Evidence Summary: Neurohormones 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 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 neurohormones 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?

- Neurohormones such as secretin and oxytocin are often prescribed to people with ASD to reduce behaviours of concern.

- Best evidence for the effectiveness of neurohormones 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 neurohormone 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:
    - Neurohormones did not reduce behaviours of concern when compared to placebo.
    - There were no differences between the groups for any of the reported adverse effects.
- 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.
- If participants are receiving neurohormones 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

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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). The use of neurohormones such as oxytocin or secretin for people with ASD has increased in recent years, mainly as a treatment for the core symptoms of autism and as an alternative to psychotropic drugs. Neurohormones are thought to regulate emotions and promote social bonding including reciprocity. As such, neurohormones may target the core features of ASD and in turn decrease associated behaviours of concern. There is a need for high quality evidence on the effectiveness and harms associated with the use of neurohormones to manage behaviours of concern in people with ASD.

Review question

To determine the effectiveness of neurohormones such as secretin, oxytocin and adrenocorticotropic hormone (ACTH) 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 neurohormone use.

What was studied in the review?

All trials that compared the effectiveness of neurohormones 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 neurohormone use.

Twenty trials involving 883 participants comparing neurohormones to placebo were included in the analysis. Five trials compared the effectiveness of secretin to placebo (211 participants), eleven trials compared oxytocin to placebo (378 participants), one trial compared ACTH to a placebo (14 participants), one trial compared balovaptan to placebo (213 participants), two trials (67 participants) compared vasopressin to a placebo in reducing behaviours of concern or reported adverse effects. All trials of effectiveness were 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 a neurohormone such as oxytocin or secretin 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?

Irritability was reported in six of the trials (167 participants). There was no evidence of a significant effect of ACTH, oxytocin, secretin, or vasopressin on irritability in the short-term. Aggression and self- injurious behaviour were not reported. Quality of life was reported in three trials with 67 participants but there was no significant difference between oxytocin and placebo, or vasopressin and placebo. Adverse effects were also reported but there were no differences between the groups.

How reliable are the results of analyses in this review?

The finding that neurohormone use did not result in a significant reduction of behaviours of concern is consistent with previous reviews on the use of neurohormones for people with ASD. However, because of the low quality of evidence due to the small number of trials and participants in analyses that compared neurohormones 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 neurohormone 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 did not find any evidence that neurohormones decrease behaviours of concern in people with autism spectrum disorder in the short-term. In addition, neurohormones did not result in any significant effect on adverse effects. Because no trials

reported effectiveness for periods of more than 4 months there is no evidence of the benefits and harms of neurohormones for longer periods.

Before considering medications to manage a person's behaviour of concern, a comprehensive assessment should be undertaken to identify factors that may trigger or maintain the behaviour and non-pharmacological interventions trialled. If these interventions are not effective, a qualified medical practitioner should be consulted on the benefits and risks of using medications to manage behaviour.

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 neurohormone 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 (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 ASD and comorbid intellectual disability compared to typically developing peers (Ali et al., 2015; National Institute for health & Care Excellence, 2015; Rzepecka et al., 2011) with estimates of between 5 and 15% (National Institute for health & 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).

Neurohormones are a heterogeneous group with varying mechanisms of action and sites of origin. Oxytocin is produced in the hypothalamus (Wilczynski 2019) with the primary role of promoting lactation, facilitating contractions, and promote bonding between mother and infant (Andari et al., 2010; Green & Hollander, 2010; Taylor et al., 2018). It is hypothesised that increasing rates and severity of behaviours of concern are positively correlated with the severity of the core traits of autism (Cohen 2014). As such, neurohormones may be effective in reducing behaviours of concern by reducing the core traits of autism (Alvares et al., 2017; Cohen 2014; Whitehouse, 2013).

