



Evidence Summary: Anticonvulsants for behaviours of concern in children, adolescents and adults 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 plans with the most up-to-date research evidence on the benefits and harms of anticonvulsant medications 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?

- Anticonvulsant medications are often prescribed to people with ASD to reduce behaviours of concern.

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- Best evidence for the effectiveness of anticonvulsant medications 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 anticonvulsant medication use 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:
 - Anticonvulsant medications did not reduce behaviours of concern when compared to placebo.
 - Adverse effects associated with anticonvulsants were minimal with only one adverse effect showing a higher (up to 5.5 times) risk in the anticonvulsant drug groups compared to placebo.
 - All other adverse effects did not show a difference between anticonvulsant groups and 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 anticonvulsant drugs included:
 - Decreased appetite (up to 5.5 fold increased risk)

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.
- If participants are receiving anticonvulsant 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). Anticonvulsants (also known as antiepileptic drugs or mood stabilisers) are prescribed for people with epilepsy to reduce seizures, although anticonvulsants are also prescribed for a range of other neurological and psychiatric conditions including bipolar disorder, schizophrenia, migraines, and neuropathic pain. Anticonvulsants have also been proposed for the pharmacological management of behaviours of concern for children, adolescents and adults who have an ASD. There is a need for high quality evidence on the effectiveness and harms associated with the use of anticonvulsants to manage behaviours of concern in people with ASD.

Review question

To determine the effectiveness of anticonvulsants 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 anticonvulsant use.

What was studied in the review?

All trials that compared the effectiveness of anticonvulsants to a placebo in reducing behaviours of concern or reported adverse effects. Six trials involving 165 participants comparing anticonvulsants to a placebo were included in the analysis. The anticonvulsants that were compared were divalproex sodium, lamotrigine, levetiracetam, topiramate, and valproate. All trials of effectiveness were short-term i.e. 4 months or less in duration and all participants apart from one adult were children or adolescents (<18 years).

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 anticonvulsant medications to a placebo. Two researchers 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?

Anticonvulsants had little to no effect on the outcome of irritability (3 trials, 97 participants) or aggression in the short-term (2 trials, 57 participants). The outcome of self-injurious behaviour was not reported.

In the short-term, anticonvulsants were associated with a significant decrease in appetite (2 trials, 60 participants). There was no apparent effect on the other adverse effects of cardiovascular, gastrointestinal, neurological, immune, psychological, skin or urinary.

How reliable are the results of analyses in this review?

The review did not find any evidence that anticonvulsant use can reduce behaviours of concern, but findings are limited by the relatively small number of identified trials with total participant numbers of less than 180.

However, we are not able to make any conclusions about the benefits and harms of anticonvulsant medication 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 there is currently no evidence that anticonvulsants can reduce the severity of the behaviours of concern of irritability, aggression and self-injury in people with ASD in the short-term. Anticonvulsants were also associated with decreased appetite.

Because all trials reporting effectiveness were short-term, there is currently no evidence of the benefits and harms of using anticonvulsants for periods of more than 4 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 anticonvulsant medication use 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 (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) although 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 (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).

Seizures associated with epilepsy are caused by abnormal and asynchronous firing of neurons (nerve cells) which usually end abruptly (DeLorenzo et al., 2005; Geiger et al., 2011; Kusmakar et al., 2018; Proix et al., 2018). Anticonvulsants are the pharmacological interventions used to reduce seizures (Włodarczyk et al., 2012; Wassenaar et al., 2013). Most anticonvulsants such as carbamazepine, phenobarbital and valproate block voltage-gated sodium channels (Verrotti et al., 2009) to reduce the firing of neurons. Some anticonvulsants such as Leviteracetam, topiramate or valproate also have a role in the release or modulation of the inhibitory neurotransmitter GABA (Cortes-Altamirano et al., 2016) thereby decreasing the speed and firing of neurons.

Epilepsy is more prevalent among people with ASD compared to the general population, with large-scale studies indicating between a 4-fold and 8-fold increased prevalence of epilepsy among people with ASD compared to the general population (Chen et al., 2009; Schendel et al., 2016; Thomas et al., 2016; Vohra et al., 2017). However, anticonvulsants are

sometimes used for behaviours of concern in people with ASD due to the mood stabilization role of anticonvulsants (Bertelli et al., 2016; Canitano, 2015; Deb et al., 2009; Kaplin & McCracken, 2012; Politte et al., 2014).

