



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

July 2022

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 antidepressants 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?

- Antidepressants are often prescribed to people with ASD without a mental health diagnosis to reduce behaviours of concern.
- Best evidence for the effectiveness of antidepressants 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 antidepressant medications 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:
 - Antidepressants did not appear to reduce behaviours of concern when compared to placebo
 - There were minimal adverse effects associated with antidepressants with only four adverse effects higher in the antidepressant groups compared to placebo
- The side effects reported in people receiving antidepressant drugs included:
 - decreased attention;
 - decreased energy;
 - impulsive/ intrusive behaviour;
 - and increased stereotypes
- We could not make any conclusion about long-term effects as long-term effects were not reported in any of the identified trials.

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 receives a comprehensive health assessment by a general practitioner as this 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 can be consulted on the benefits and risks of using medication to manage behaviour.

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

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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

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PLAIN LANGUAGE SUMMARY

Background

Behaviours of concern such as irritability, aggression and self-injurious behaviour are common in people with Autism Spectrum Disorder (ASD). Antidepressants are usually prescribed to treat symptoms associated with anxiety, depression and obsessive compulsive disorder. Antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRIs) and tricyclic antidepressants are sometimes prescribed for people with ASD with psychiatric comorbidities such as anxiety or depression, which may in turn reduce behaviours of concern. However, to date there has not been adequate evidence regarding the effectiveness of antidepressants for people with ASD and as such, there is a need for high quality evidence on the effectiveness and harms associated with the use of antidepressants to manage behaviours of concern in people with ASD.

Review question

To determine the effectiveness of antidepressants 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 antidepressant use for behaviours of concern.

What was studied in the review?

All trials compared the effectiveness of antidepressants to placebo in reducing behaviours of concern or reported adverse effects. Eleven trials involving 698 participants comparing antidepressants (SSRIs, tricyclic or μ -Opioid agonist) to placebo were included in the analysis. Three of the trials included children only (<12 years of age), four of the trials included children and adolescents, two trials included children, adolescents and adults, and two trials included adults only. All trials of effectiveness were short-term i.e. 3 months or less in duration.

What was done?

A systematic review of all Randomised Controlled Trials (RCTs) involving children, adolescents or adults with ASD and behaviours of concern that compared an antidepressant

to a placebo. Two reviewers independently screened papers to determine if the trials met the inclusion criteria, recorded trial 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.

What are the main results of the review?

Antidepressants had little to no effect on irritability or self-injury in the short-term (Irritability: three trials, 267 participants, mean difference -0.55, 95% CI -2.77 to 1.66; self-injury: one trial, 106 participants, mean difference -1.46, 95% CI -2.94 to 0.02). The behaviour of concern of aggression was not reported.

A number of side effects were markedly higher in participants receiving antidepressants. These included decreased attention, decreased energy, increased stereotypies and impulsive/ intrusive behaviour. No other adverse effects were associated with antidepressants.

How reliable are the results of analyses in this review?

The finding that antidepressant use did not result in a significant reduction of behaviours of concern is consistent with previous reviews on the use of SSRIs and tricyclic antidepressants for people with ASD. However, because of the low to very low quality of evidence due to the small number of identified trials that compared antidepressants to placebo and potential biases in identified trials means that confidence in these estimates is limited.

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

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What are the implications of this review?

This systematic review and meta-analysis has shown that there is currently no evidence that antidepressants reduce the behaviours of concern of irritability, aggression, and self-injury. Antidepressants were also associated with increased rates of behavioural and neurological side effects in the short-term.

Because all trials reporting effectiveness were short-term there was no evidence of the benefits and harms of using antidepressants for periods of more than 3 months.

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 antidepressant use in adults with ASD.

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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 et al., 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 dual diagnoses of ASD and intellectual disability compared to typically developing peers (Ali et al., 2015; 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).

The primary use of antidepressant drugs is to treat clinical depression in adults.

Antidepressant drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs) and tricyclic antidepressants are also commonly prescribed psychotropic agents for people with ASD (Coury et al., 2012; Howes et al., 2018; Murray et al., 2013) and often in the absence of a diagnosed mental disorder (Cvejic et al., 2018; Sheehan et al., 2015; Tsiouris et al., 2013). Large-scale studies involving people with ASD have found that antidepressants are prescribed at similar rates to antipsychotics and stimulants and often concurrently (up to 40%) with antipsychotics (Branford et al., 2019; Cvejic et al., 2018; Esbensen et al., 2009). In addition, the use of antidepressants among people with ASD in large-scale studies is approximately 8 times higher than people without ASD (Madden et al., 2017).

The high rates of antidepressant prescription and use are likely to be related to the high prevalence of mental health conditions among people with ASD compared to the general population (Lever & Guerts, 2016). Depression and anxiety being the two most commonly

diagnosed mental health conditions (Cvejic et al., 2018; Lever & Guerts, 2016) with over 20% of adults with ASD reported to have a current diagnosis of depression (Van Steensel et al., 2011). However, the effectiveness of antidepressants as an intervention to reduce behaviours of concern has raised concerns and doubts internationally (Branford et al., 2019; Williams et al., 2013).

