused on children and adolescents to investigate the prevalence of AEs and the relative risk of AEs associated with antipsychotic medication use.

2. METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25] and registered with the International Prospective Register of Systematic Reviews PROSPERO (CRD42018083632) by the Centre for Reviews and Dissemination (CRD).

2.1 Search strategy

The Cochrane Library, Medline, Embase and PsycINFO databases were searched from their inception dates until January 15th 2018 using appropriate MeSH terms and keywords. The literature retrieval was supplemented by manually searching the reference list of all identified articles with regard to the inclusion criteria. See Appendix A (Online Resource 1) for the complete search strategy.

2.2 Inclusion and exclusion criteria

Eligibility criteria were developed based on the Participant-Intervention-Comparison-Outcome-Study Design (PICOS) framework [26].

Studies were included if they were RCTs or observational studies. We only included studies in which the participants were diagnosed with ASD according to the DSM-IV, DSM-5 or the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) with no age restrictions to the participants. The intervention of interest was antipsychotic medication (first or second generation) in any dose or frequency. The intervention could be compared with placebo, other medications or non-pharmacological therapy, or could be without comparison. We included studies which reported adverse events as the primary or secondary outcome. Only full-text papers published in English were included.

Exclusion criteria were: studies published as case reports, narrative reviews, commentaries, editorials, book chapters, grey literature and other summaries. Studies carried out on animals were also excluded.

2.3 Study selection process

Two authors (BA and ZW) independently screened the titles, abstracts and full texts of the retrieved papers. Full-text exclusion was based on our inclusion/exclusion criteria and inconsistent decisions were resolved through consensus.

2.4 Data extraction and management

Studies meeting the eligibility criteria were extracted independently by two investigators (BA and PM) using a pre-designed extraction form. The following information was extracted: research design, location and setting, participants, intervention, outcome measures and quality assessments. Any discrepancies between two reviewers were resolved through discussion. Kappa statistics were calculated to assess the agreements between the two reviewers on the included studies. Kappa values ranged between zero and one, zero reflects complete inter-rater disagreement and one reflects complete inter-rater agreement. The agreement can range between fair agreement, good agreement and excellent agreement if the kappa values were 0.40-0.59, 0.60-0.74 or ≥0.75, respectively [27].

2.5 Assessment of risk of bias in included studies

Two authors (BA and PM) independently evaluated the risk of bias in each study using the Cochrane Collaboration tool for RCTs, which considers the following six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. A judgment of "high," "low," or "unclear" risk of bias was made for each paper. A study was considered to have a high risk of bias if one or more key domains were at high risk. A study was considered to have a low risk of bias if all key domains were at low risk. Otherwise, the study was regarded as having an unclear risk of bias [28].

The modified Newcastle-Ottawa scale (NOS) was used for the methodological quality assessment of the observational studies. It consists of five domains of evaluation: methods for selecting study participants (i.e. selection bias), methods to control for confounding (i.e. performance bias), statistical methods (i.e. detection bias), methods of measuring outcome variables (i.e. information bias) and subject follow-up [29]. Each domain ranges between zero (high risk of bias) and three (low risk of bias). Based on the current authors' judgment, the included observational studies were classified as high, moderate or low risk of bias if the overall scores were 0-1, >1 and <2, or 2-3, respectively.

Any discrepancy in bias assessment was resolved by discussion and group consensus among the authors. Kappa value was calculated to assess the agreement between the two reviewers on the quality assessment of the included papers. (A table of the quality assessment of the included studies is provided in Appendix B (Online Resource 1))

2.6 Data synthesis

Study results were summarised by reporting the adverse events as percentages; a systematic narrative synthesis was provided with information presented in the text, tables and graphs to summarise and explain the characteristics and findings of the included studies.

We performed meta-analyses under the DerSimonian-Laird random-effects model to estimate the RR with 95% confidence intervals (CIs) for the risk of adverse events in RCTs and pooled the prevalence of adverse events across observational studies. Only studies conducted in children and adolescents were included in the meta-analyses (mean age of participants ≤ 18 years). RCTs which provided enough information to calculate the RR i.e. the number of patients who had AEs in both intervention and placebo groups and number of patients who did not have AEs. Observational studies which reported the number of patients who had AEs and the total sample size number were included in the meta-analysis of the estimated pooled prevalence of AEs. To measure the degree of statistical heterogeneity between studies, I^2 was used, which rates the heterogeneity between the studies in percentages from 0 to 100%, where I^2 value <25% indicated low, 25–75% moderate, and >75% high heterogeneity [30]. To explore possible sources of heterogeneity, subgroup analyses were performed by medication. The results are presented using forest plots. All analyses were conducted using STATA, v14.1.

