Evidence Summary: Antipsychotics for behaviours of concern in children, adolescents and adults with autism

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This evidence summary is intended to be used as an education resource and to assist with training and advice on the use of behaviour supports and the reduction and elimination of the use of restrictive practices by NDIS providers.

It has been prepared by the NDIS Quality and Safeguards Commission in the course of undertaking and publishing research to inform the development and evaluation of the use of behaviour supports and to develop strategies to encourage the reduction and elimination of restrictive practices by NDIS providers.

Who is this evidence summary for?

- It is for NDIS behaviour support practitioners and registered NDIS providers who implement behaviour support plans and who work with children, teenagers and adults who have autism and behaviours of concern

What is the purpose of this evidence summary?

- To provide NDIS behaviour support practitioners and registered NDIS providers who implement behaviour support plans with the most up-to-date research evidence on the benefits and harms of antipsychotics when they are used to manage behaviours of concern in children, adolescents and adults with Autism Spectrum Disorder (ASD).
- The behaviours of concern include:
    - irritability;
    - aggression; and
    - behaviours that result in self-injury.

Why are we providing this information?

- Antipsychotics are often prescribed to people with ASD without a mental health diagnosis to reduce behaviours of concern.
- Best evidence for the effectiveness of antipsychotics in reducing behaviours of concern, and any associated adverse effects, comes from high quality systematic reviews of randomised controlled trials.

What did we learn?

We are not able to make any conclusions about the benefits and harms of antipsychotics in adults with ASD as the majority of participants in these trials were under the age of 18.

What we did find across these trials was that:

- In the short-term:
    - Atypical antipsychotics reduced all behaviours of concern by a significant amount (up to 33%)
    - Adverse effects were also markedly (up to 7.5 times) higher in the antipsychotic groups compared to placebo
- We could not make any conclusion about long-term effects as long-term effects were not reported in any of the identified trials.

- The side effects reported in people receiving antipsychotics included:
    - constipation;
    - excessive salivation;
    - increased weight;
    - raised heart rate;
    - sedation;
    - and tremor

How can providers use this information?

Before considering referral to a medical practitioner who can prescribe medications to help manage someone's behaviour of concern, providers should make sure the following is carried out:

    - The person received a comprehensive behaviour assessment that may identify factors that trigger or maintain behaviour of concern such as communication or environmental factors.
    - The person received a comprehensive health assessment by a general practitioner may identify the presence of physical health problems that can cause behaviours of concern.
- Positive Behaviour Support strategies should be trialled to manage behaviours of concern before considering medications to manage behaviour.
- If Positive Behaviour Support strategies are not effective, a qualified medical practitioner should be consulted on the benefits and risks of using medication to manage behaviour.

- If participants are receiving antipsychotics to manage behaviours of concern, providers can support them to ensure they are reviewed regularly by a qualified medical practitioner.

Contents

Disclaimer

This document has been prepared by the National Disability Insurance Scheme Quality and Safeguards Commission for educational and informational purposes only. The information contained in this document relates to use of medication for the primary purpose of influencing a person's behaviour.

This document is only intended to provide a general summary of information in relation to third-party studies conducted in relation to the use of this specific medication. The information is general in nature, is not intended to be a substitute for medical advice and does not take into account individual

circumstances. It makes no recommendation about whether the use of this medication is appropriate for an individual. You should not rely on this information to make decisions and medical advice should be sought from a qualified health professional about individual circumstances

PLAIN LANGUAGE SUMMARY

Background

Behaviours of concern such as irritability, aggression and self-injurious behaviour are common in people with Autism Spectrum Disorder (ASD). Atypical antipsychotics such as aripiprazole and risperidone are second-generation antipsychotics which are frequently prescribed for people with ASD and/or intellectual disability, often in the absence of a mental health diagnosis to manage behaviours of concern.

Typical antipsychotics are first-generation antipsychotics which, compared to atypical antipsychotics, have greater and sometimes irreversible adverse effects. Typical antipsychotics were first used in the 1950s to treat patients with schizophrenia and atypical antipsychotics were introduced in the 1980s because of their reduced risk of adverse effects compared to original antipsychotics and were therefore named 'atypical antipsychotics'.

