Evidence Summary: Risperidone 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 risperidone when it is 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?

- Risperidone is often prescribed to people with ASD to reduce behaviours of concern.

- Best evidence for the effectiveness of risperidone 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 risperidone use in adults with ASD as the clear 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:
    - Risperidone reduced behaviours of concern by around 30%
    - There were no apparent differences between low and high dose risperidone;
- We could not make any conclusion about long-term effects, as long-term effects were not reported in any of the identified trials.

- Side effects were reported in people receiving risperidone. These included:
    - sedation;
    - raised heart rate;
    - tremor;
    - increased weight;
    - excessive salivation;
    - and constipation.

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 that:

- The person receives a comprehensive behaviour assessment that may identify factors that could trigger or maintain behaviour of concern such as communication difficulties or environmental factors.
- The person receives a comprehensive health assessment by a general practitioner as this may identify the presence of physical or mental 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 risperidone 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

To the extent permitted by law, the Commonwealth of Australia excludes all liability for loss or damage arising from the use of, or reliance on, the information contained in this document whether or not caused by any negligence on the part of the Commonwealth or its agents. The Commonwealth of Australia accepts no responsibility for the completeness or accuracy of the information summarised in this document.

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 antipsychotic drug risperidone is commonly prescribed for people with ASD in the absence of a mental health diagnosis to reduce behaviours of concern. There is a need for high quality evidence on the effectiveness and harms associated with the use of risperidone to manage behaviours of concern in people with ASD.

Review question

To determine the effectiveness of risperidone 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 risperidone use.

What was studied in the review?

All trials that compared the effectiveness of risperidone to a placebo in reducing behaviours of concern or reported adverse effects. Eight trials comparing risperidone to placebo were included in the analysis. 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 risperidone 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?

Risperidone reduced behaviours of concern by around 30% in the short-term with no differences between low and high dose risperidone. However, a number of short-term side effects were markedly higher in participants receiving risperidone. These included sedation, raised heart rate, tremor, increased weight, excessive salivation, and constipation.

How reliable are the results of analyses in this review?

Although the finding that risperidone use resulted in a marked reduction in behaviours of concern was consistent across all trials, potential biases in these trials means our confidence in the estimates is limited. Factors that decrease our confidence in the quality of the evidence include the small number of identified trials and small sample sizes in the analyses; as well as potential biases in trial design; and differences between trials.

However, we are not able to make any conclusions about the benefits and harms of risperidone 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 provides evidence that risperidone can reduce the behaviours of concern: irritability, aggression, and self-injury in the short-term. However, short-term risperidone was also associated with very considerable increases in cardiovascular, gastrointestinal, metabolic and neurological side effects. Therefore, any possible beneficial effects of risperidone need to be considered in light of the high rates of adverse effects.

Because all trials reporting effectiveness were short-term there is no evidence of the benefits and harms of using risperidone for periods of more than 3 months. These results highlight the need to investigate the long-term benefits and harms associated with risperidone use in people with autism.

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 risperidone 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) 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; McTiernan et al., 2011).

Risperidone and other antipsychotics are primarily prescribed for psychiatric disorders such as schizophrenia or bipolar disorder (Burness et al., 2021; Marston et al., 2014) but risperidone is also one of the most commonly prescribed psychotropics for the management of behaviours of concern in people with autism (Deb et al., 2015; Hsia et al., 2014; Murray et al., 2013). There is limited evidence that risperidone is effective in the management of behaviours of concern in people with autism (Howes et al., 2018; Jesner et al., 2007; National Institute for Health and Care Excellence, 2015). Long-term risperidone use is also associated with an increased risk of significant adverse effects such as weight-gain (Alvarez-Jimenez et al., 2008; Bak et al., 2013; Lake et al., 2017) diabetes mellitus (Pillinger et al., 2020), and cardiovascular effects such as stroke and heart attack (Pillinger et al., 2020).

Objectives

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

Methods

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

Inclusion criteria

All randomised controlled trials of risperidone versus placebo for people of any age with ASD 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 trial details and data using standardised forms. Any disagreements were resolved by discussion or referral to a third reviewer. Where insufficient details were provided in publications or trial 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, measurement and performance biases, 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 of 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 2020).

Results

Characteristics of included trials

Nine trials were included in the analysis with 435 participants. Only 50 participants in these trials were adults with the remaining 385 participants aged between 3 and 17 years. All

trials reporting behaviours of concern were short-term (i.e. 3 months or less). Only one trial reporting adverse events was longer than three months.