Secretin is produced in the gastrointestinal tract and has digestive and neurological functions (Banko et al., 2011; Welch et al., 2004). The primary function of secretin is to secrete pancreatic fluid (Banko et al., 2011) although secretin receptors are also located in the brain particularly in areas such as the amygdala which regulate emotions and mood and the hippocampus which is associated with memory formation (Banko et al., 2011; Qi &

Zhang, 2020). Impairments or irregularities in either of these areas of the brain are commonly associated with ASD (Chaddad et al., 2017; Gibbard et al., 2018) and as such, secretin has been suggested as a potential intervention in the management of autism (McQueen & Heck, 2002; Tanaka et al., 2018).

Objectives

To determine the effectiveness of neurohormones 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 neurohormones increase the risk of these adverse effects.

Methods

This systematic review of the benefits and harms associated with the use of neurohormones 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 neurohormones to placebo in the management of behaviours of concern in people with ASD.

Inclusion criteria

All randomised controlled trials (RCTs) of neurohormones 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 review authors 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 authors. 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 authors 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).

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Results

Characteristics of included trials

Eighteen trials were included in the analysis of 753 participants. Seven studies involved adult participants only, one study involved adolescents and adults, one study involved adolescents and nine studies involved children only. All trials reporting behaviours of concern were short-term (i.e. 4 months or less).

Behaviours of concern

Irritability

Six trials involving 167 participants provided data for the outcome of irritability. Three trials compared secretin to placebo, and one each compared ACTH, oxytocin, and vasopressin to placebo. All six trials used the ABC-Irritability subscale to measure the outcome of irritability. There was no significant effect on irritability over the six trials (SMD -0.05; 95% CI -0.35 to 0.26). There was also no apparent difference in any of the subgroup analyses comparing secretin, ACTH, oxytocin, and vasopressin to placebo.

Aggression

The outcome of aggression was not reported.

Self-injurious behaviour

The outcome of self-injurious behaviour was not reported.

Quality of life

Three trials involving 67 participants reported quality of life when oxytocin (two studies) and vasopressin (one study) was compared to placebo. The two trials comparing oxytocin both used the WHO Quality of life Questionnaire while the study comparing vasopressin used the parent-rated Pediatric Quality of Life (PedsQoL) scale. There was no evidence that oxytocin or vasopressin had an effect on quality of life scores (SMD 1.09; 95% CI -2.61 to 4.80).

Adverse effects

Gastrointestinal, metabolic, musculoskeletal, neurological, psychological, respiratory, and skin-related adverse effects were reported. There were no significant differences between the groups.

Risk of Bias

Due to the small number of trials and overall low sample size in in individual meta-analyses and potential sources of bias that could affect accuracy of estimates, we rated the trials as low quality of evidence. Potential sources of bias that may have decreased the quality of evidence include potential awareness of group allocation, reporting bias and external funding.

Discussion

There was no apparent evidence that neurohormones decrease behaviours of concern in people with autism. There was also no evidence of adverse effects associated with neurohormones. Because all trials were four months or less in duration, it is unclear if any benefits or adverse effects would be observed over longer periods.

These findings are consistent with other reviews (Krishnaswami et al., 2011; Williams et al., 2012) that found neurohormones have very little to no evidence of an effect on behaviours of concern in people with ASD. Due to the lack of evidence to support their use, international guidelines advise against the use of neurohormones such as secretin for children and adolescents with ASD, (National Collaborating Centre for Mental Health 2013, National Institute for health & Care Excellence, 2013).

We are not able to make any conclusions about the benefits and harms of neurohormone 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 to very low quality of evidence due to the small number of identified trials that compared neurohormones to placebo, more high quality trials are required. As all included trials only followed up participants for four months or less, future trials should focus on the longer-term follow-up of behaviours of concern and adverse effects in response to neurohormone use.

Implications for practice

Based on data from all identified trials, there was no evidence that any benefits or adverse effects were associated with neurohormones in the short-term. These findings are in line with international guidelines that advise against the use of neurohormones in the treatment of autism because of insufficient evidence of a beneficial effect.

> Providers can support participants to ensure they are reviewed regularly by a qualified medical practitioner. A comprehensive health assessment by a general practitioner may identify the presence of physical health or mental health problems that can cause behaviours of concern (National Institute for health & 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 & 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 neurohormones can be discussed with the person and other support persons such a family members.

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