Concerns have been raised internationally regarding the effectiveness of antipsychotics (Branford et al., 2019; Deb et al., 2015) in reducing behaviours of concern in people with disability, particularly in light of serious and long-term adverse effects such as substantial weight-gain, and increased risk of diabetes and heart disorders (Kaplin & McCracken, 2012; Tsiouris et al., 2013).

There is a need for high quality evidence on the effectiveness and harms associated with the use of antipsychotics to manage behaviours of concern in people with ASD.

Review question

To determine the effectiveness of typical and atypical antipsychotics in reducing the behaviours of concern of irritability, aggression and self-injurious behaviours in people with ASD and the likelihood of adverse effects associated with antipsychotic use.

What was studied in the review?

Eighteen trials were included. Sixteen trials compared an atypical antipsychotic (aripiprazole, lurasidone, or risperidone) to a placebo (1055 participants) and two trials compared a typical antipsychotic (haloperidol) to a placebo (43 participants). The majority of participants were children and adolescents although there were 49 adult participants in two of the atypical antipsychotic versus placebo trials and 14 adults in two of the typical antipsychotic (haloperidol) versus placebo trials. All trials of effectiveness comparing atypical or typical antipsychotics to a placebo were six months or less in duration.

What was done?

A systematic review of all Randomised Controlled Trials (RCTs) involving children, adolescents or adults with ASD that compared one atypical or typical antipsychotic to a placebo. Two researchers independently screened papers to determine if the studies met the inclusion criteria, recorded study details, extracted outcome data and rated the quality of papers (risk of bias). Any disagreement between reviewers was resolved through discussion or by referral to a third reviewer in order to reach consensus.

What are the main results of the review?

All trials of effectiveness comparing an atypical or typical antipsychotic to a placebo were short-term i.e. 3 months or less in duration.

Atypical antipsychotics reduced all behaviours of concern by a significant amount (up to 33%). However, a number of side effects were markedly higher in participants receiving atypical antipsychotics in the short-term. These included sedation, tremor, increased weight, increased appetite and constipation.

Only the behaviour of concern of self-injurious behaviour was reported in the typical versus placebo trials and there was no evidence of an effect. Similarly, the two trials of typical antipsychotics versus placebo showed no apparent differences in reported musculoskeletal, neurological or psychological adverse effects.

How reliable are the results of analyses in this review?

The finding that atypical antipsychotic use resulted in significant reductions in behaviours of concern is consistent with previous reviews on the use of atypical antipsychotics for people with autism and behaviours of concern. Other factors that are likely to have influenced the quality of the evidence include the small sample sizes; potential biases in trial design such as awareness of group allocation, funding by pharmaceutical companies; and between-trial differences (heterogeneity).

However, we are not able to make any conclusions about the benefits and harms of antipsychotic use in adults with ASD as the clear majority of participants in these trials were under the age of 18

What are the implications of this review?

This systematic review has shown moderate level evidence that short-term use of atypical antipsychotics significantly reduce the behaviours of concern of irritability, and low level evidence that aggression, and self-injury. However, atypical antipsychotics were also associated with a range of adverse effects in the short-term including sedation, tremor and heart disorders. Therefore, any benefit that antipsychotics may have in reducing behaviours of concern should be considered with the significant increase in adverse effects.

Also, because the majority of participants in these trials were under the age of 18, we are not able to make any conclusions about the benefits and harms of antipsychotics in adults with ASD.

Background

Autism spectrum disorder (ASD) is characterised by persistent deficits in social communication and social interaction across multiple contexts, as well as restricted repetitive patterns of behaviour, interests, or activities (American Psychiatric Association, 2013). ASD is usually diagnosed during childhood and persists throughout the life of a person (Australian Psychological Society, 2020; DSM-5, 2013). ASDs affect roughly one percent of the total population across most countries (Arora, 2018; Australian Institute of Health and Welfare, 2017; Cleaton & Kirby, 2018; Elsabbagh et al., 2012; Ritchie, 2020) while the prevalence in Western countries is reported as up to three percent (Australian Institute of Health and Welfare, 2020; Cleaton & Kirby, 2018; Mencap, 2019).