The majority of antidepressants prescribed to people with ASD are SSRIs (Aman et al., 2005) due to the relatively few adverse effects and increased effectiveness compared to older tricyclic antidepressants (Scates & Doraiswamy, 1998). The SSRI reuptake mechanism inhibits excess serotonin reuptake in the brain (Williams et al., 2013) and inhibits serotonin transporters thereby increasing serotonin transmission and availability at the synaptic level (Kohler et al., 2016). Increased levels of serotonin transporters have been observed in people with ASD (Lewis & Lazoritz, 2005; Marler et al., 2015) and serotonin has a mediating role in several psychological processes such as aggression, irritability, mood and aggression (Williams et al., 2013). As such, pharmacological interventions that inhibit serotonin transporters may have an effect on behaviours of concern associated with ASD although there is very limited evidence suggesting such an effect (Fusar-Poli et al., 2019; Lewis & Lazoritz, 2005; Williams et al., 2013).

Objectives

To determine the effectiveness of antidepressants in decreasing the behaviours of concern of irritability, aggression and self-injurious behaviour, in people with ASD as well as determining the most common adverse effects and the extent to which antidepressants increases the risk of these adverse effects.

Methods

This systematic review of the benefits and harms associated with the use of antidepressants 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 synthesis and analysis of data from all trials comparing antidepressants to placebo in the management of behaviours of concern in people with ASD.

Inclusion criteria

All randomised controlled trials (RCTs) of antidepressants 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 reviewer. 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 reviewer. 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

Eleven trials were included in the analyses with 698 participants. Only 80 participants in these trials were adults with the remaining 618 participants aged between 3 and 17 years. All trials reporting behaviours of concern were short-term (i.e. 3 months or less).

Behaviours of concern

Irritability

Three trials involving 267 participants provided data for the outcome of irritability. All trials involved children and adolescents used the ABC subscale to measure irritability. There was no apparent difference between antidepressant and placebo groups (Mean difference -0.55, 95% CI -2.77 to 1.66).

Aggression

No included trials reported the outcome of aggression.

Self-injurious behaviour

One trial involving 106 participants provided data for the outcome of self-injurious behaviour. This was measured with the Repetitive Behaviour Scale subscale to measure self-injurious behaviour. There was no apparent difference between antidepressant and placebo groups (MD -1.46, 95% CI -2.94 to 0.02).

Quality of life

No included trials reported quality of life.

Adverse effects

The types of adverse effects reported include gastrointestinal, metabolic, neurological, and psychological effects.

Gastrointestinal adverse effects

There were no differences between the antidepressant and placebo groups in the rates of reported gastrointestinal adverse effects.

Metabolic adverse effects

Decreased energy

Antidepressants were associated with an almost twice as many participants with decreased energy (1 trial, 149 participants, RR 1.94, 95% CI 1.13 to 3.33).

Neurological adverse effects

Decreased attention

The number of participants with decreased attention in the antidepressant group was more than 4-fold higher compared to the placebo group (2 trials, 207 participants, RR 4.16, 95% CI 1.07 to 16.11).

Psychological adverse effects

Impulsive/ intrusive behaviour

Antidepressants were associated with an almost 3-fold increase in impulsive or intrusive behaviour (1 trial, 149 participants, RR 2.92, 95% CI 1.11 to 7.68).

Increased stereotypies

Antidepressants were associated with more than an 8-fold increase in stereotypies (1 trial, 149 participants, RR 8.33, 95% CI 1.07 to 64.95).

Other adverse effects

There were no differences between the antidepressant and placebo groups in the rates of reported cardiovascular, immune, musculoskeletal, respiratory, skin, or urinary adverse effects.

Risk of Bias

Due to the relatively small number of trials and limited sample size in meta-analyses as well as potential biases in included trials, we rated the evidence as low quality. Potential biases likely to have influenced the quality of the evidence include potential awareness of group allocation, reporting bias and external funding.

Discussion

There was no apparent evidence that antidepressants decrease behaviours of concern in people with ASD. These findings are consistent with other reviews (Hurwitz et al., 2012; Williams et al., 2013) that antidepressants have very little to no evidence of an effect on behaviours of concern in people with ASD.

There were also relatively few adverse effects associated with antidepressants however, the small number of included trials and small sample sizes in analyses limits the quality of this evidence. In addition, because all trials were three months or less in duration, it is unclear if

adverse effects would be more likely to be observed with antidepressant use over longer periods.

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

Implications for Research

Because of the low quality of evidence due to the small number of identified trials that compared antidepressants to placebo, more high quality trials are required. As all included trials only followed up participants for three months or less, future trials should focus on the longer-term follow-up of behaviours of concern and adverse effects in response to antidepressant use.

Implications for practice

Based on data from all identified trials, antidepressants do not appear to reduce behaviours of concern. In addition, there were very few adverse effects associated with antidepressants.

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 antidepressants can be discussed with the person and other support persons such as family members.

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

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