Behaviours of concern

Irritability

Seven trials involving 402 participants provided data for the outcome of irritability. Five of these trials used the ABC-Irritability subscale to measure irritability in children and adolescents. The other trial used the Ritvo-Freeman Real Life Rating Scale.

There was an SMD of -1.01 (95% CI -1.37 to -0.66) when those receiving risperidone were compared to placebo. This corresponded to a mean ABC-Irritability decrease of 36% compared to the placebo group.

Aggression

Two trials involving 93 participants provided data for the outcome of aggression. Both trials used the Nisonger Child Behavior Rating Form (Conduct Problem subscale) to measure aggression. There was an SMD of -0.52 (95% CI -0.94 to -0.11), indicating a 33% decrease in aggression in the risperidone groups compared to placebo groups.

Self-injurious behaviour

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.

Improvement and Relapse

There was a greater than threefold improvement in pre-defined irritability scores (measured using the ABC-Irritability subscale) in participants given risperidone compared to those

receiving placebo (two trials, 157 participants, RR 3.37, 95% CI 1.21 to 9.43). 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.

Quality of life

No included trials reported this outcome.

Adverse effects

The types of adverse effects that were reported included cardiovascular, gastrointestinal, immune, metabolic, musculoskeletal, neurological, psychological, respiratory, skin, and urinary effects. There were inadequate data to compare the rates of adverse effects between high-dose risperidone and low-dose risperidone trials.

Cardiovascular adverse effects

- **Tachycardia**: Risperidone was associated with a nearly eight-fold increase in the risk of tachycardia (rapid heart rate; 2 trials, 179 participants, RR 7.53; 95% CI: 1.40 to 40.52).

Gastrointestinal adverse effects

- **Constipation**: Risperidone was associated with a nearly three-fold increase in the risk of constipation (5 trials, 299 participants (RR 2.70; 95% CI: 1.31 to 5.54).
- **Excessive salivation**: Risperidone was associated with a four-fold increase in the risk of excessive salivation (4 trials, 233 participants, RR 4.33; 95% CI: 1.70 to 11.06).

Metabolic adverse effects

- **Weight gain**: Risperidone was associated with a nearly three-fold risk of weight gain (4 trials, 256 participants; RR 2.77; 95% CI: 1.64 to 4.65).

- **Increased appetite**: Risperidone was associated with a more than two-fold risk of increased appetite (4 trials, 268 participants; RR 2.58; 95% CI: 1.77 to 3.78)

Neurological adverse effects

- **Sedation**: Risperidone was associated with an eight-fold increased risk of sedation (4 trials, 196 participants, RR 8.21; 95% CI: 1.27 to 53.14).
- **Somnolence**: Risperidone was associated with a nearly six-fold increase in the risk of somnolence (4 trials, 276 participants; RR 5.90; 95% CI: 3.22 to 10.81).
- **Fatigue**: Risperidone was associated with a two-fold increase in fatigue (3 trials, 245 participants; RR 2.25; 95% CI: 1.38 to 3.64).
- **Tremor**: Risperidone was associated with a nearly eight-fold increase in the risk of tremor (2 trials, 179 participants; RR 7.76; 95% CI: 1.45 to 41.48).

Other adverse effects

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

Risk of Bias

The quality of evidence from this systematic review and meta-analyses is limited by the relatively small number of identified trials, small overall sample size, potential biases and differences between trials.

Discussion

There is moderate quality evidence that risperidone decreases irritability in people with autism; low quality evidence that risperidone decreases aggression, and very low quality evidence that it decrease self-injurious behaviour. Although the decreases were marked (around 30%) and highly consistent across trials, the findings are limited by the number of identified trials, overall samples size, potential biases in trial design, and differences between trials. Also, given the very marked increases in sedation-related adverse effects (up

to eight-fold higher) it is unclear to what extent these apparent improvements in behaviours of concern are related to sedation. However, the findings are consistent with earlier systematic reviews that found that risperidone appears to reduce behaviours of concern in the short-term (Jesner et al., 2007).

Because all trials reporting behaviours of concern were short-term trials of 3 months or less, it is unclear whether the apparent behavioural effects would be maintained over longer periods. Similarly, we cannot say whether the marked increases in risk of adverse effects would be maintained beyond the trial period. In particular, we not able to ascertain the risk of longer-term adverse effects, such as cardiovascular events and diabetes mellitus, which are associated with the longer-term use of atypical antipsychotics such as risperidone.