Behaviours of concern are more prevalent in people with ASD or ASD and comorbid intellectual disability compared to typically developing peers (Deb et al., 2007; Kaplin & McCracken, 2012; National Institute for Health and Care Excellence, 2015; Rzepecka et al., 2011) with estimates of between 5 and 15% (National Institute for Health and Care Excellence, 2015; Oliphant et al., 2020). The behaviours which are most commonly considered concerning are irritability, aggression, and self-injury (Lecavalier, 2006). The likelihood and severity of behaviours of concern is also increased by the severity of ASD (Emerson et al., 2000; Matson et al., 2008).

Antipsychotics are primarily prescribed for psychiatric disorders such as bipolar disorder or schizophrenia (Burness et al., 2021; Marston et al., 2014). Antipsychotics are also commonly prescribed for the management of behaviours of concern in people with autism (Deb et al., 2015; Hsia et al., 2014; Murray et al., 2013) and often in the absence of a diagnosed mental disorder (Cvejic et al., 2018; Deb 2009; Deb et al., 2015; Sheehan et al., 2015). Large-scale studies have shown that around 30% of people with ASD are prescribed antipsychotics (Coury et al., 2012; Lake et al., 2017; Howes et al., 2018; Murray et al., 2013). Although atypical antipsychotics are not recommended for the treatment of core symptoms of autism (Howes et al., 2018) there is limited evidence that they can decrease behaviours of concern in people with ASD (Howes et al., 2018; Jesner et al., 2007). In addition to the limited evidence base for the effectiveness of antipsychotics, there is concern regarding the health outcomes of long-term use such as significant weight-gain (Alvarez-Jimenez et al., 2008; Bak

et al., 2014; Lake et al., 2017) increased risk of diabetes mellitus (Holt, 2019), and increased rates of cardiovascular risk such as stroke and heart attack (Zivkovic et al., 2019).

Atypical antipsychotics are second-generation antipsychotics and as such, are considered to be more effective and with fewer adverse effects compared to typical antipsychotics (Kumar et al., 2013). Antipsychotics were first introduced in the 1940s to treat patients with schizophrenia (Grunder et al., 2009) with the second-generation atypicals introduced later as a better alternative with fewer and less severe adverse effects (Slim et al., 2016). The atypical antipsychotics, aripiprazole and risperidone are the only drugs approved by the Food and Drug Administration (FDA) for the treatment of irritability in children with ASD 5-17 years and five years and older respectively in the US (LeClerc & Easley, 2015) and in Australia, risperidone is the only subsidised pharmacological interventions for behaviours of concern associated with autism (Rasmussan et al., 2018).

Typical and atypical antipsychotics can all block dopamine receptors in the brain (Douglas-Hall et al., 2011; Hirsch & Pringsheim, 2016; Jesner et al., 2007; Philpott et al., 2014). Increased or excessive levels of dopamine are believed to play a role in behaviours of concern such as aggression and irritability (Loy et al., 2017). Therefore, antipsychotics may reduce behaviours of concern through dopamine blockade (Nagaraj et al., 2006).

Objectives

To determine the effectiveness of typical and atypical antipsychotic medications in decreasing the behaviours of concern of irritability, aggression and self-injury in people with ASD, as well as determining the most common adverse effects and the extent to which antipsychotics increase the risk of these adverse effects.

Methods

This systematic review of the benefits and harms associated with the use of antipsychotics was part of a larger Cochrane systematic review investigating the benefits and harms of all pharmacological agents for the management of behaviours of concern in people with autism. As such, we used rigorous Cochrane methods to ensure that we identified all

relevant trials and there were no biases in trial identification such as limiting language or type of publication.