Objectives

To determine the effectiveness of anticonvulsants 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 anticonvulsants increases the risk of these adverse effects.

Methods

This systematic review of the benefits and harms associated with the use of Anticonvulsants was part of a larger Cochrane systematic review investigating the relative 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 anticonvulsants to placebo in the management of behaviours of concern in people with ASD.

Inclusion criteria

All randomised controlled trials (RCTs) of anticonvulsants 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).

Inclusion criteria

All randomised controlled trials of anticonvulsants 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).

Results

Characteristics of included trials

Six trials were included in the analysis with 165 participants. All trials included children and adolescents although one trial also included adults up to 20 years, however it is unclear how many adults were involved. All trials reporting behaviours of concern or adverse effects were short-term (i.e. 3 months or less).

Due to the small sample sizes as well as sources of bias affecting accuracy of estimates, we rated the trials as having weak quality of evidence.

Behaviours of concern

Irritability

Three trials involving 97 participants provided data for the outcome of irritability. All trials used the ABC-Irritability subscale to measure irritability.

There was no evidence of an effect on irritability (SMD of -0.67, 95% CI -1.93 to 0.59, $I^2 = 88\%$) when those receiving anticonvulsants were compared to placebo.

Aggression

Two trials involving 57 participants provided data for the outcome of aggression. There was no evidence of an effect on aggression when those receiving anticonvulsants were compared to placebo (SMD -0.18, 95% CI -0.71 to 0.35, $I^2 = 0\%$).

Self-injurious behaviour

No included trials reported self-injurious behaviour.

Quality of life

No included trials reported quality of life.

Adverse effects

The types of adverse effects that were reported included cardiovascular, gastrointestinal, immune, metabolic, musculoskeletal, neurological, psychological, respiratory, skin, and urinary effects. A systematic review reported the adverse effects associated with different anticonvulsants among people with epilepsy (Costa et al., 2011). It was reported that those in the topiramate group had an almost 3-fold increased risk of fatigue compared to those on placebo or other anticonvulsant (8 trials, 1092 participants, Odds Ratio 2.74, 95% CI 1.81 to 4.14). There were no differences between the levetiracetam and lamotrigine groups compared to placebo for any reported adverse effects. Divalproex sodium and valproate were not included in the Costa et al. (2011) systematic review.

Metabolic adverse effects

Decreased appetite

Anticonvulsants were associated with an almost 5.5-fold increase in risk of decreased appetite (two trials, 60 participants, RR 5.45, 95% CI 1.02 to 29.23).

Other adverse effects

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

Risk of Bias

Due to the small number of identified trials, overall low number of participants, and potential biases in included trials, we rated the evidence for the benefits and harms of

anticonvulsants as low quality. Potential biases in trial design included methods of randomisation, awareness of group allocation (blinding), reporting bias, and external funding.

Discussion

There is low-level evidence that anticonvulsants had no effect on irritability and aggression in people with autism. The evidence is limited by the small number of included trials and the relatively small sample sizes. Apart from decreased appetite, there were no associated adverse effects and because all trials were short-term it is unclear if this adverse effect would be observed beyond three months.

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

Implications for Research

In this review, there were only a few identified trials of anticonvulsants, which also had potential biases. Therefore, there is a need for high quality trials of the effectiveness of anticonvulsants on behaviours of concern in people with autism. As the maximum length of identified trials was three months, trials which evaluate the long-term effectiveness of anticonvulsants and associated adverse effects are also required.

Implications for practice

Based on data from all identified trials that compared anticonvulsants to placebo, anticonvulsants do not appear to reduce behaviours of concern. Anticonvulsants were associated with minimal adverse effects; however, as all trials were short-term, it remains unclear whether these adverse effects occur beyond 3 months.

Before considering medications to manage a person's behaviour of concern, a comprehensive health 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 should be consulted so that the risks and benefits associated with anticonvulsant medications can be discussed with the person and other support persons such as family members.

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

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