Publication bias was assessed for the observational studies used to pool the estimated prevalence of AEs and for the RCTs used to pool the estimated RR of antipsychotic use by using Funnel plots; Begg's test and Egger's test were used to test the significance.

3. RESULTS

3.1 Search results

We identified 2805 citations in the databases search **(Fig. 1)**; 2620 citations were removed after identification of duplicates or after screening of titles and abstracts. One hundred and eighty-five full-text citations were assessed for eligibility. From those, 54 citations met our inclusion criteria and provided the data for our meta-analysis and narrative review. The kappa value of full text screening was 0.72 (95% CI: 0.54-0.88) which indicates good agreement.

3.2 Included studies

From the 54 included studies **(Table 1 and 2)**, 14 were observational and 40 were RCTs involving 3216 participants in total. Of the 3216 participants, 2034 participated in the RCTs, while 1182 were in the

observational studies. Male gender comprised 70% or more of the participants in most of the included studies. In one study the male participants were two out of a total of six participants [31]. The overall mean age of participants was 9.6 years. The sample size of the included studies ranged between 6 and 330 participants in RCTs and between 6 and 203 participants for observational studies. The shortest duration of follow up was six weeks and the longest duration was approximately five and a half years in two studies; one of these was an open-label study and the other was a prospective cohort study. Detailed descriptions of the included studies are in table 1 and table 2. Most of the participants were medication free for at least one week before the studies started; in some studies, anticonvulsants used for the treatment of a seizure disorder were permitted if the dose had been stable for at least 4 weeks and the patient was seizure free for at least 6 months. Stimulants were permitted in some studies for the management of attention deficit hyperactivity disorder (ADHD) if there was no change in the dose.

From the included RCTs, 18 studies were blinded trials and 22 were open-label trials. Most of the observational studies were composed of a treatment group only with no control group; only one observational study was a retrospective cohort study comparing the effect of risperidone and aripiprazole on body mass index (BMI) change [32]. Fifty-one studies examined the effect of second-generation antipsychotics (mainly risperidone and aripiprazole), while two studies examined the effect of a first-generation antipsychotic (haloperidol) and one study examined the effect of 14 different first-generation and second-generation antipsychotics [33].

3.3 Excluded studies

The majority of excluded studies were carried out on psychiatric patients in general (i.e. the population included multiple mental health diagnoses e.g. ADHD, schizophrenia, mood disorders and psychosis) in addition to those with ASD. Extraction of distinct safety information related to the ASD population in these studies was not feasible. Thirty-six excluded citations were conference abstracts and 13 were for study design irrelevant to our inclusion criteria, for example reviews, case reports and letters to editors. Nine studies did not meet the eligibility criteria because they used the DSM-III criteria for ASD diagnosis.

3.4 Quality assessment

The included RCTs were assessed using the Cochrane Collaboration tool for assessing the risk of bias. Four RCTs were considered as low risk of bias in all six domains [15, 61, 57, 50]. Twenty-two studies were considered as high risk of bias in the study performance domain due to the open label design [68, 67, 62, 16, 60, 59, 58, 55, 54, 53, 52, 48, 47, 45, 43, 42, 40, 39, 38, 37, 35, 34]. According to the selection bias domain, 12 studies were judged as an unclear risk of bias because the random sequence generation and allocation concealment were not clearly described [14, 66, 65, 64, 63, 56, 17, 51, 18, 46, 44, 41]. One included study was judged to have a high risk of bias due to lack of blinding of the outcome assessment [49].

For observational studies, eight studies were judged to have low risk of bias [71, 73-78, 33]. Six studies fell under the moderate risk of bias category [69, 70, 31, 72, 32, 79]. The agreement between the two reviewers on the quality assessment of the included papers was good (kappa value =0.63, 95%CI: -0.025 - 1.000).