The findings of this evidence summary are from the analysis and synthesis of data from all trials comparing antipsychotics to placebo in the management of behaviours of concern in people with ASD.

Inclusion criteria

All randomised controlled trials (RCTs) of antipsychotics versus placebo for people with ASD of any age were considered for inclusion in the review. All included trials were required to report any one of the outcomes: irritability; aggression; self-injurious behaviour; quality of life; or adverse effects. Measures of behaviour had to use a validated scale such as the Aberrant Behaviour Checklist (ABC).

Data collection

Two reviewers independently assessed each trial for inclusion and extracted data using standardised forms. Trial details, including inclusion and exclusion criteria, setting, interventions, and outcome data; were recorded and agreed by two reviewers. Any disagreements were resolved by discussion or referral to a third author. Where insufficient details were provided in trial publications or registries, the contact author was emailed requesting further information. Two attempts were made to contact authors and if no reply was received this was noted.

When determining quality of evidence, the overall risk of bias of each trial was assessed independently by two of the three reviewers and agreed by consensus or referral to a third author. Biases that were evaluated included selection and allocation bias, and measurement and performance biases including lack of blinding, selective reporting, and attrition bias.

Data analysis

Continuous data were meta-analysed using Standardised Mean Difference (SMD) and the 95% confidence interval (95% CI) to account for the use of different measures for a given outcome such as aggression. Results between experimental and control groups are

considered different for continuous measures when the 95% CI does not include 0. Negative values indicate the measure is lower in the experimental group while positive values indicate higher values in the experimental group.

Dichotomous data were meta-analysed using Relative Risk (RR) and the 95% CI. For dichotomous data a 95% confidence interval that does not include 1 indicates a difference between experimental and control groups. A RR less than 1 indicates a decreased risk in the experimental group, while an RR more than 1 indicates an increased risk in the experimental group.

Heterogeneity was also calculated to identify the whether there were high levels of variation that could be attributed to differences between trials, rather than by chance (Deeks et al., 2020).

Results

Characteristics of included trials

The analyses of atypical antipsychotics versus placebo included 15 trials, 19 datasets and 1048 participants. Two trials included 19 adults aged 19-56 years and 31 adults 21-25 years respectively. The other 998 participants were aged 5-17 years. The atypical antipsychotics used were aripiprazole, lurasidone, olanzapine, and risperidone. All trials reporting behaviours of concern were short-term (less than 3 months) although one trial that reported adverse effects associated with risperidone was six months in duration.

The two included trials comparing typical antipsychotics to placebo had 42 participants overall, 11 of whom were adults. Both trials involved haloperidol and were short-term in duration (less than three months).

Behaviours of concern

Irritability

Atypical antipsychotic versus placebo

Eleven trials involving 1029 participants provided data for the outcome of irritability. Four trials compared aripiprazole to placebo (479 participants), and seven trials compared risperidone to placebo (402 participants). Ten of these trials used the ABC-Irritability subscale to measure irritability and one trial used the Ritvo-Freeman Real Life Rating Scale to measure irritability.

There was a significant decrease when those receiving aripiprazole were compared to those receiving placebo (SMD -0.99, 95% CI -1.65 to -0.33); and when those receiving risperidone were compared to a placebo group (SMD of -1.01 95% CI -1.37 to -0.66). This corresponded to a mean ABC-I decrease of 32% in aripiprazole groups, and a 35% mean ABC-I decrease in risperidone groups compared to placebo. There was no difference in the one trial that compared lurasidone to placebo.

Typical antipsychotic versus placebo

No included trials reported irritability.

Aggression

Atypical antipsychotic versus placebo

Two trials involving 113 participants reported the outcome of aggression. Both trials used the Nisonger Child Behaviour Rating Scale (conduct problem) to measure aggression. There was a significant decrease when those receiving risperidone were compared to a placebo group (SMD of -0.52, 95% CI -0.90 to -0.14). This corresponded to a mean Nisonger Child Behaviour Rating Scale (conduct problem) decrease of 33% in risperidone groups compared to placebo. The aripiprazole and lurasidone trials did not report aggression.