As there was no evidence of higher doses being more effective than lower doses in reducing behaviours of concern, it may be more appropriate to use lower doses. This is in line with the NICE guidelines recommendations to "start with a low dose and use the minimum effective dose needed" when prescribing antipsychotics such as risperidone for the management of behaviours of concern in people with an intellectual disability (National Institute for Health and Care Excellence, 2015).

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

Implications for Research

Length of follow-up emerged as a major issue in the included trials, with only one trial following up participants for more than three months. This highlights the need for long-term trials of the effectiveness and adverse effects associated with risperidone.

Population-based studies are also needed to identify the effectiveness and long-term health effects of the use of risperidone in people with ASD and people with ASD.

Implications for practice

Based on data from all identified trials that compared risperidone to placebo, risperidone appears to reduce irritability by approximately 30%; however there was also considerable evidence that significant adverse events were associated with risperidone in the short-term.

A person with autism who is demonstrating behaviours of concern, can receive a comprehensive health assessment by a general practitioner as this may identify the presence of physical 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 risperidone can be discussed with the person and other support persons such a family members.

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

References

American Psychiatric Association (APA). (2013). *Diagnostic and Statistical Manual of Mental Disorders. 5th Edition*. Arlington, VA: American Psychiatric Association.

Alvarez-Jimenez, M., Gonzalez-Blanch, C., Crespo-Facorro, B., Hetrick, S., Jose Manuel Rodriguez-Sanchez, Perez-Iglesias, R., & Vazquez-Barquero, J. L. (2008). Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: A systematic critical reappraisal. *CNS Drugs*, *22*(7), 547–562. https://doi.org/10.2165/00023210-200822070-00002

Arora, N. K., Nair, M. K. C., Gulati, S., Deshmukh, V., Mohapatra, A., Mishra, D., ... & Vajaratkar, V. (2018). Neurodevelopmental disorders in children aged 2–9 years: Population-based burden estimates across five regions in India. *PLoS medicine*, *15*(7), e1002615 - e1002615. https://doi.org/10.1371/journal.pmed.1002615

Australian Institute of Health and Welfare (AIHW). (2017). *Autism in Australia*. www.aihw.gov.au/reports/disability/autism-inaustralia/contents/autism

Australian Institute of Health and Welfare (AIHW). (2020). *Autism in Australia*. https://www.aihw.gov.au/reports/disability/autism-in-australia/contents/autism

Australian Psychological Society. (2020). *Autism Spectrum Disorder in Children.* https://www.psychology.org.au/for-the-public/Psychology-topics/Autism-spectrum-disorder-in-children Accessed23/10/2020

Bak, M., Fransen, A., Janssen, J., van Os, J., & kker, M. (2014). Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. *PloS One*, *9*(4), e94112–. https://doi.org/10.1371/journal.pone.0094112

Burness, C., Corbet, C., Beyene, K., Webby, C., Nankivell, C., Cabasag, P., Hari, K., Fraser, A., Gray, S., Harrison, J., & Chan, A. H. Y. (2021). Factors predicting high-dose and combined antipsychotic prescribing in New Zealand; High-dose antipsychotic prescribing. *Psychiatry Research*, *302*, 113996–113996. https://doi.org/10.1016/j.psychres.2021.113996

Cleaton M. M. A., & Kirby A. (2018). Why do we find it so hard to calculate the burden of neurodevelopmental disorders? *Journal of childhood and developmental disorders, 4*(3): 330-338.

Deb, S., Unwin, G., & Deb, T. (2015). Characteristics and the trajectory of psychotropic medication use in general and antipsychotics in particular among adults with an intellectual disability who exhibit aggressive behaviour. *Journal of Intellectual Disability Research*, *59*(1), 11–25. https://doi.org/10.1111/jir.12119

DSM-5. (2013). *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th edition*. Arlington (VT): American Psychiatric Publishing.