The papers included in the meta-analyses were either with low or moderate risk of bias; none of the papers with high risk of bias was included. The details of the quality assessment are shown in Appendix B (Online Resource 1).

3.5 Adverse event occurrence based on body systems classification

A total of 127 AEs were identified in the included studies., Central nervous system (CNS) events were the most frequent AEs identified in the RCTs included, followed by endocrine disorders and gastro-intestinal disorders, respectively **(Fig. 2)**. In the observational studies endocrine disorders were the most frequent AEs identified, followed by CNS events and then gastro-intestinal disorders.

3.6 Adverse events relative risk and prevalence

From the eight RCTs which were included in the meta-analysis to estimate the RR of AEs associated with antipsychotic use, we found that antipsychotic treatment increased the risk of developing AEs by 22% compared to placebo (RR= 1.22, 95% CI: 1.11-1.34, I^2= 30.6%, p= 0.184) **(Fig. 3 (A)).**

Seven observational studies reported the total number of participants who had AEs and were included in the meta-analysis to estimate the pooled prevalence of AEs, which was 50.5% (95% CI: 33-67). However, there was significant heterogeneity in the results of the articles (I^2 = 99.9%) **(Fig. 3 (B))**

3.7 CNS adverse events

A wide range of CNS AEs was reported. Appetite increase was the most frequently reported, followed by sedation, somnolence and headache. Extrapyramidal symptoms, including tremor, akathisia and tardive dyskinesia were also reported frequently. Some AEs were infrequently reported but could potentially be serious. Examples included seizure reported by two patients, intentional self-injury and suicidal ideation each of which were reported once [57, 58, 64, 15]. Moreover, CNS AEs caused many participants to drop out from the study or discontinue the use of antipsychotic medication [80, 41, 17, 53, 56, 71, 57, 60, 16].

3.8 Endocrine adverse events

Weight gain and hyperprolactinemia were prominently reported. The result from the meta-analysis of seven RCTs demonstrated that antipsychotic medication was associated with an increase in the mean weight by 1.4 kg compared to the placebo (I^2 = 9.2%, p = 0.359). Weight increase has been reported as one of the leading causes of study discontinuation for many participants [70, 48, 53, 57, 60, 67]. Hyperglycaemia, hyperleptinemia and increased insulin resistance were prominently reported endocrine disorders. The mean serum prolactin increased by 17.7 ng/ml compared to the placebo (I^2 = 97.9%, p <0.001). The forest plots of the meta-analysis of mean weight change and mean serum prolactin change are shown in **Fig. 4**.

3.9 Cardiovascular system and other adverse events

Cardiovascular AEs were identified less frequently. Change in heart rate and prolonged QT interval were reported in ten participants in RCTs looking for cardiac conduction effects of risperidone in children with ASD [66].

The other main AEs were: vomiting, constipation, upper respiratory tract infection, nasopharyngitis, coughing, enuresis and fatigue.

3.10 Publication bias

The publication bias assessment of the included studies in the meta-analysis of the RR resulted in a symmetric funnel plot. In addition, there was no evidence of publication bias from the Begg's test and Egger's test (P-value =0.54 and 0.47, respectively). Similar findings were identified for the observational studies included in the meta-analysis of the prevalence of AEs. (Appendix C (Online Resource 1))

4. DISCUSSION

4.1 Main findings

This is an extensive systematic review and meta-analysis to evaluate the safety of and tolerability of antipsychotic medication in individuals with ASD. The meta-analysis from eight RCTs demonstrated that the RR of developing AEs was 22% higher with antipsychotic than with placebo. The overall RR was similar to the RR stratified by the drug. The meta-analysis of seven observational studies resulted in an estimated overall AE prevalence of 50%. However, this estimated prevalence might be imprecise because of the high heterogeneity and a small number of included studies. The heterogeneity could be due to different geographic locations of the included studies, drug type and variability of follow-up periods, which ranged from one to 68 months.

The frequently reported AEs identified in this review were: weight gain, enuresis, somnolence, increased appetite and extrapyramidal symptoms. These findings are similar to those that have been identified by a systematic review of antipsychotic use for challenging behaviours in people with learning disabilities [81].