Typical antipsychotic versus placebo

No included trials reported irritability.

Self-injurious behaviour

Atypical antipsychotic versus placebo

One trial comparing risperidone to placebo in 30 participants provided data for the outcome of self-injurious behaviour. The trial used the Self-Injurious Behaviour Questionnaire to

measure aggression. There was a significant decrease in self-injurious behaviour in the risperidone group (SMD of -18.70, 95% CI -27.58 to -9.82). This corresponds to mean Nisonger Child Behaviour Rating Scale (self-injurious) decrease of 26% in risperidone groups compared to placebo. The aripiprazole and lurasidone trials did not report self-injurious behaviour.

Typical antipsychotic versus placebo

There was no difference between typical antipsychotics and placebo (one trial, 17 participants, MD -86.80, 95% CI -225.64 to 52.04).

Improvement and relapse

Atypical antipsychotic versus placebo

Amongst those taking risperidone or aripiprazole there was a 2-fold greater chance of improvement (according to pre-defined irritability scores measured using the ABC-Irritability) in participants given risperidone or aripiprazole compared to those receiving placebo (four trials, 470 participants, RR 2.08, 95% CI 1.39 to 3.12).

Also amongst participants who had improved, those who remained on risperidone were around 70% less likely to relapse compared to those who were then given placebo (two trials, 56 participants, RR 0.30, 95% CI 0.13 to 0.68). Both trials defined relapse as a minimum increase of 25% in ABC-Irritability scores during a discontinuation phase. The aripiprazole trials did not report relapse.

Typical antipsychotic versus placebo

No included trials reported improvement or relapse.

Quality of life

Atypical antipsychotic versus placebo

Two trials provided data for quality of life. Both trials (188 participants) compared aripiprazole to placebo and used the Pediatric Quality of Life (PedsQL) Inventory as a

measure. Among those receiving aripiprazole, there was a significant improvement in quality of life scores compared to those who were given placebo (Mean Difference 7.64, 95% CI 1.02 to 14.26).

Typical antipsychotic versus placebo

No included trials reported quality of life.

Adverse effects

The types of adverse effects reported include cardiovascular, gastrointestinal, immune, metabolic, musculoskeletal, neurological, psychological, respiratory, skin, and urinary effects.

Atypical antipsychotic versus placebo

Cardiovascular adverse effects

Tachycardia (fast heart rate)

Atypical antipsychotics (risperidone) were associated with a greater than 7.5-fold increase in tachycardia (two trials, 179 participants, RR 7.53; 95% CI 1.40 to 40.52).

Gastrointestinal adverse effects

Vomiting/ Nausea

Atypical antipsychotics were associated with approximately 80% increase in vomiting/nausea (nine trials, 920 participants, RR 1.79; 95% CI 1.16 to 2.74).

Constipation

Atypical antipsychotics were associated with a greater than 2-fold increase in constipation (seven trials, 596 participants, RR 2.36; 95% CI 1.28 to 4.34).

Drooling

Atypical antipsychotics were associated with a greater than 9-fold increase in drooling (two trials, 313 participants, RR 9.64; 95% CI 1.29 to 72.10).

Hypersalivation

Atypical antipsychotics were associated with a greater than 4-fold increase in hypersalivation (five trials, 449 participants, RR 4.15; 95% CI 1.77 to 9.71).

Metabolic adverse effects

Weight gain

Atypical antipsychotics were associated with a greater than 2-fold increase in risk of weight gain (five trials, 496 participants, RR 2.10; 95% CI 1.15 to 3.84).

Increased appetite

Atypical antipsychotics were associated with more than twice as many participants having an increased appetite (eight trials, 702 participants, RR 2.38; 95% CI 1.69 to 3.34).

Neurological adverse effects

Sedation

Atypical antipsychotics were associated with a greater than 4-fold increased risk of sedation (six trials, 442 participants, RR 4.14; 95% CI 1.47 to 11.63).