Elsabbagh, M., Divan, G., Koh, Y.-J., Kim, Y. S., Kauchali, S., Marcín, C., Montiel-Nava, C., Patel, V., Paula, C. S., Wang, C., Yasamy, M. T., & Fombonne, E. (2012). Global prevalence of autism and other pervasive developmental disorders. *Autism Research*, *5*(3), 160–179. https://doi.org/10.1002/aur.239

Emerson, E., Robertson, J., Gregory, N., Hatton, C., Kessissoglou, S., Hallam, A., & Hillery, J. (2000). Treatment and management of challenging behaviours in residential settings. *Journal of Applied Research in Intellectual Disabilities*, *13*(4), 197–215. https://doi.org/10.1046/j.1468-3148.2000.00036.x

Howes, O., Rogdaki, M., Findon, J. L., Wichers, R. H., Charman, T., King, B. H., Loth, E., McAlonan, G. M., McCracken, J. T., Parr, J. R., Povey, C., Santosh, P., Wallace, S., Simonoff, E., & Murphy, D. G. (2018). Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British association for psychopharmacology. *Journal of Psychopharmacology*, *32*(1), 3–29. https://doi.org/10.1177/0269881117741766

Hsia, Y., Wong, A., Murphy, D. G., Simonoff, E., Buitelaar, J., & Wong, I. (2014). Psychopharmacological prescriptions for people with autism spectrum disorder (ASD): A multinational study. *Psychopharmacology*, *231*(6), 999–1009. https://doi.org/10.1007/s00213-013-3263-x

Jesner, O.S., Aref-Adib, M., & Coren, E. (2007). Risperidone for autism spectrum disorder. Cochrane Database of Systematic Reviews, Issue 1. doi: 10.1002/ 14651858.CD005040.pub2

Lake, J., Denton, D., Lunsky, Y., Shui, A. M., Veenstra-VanderWeele, J., & Anagnostou, E. (2017). Medical conditions and demographic, service and clinical factors associated with atypical antipsychotic medication use among children with an autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *47*(5), 1391–1402. https://doi.org/10.1007/s10803-017-3058-8

Lecavalier, L. (2006). Behavioral and emotional problems in young people with pervasive developmental disorders: Relative prevalence, effects of subject characteristics, and empirical classification. *Journal of Autism and Developmental Disorders*, *36*(8), 1101–1114. https://doi.org/10.1007/s10803-006-0147-5

Marston, L., Nazareth, I., Petersen, I., Walters, K., & Osborn, D. P. J. (2014). Prescribing of antipsychotics in UK primary care: a cohort study. *BMJ Open*, *4*(12), e006135–e006135. https://doi.org/10.1136/bmjopen-2014-006135

Matson, J., Wilkins, J., & Macken, J. (2008). The relationship of challenging behaviors to severity and symptoms of autism spectrum disorders. *Journal of Mental Health Research in Intellectual Disabilities*, *2*(1), 29–44. https://doi.org/10.1080/19315860802611415

McTiernan, A., Leader, G., Healy, O., & Mannion, A. (2011). Analysis of risk factors and early predictors of challenging behavior for children with autism spectrum disorder. *Research in Autism Spectrum Disorders*, *5*(3), 1215–1222. https://doi.org/10.1016/j.rasd.2011.01.009

Mencap. (2019). How common is learning disability in the UK. https://www.mencap.org.uk/learning-disability-explained/researchand-statistics/how-common-learning-disability 2019

Murray, M., Hsia, Y., Glaser, K., Simonoff, E., Murphy, D. G. M., Asherson, P. J., Eklund, H., & Wong, I. C. K. (2013). Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. *Psychopharmacology*, *231*(6), 1011–1021. https://doi.org/10.1007/s00213-013-3140-7

National Institute for Health and Care Excellence (NICE). (2015). Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges. https://www.nice.org.uk/guidance/ng11/resources/challenging-behaviour-and-learning-disabilities-prevention-and-interventions-for-people-with-learning-disabilities-whose-behaviour-challenges-1837266392005

Oliphant, R., Smith, E. M., & Grahame, V. (2020). What is the prevalence of self-harming and suicidal behaviour in under 18s with ASD, with or without an intellectual disability? *Journal of Autism and Developmental Disorders*, *50*(10), 3510–3524. https://doi.org/10.1007/s10803-020-04422-6

Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., & Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *The lancet. Psychiatry*, *7*(1), 64–77. https://doi.org/10.1016/S2215-0366(19)30416-X

Ritchie, H. (2020). Neurodevelopmental disorders. www.ourworldindata.org/neurodevelopmental-disorders

Rzepecka, H., McKenzie, K., McClure, I., & Murphy, S. (2011). Sleep, anxiety and challenging behaviour in children with intellectual disability and/or autism spectrum disorder. *Research in Developmental Disabilities*, *32*(6), 2758–2766. https://doi.org/10.1016/j.ridd.2011.05.034