The majority of the articles reported weight gain. Both short-term and long-term studies reported a greater mean weight increase with risperidone than with placebo [49-51, 17, 61]. We noted that long-term therapy was associated with more weight gain compared with short-term therapy. Furthermore, weight gain led to study discontinuation for many participants. Psychiatrists are encouraged to consider weight gain evaluation in individuals on antipsychotic therapy. Although hyperprolactinemia was one of the frequently identified AEs, elevated serum prolactin was not reported in any of the studies on aripiprazole. This finding is consistent with what has been published previously regarding the relationship between hyperprolactinemia and aripiprazole compared to other antipsychotic therapy [82]. There are reports of elevated prolactin with risperidone being decreased by the addition of aripiprazole [83, 84].

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal AE that may occur with antipsychotic treatment. In this systematic review, we were unable to identify any cases of NMS, most probably

because there are no published observational studies or RCTs investigating the association between the use of antipsychotic medication in individuals diagnosed with ASD and the risk of developing NMS and this serious adverse event appears to be rare. The implication is that very large numbers would be required to yield valid frequency data.

4.2 Strengths and limitations

This is the first systematic review to assess the safety of both first-generation and second-generation antipsychotics in individuals with ASD. It provides an evidence-based overview of the prevalence and type of AEs associated with antipsychotic medication use in people with ASD. The publications included in this review were identified through electronic searches from four different databases using a comprehensive search strategy to provide the best chance of identifying all relevant citations. In addition, our review follows the standard methodology of systematic review and meta-analysis which is recommended by the Cochrane and PRISMA checklists [26, 25] .

The potential limitations of our systematic review include the following: i) one of the major limitations in most of the included studies was that the safety of the antipsychotic medication was a secondary outcome and the primary outcome was its efficacy. This reflects on the quality and completeness of safety data. ii) the quality of included studies was questionable. First, most of the observational studies were composed of one group (intervention arm), which did not allow us to draw any comparisons. Second, almost half of the RCTs included were open-label studies, which increases the risk of bias in outcome measurement. Third, the sample sizes were very small in many reviewed studies, and could be unrepresentative: eight studies had a sample size of fewer than 20 participants. However, we decided to include these studies due to lack of well-designed clinical trials investigating the safety of antipsychotics in the ASD population. Fourth, even though the agreement between the two reviewers on the quality of the included paper was good, there was a wide CI, hence this value may not provide enough information to make a decision and should be interpreted with caution. iii) the overall I^2 values were markedly high for the meta-analysis of adverse events prevalence and the mean serum prolactin change, 99% and 97%, respectively. This indicates high heterogeneity between the studies included in the meta-analysis. iv) although no evidence of publication bias was identified by the Begg's test and Egger's test, these tests could be underpowered due to the small number of studies included in the analysis. v) only studies published in English were included in this review, this may lead to language bias. However, Moher et al. found that the exclusion of trials published in non-English language had no significant effect on the meta-analyses results [85].

Furthermore, over the past two decades, the number of RCTs published in a language other than English has been declining which may diminish the extent of language bias introduced [86].

5. CONCLUSIONS

AEs are highly prevalent in individuals who take antipsychotic medication. The relative risk of developing AEs with antipsychotics was 22% higher than the relative risk with placebo. The most frequent AEs were in the CNS. Weight gain and hyperprolactinemia were particularly associated with antipsychotics, although hyperprolactinaemia depends on the antipsychotic. Hyperprolactinaemia is common with risperidone but does not appear to be associated with aripiprazole. Aripiprazole and risperidone are the only antipsychotics that have been licensed for children with ASD. Several studies have been carried out by using other antipsychotics, which indicates the off-license use of antipsychotics in ASD management. Currently, the available evidence on the association between antipsychotic use in individuals with ASD and the risk of developing AEs is limited. The findings of this review highlight the need for well-designed safety and tolerability studies to investigate the association between antipsychotics in individuals with ASD and adverse events.

COMPLIANCE WITH ETHICAL STANDARDS:

Conflict of Interest:

IW has received educational grants from pharmaceutical companies which manufacture antipsychotic medicines on projects unrelated to the current study. IW has also received research grant from the European Commission and Hong Kong Research Grant Council in the evaluation of antipsychotic drugs use in patients.

BA, ZW, PM, FB, TA and RB have no conflict of interest to declare.

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Ethical approval:

This article does not contain any studies with human participants or animals performed by any of the authors.

DATA AVILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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