Fatigue

Atypical antipsychotics were associated with a greater than 2.5-fold increase in fatigue (eight trials, 881 participants, RR 2.58; 95% CI 1.68 to 3.97).

Tremor

Atypical antipsychotics were associated with an almost 6-fold increased risk of tremor (five trials, 574 participants, RR 5.99; 95% CI 1.87 to 19.19).

Somnolence

Atypical antipsychotics were associated with an almost 5-fold increased risk of somnolence (nine trials, 869 participants, RR 4.84; 95% CI 3.18 to 7.36).

Respiratory adverse effects

Upper respiratory tract infection

Atypical antipsychotics were associated with a 2-fold increased risk of upper respiratory tract infection (six trials, 640 participants, RR 2.15; 95% CI 1.08 to 4.27).

Other adverse effects

There were no differences between atypical antipsychotics and placebo groups in the rates of reported immune, musculoskeletal, psychological, skin, or urinary adverse effects.

Typical antipsychotic versus placebo

There were also no differences between typical antipsychotics and placebo in the rates of reported musculoskeletal (dystonia), neurological (fatigue), or psychological (behaviour problems) adverse effects.

Risk of Bias

This systematic review has shown moderate level evidence that short-term use of atypical antipsychotics significantly reduces irritability, and low and very low level evidence respectively that aggression, and self-injury are reduced. However, atypical antipsychotics were also associated with a range of adverse effects in the short-term including sedation, tremor and heart disorders. Therefore, any benefit that antipsychotics may have in reducing behaviours of concern should be considered with the significant increase in adverse effects.

Discussion

There is very low to moderate level evidence that antipsychotics decrease behaviours of concern in people with autism by up to 35% in the short-term. However, it is unclear whether these apparent improvements are influenced by the marked increases in sedation and somnolence which may reduce behaviours of concern.

Adverse effects included sedation, tremor, increased weight, increased appetite and constipation. These adverse effects are also observed in participants prescribed atypical

antipsychotics for psychiatric disorders such as bipolar or schizophrenia (Jensen et al., 2007; Yumru et al., 2006) and as such, appear to be common adverse effects associated with atypical antipsychotics.

Because all identified trials were short-term, it is unclear if these adverse effects and improvements would be observed beyond three months. As such, it is important for trials to assess the long-term effectiveness and adverse effects of antipsychotics when used for behaviours of concern for people with autism. Long-term trials are particularly relevant in light of serious metabolic disorders such as diabetes mellitus and significant weight gain associated with long-term antipsychotic use.

As most trials involved children and adolescents we were unable to establish estimates of the effectiveness and related adverse effects of antipsychotic use in adults with autism.

Implications for Research

Length of follow-up emerged as a major issue in the examined trials, with only one trial following up participants for more than three months. This highlights the need for a larger analysis of the long-term effectiveness and adverse effects associated with typical and atypical antipsychotics. In particular, population-based studies are needed to identify the long-term health effects of the use of drugs such as risperidone in people with ASD.

Implications for Practice

Based on data from all identified trials that compared antipsychotics to placebo, the atypical antipsychotics, risperidone and aripiprazole, appear to reduce behaviours of concern by around 30%; however there was also considerable evidence that significant adverse events were associated with their use in the short-term.

A person with autism who is demonstrating behaviours of concern, should receive a comprehensive health assessment by a general practitioner as this may identify the presence of physical health or mental health problems that can cause behaviours of concern (National Institute for Health and Care Excellence, 2015).

Before considering medications to manage a person's behaviour of concern, a comprehensive assessment to gain a functional understanding of their behaviours can be

undertaken and non-pharmacological interventions such as Positive Behaviour Support trialled (National Institute for Health and Care Excellence, 2015).

If Positive Behaviour Support strategies are not effective, a qualified medical practitioner can be consulted so that the risks and benefits associated with medications such as antipsychotics can be discussed with the person and other support persons such a family members.

If participants are receiving antipsychotics to manage behaviours of concern, providers can support them to ensure they are regularly reviewed by a qualified medical practitioner.

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