Evidence Summary: ADHD-related medications 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 ADHD-related medications 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?

- Stimulant and non-stimulant ADHD-related medications are often prescribed to people with ASD to reduce behaviours of concern.

- Best evidence for the effectiveness of ADHD-related 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 ADHD-related 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:
    - ADHD-related medications reduced irritability by a significant amount (up to 35%).
    - Adverse effects were also markedly higher in the ADHD-related drug groups compared to placebo.
- We could not make any conclusion about long-term effects, as long-term effects were not reported in any of the identified trials.

- The side effects reported in people receiving ADHD-related drugs included:
    - constipation;
    - decreased appetite;
    - fatigue;
    - insomnia; and
    - stomach or abdominal discomfort.

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 should be consulted on the benefits and risks of using medication to manage behaviour.
- If participants are receiving ADHD-related medications 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). Attention Deficit Hyperactivity Disorder (ADHD) related drugs are usually prescribed for people with ADHD, but they are also prescribed for people with ASD because of ADHD-related symptoms and for the management of related behaviours such as aggression and hyperactivity. There is a need for high quality evidence on the effectiveness and harms associated with the use of ADHD-related medications to manage behaviours of concern in people with ASD.

Review question

To determine the effectiveness of ADHD-related medications 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 ADHD-related drug use.

What was studied in the review?

All trials that compared the effectiveness of ADHD-related stimulants such as dexamphetamine or methylphenidate or non-stimulants such as atomoxetine, clonidine, or guanfacine to a placebo in reducing behaviours of concern or reported adverse effects.

Eleven trials involving 15 datasets and 442 participants comparing ADHD-related drugs to placebo were included in the analysis. All trials included children and adolescents (<18 years of age) and all trials were short-term i.e. 3 months or less in duration.

Trials compared methylphenidate (stimulant), atomoxetine, clonidine, and guanfacine (non-stimulants) to placebo.

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 stimulant or non-stimulant ADHD-related drug 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?

The stimulant ADHD-related drugs (methylphenidate) was associated with a significant reduction in irritability in the short-term. There was a 35% reduction in irritability scores in the stimulant (methylphenidate) groups when compared to placebo. However, the non-stimulant ADHD-related medications of atomoxetine, clonidine, and guanfacine did not show an effect on irritability. Any effect of ADHD-related medications on behaviours of concern is most likely related to the effect of stimulants and not the non-stimulant ADHD-related medications.

Participants receiving ADHD-related drugs had significantly higher rates of adverse effects in the short-term. These included gastrointestinal effects (5-fold increased risk of constipation and greater than 2-fold increased risk of stomach or abdominal discomfort), metabolic (greater than 2-fold increase in risk of decreased appetite), and neurological (greater than 4-fold increase in risk of fatigue; almost 2-fold increase in risk of insomnia). There were no significant difference between the ADHD medications and placebo groups in psychological, respiratory, skin and urinary adverse effects.

How reliable are the results of analyses in this review?

The review found low-level evidence that stimulant ADHD-related medications resulted in a significant reduction in irritability for intervals of three months or less; however, non-stimulant ADHD-related medications did not show any effect on irritability. In addition, there were also several adverse effects associated with ADHD-related medication use and as such, any reduction in irritability should be considered in light of the potential for adverse effects.

However, we are not able to make any conclusions about the benefits and harms of ADHD-related 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 low-level evidence that stimulant ADHD-related medications are associated with significant reductions in irritability in the short-term. However, because ADHD is common among people with autism, it is unclear whether the improvements observed with ADHD-related medications are due to symptoms associated with ADHD or autism.

ADHD-related medications were also associated with increases in gastrointestinal, metabolic, neurological and behavioural side effects in the short-term.

Because all trials reporting effectiveness were short-term, there is currently no evidence of the benefits and harms of using ADHD-related medications 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 ADHD-related 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 (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 (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, 2008; McTiernan et al., 2011).

ADHD-related medications are often prescribed to people with autism and behaviours of concern, due to some similarities between ASD and ADHD such as hyperactivity, inattention and social and/or communication deficits (Cortese et al., 2012; Hanson et al., 2013; Mikami et al., 2019; Rosello et al., 2018) and the high comorbidity rates of ADHD among people with ASD (Antshel et al., 2013; Sokolova et al., 2017). Stimulants such as Methylphenidate are the most commonly prescribed psychotropic medications to people with ASD and behaviours of concern aged six years and older with prescribing rates up to 34% reported in large multinational studies (Houghton et al., 2017; Hsia et al., 2014; Madden et al., 2017; Murray et al., 2013; Rasmussen et al., 2018).

Prior to the DSM-5 (2013), the DSM did not permit a diagnosis of ADHD with an existing diagnosis of ASD or other PDD (Cortese et al., 2012). The DSM-5 has now removed this exclusionary criteria for an ADHD diagnosis (Antshel et al., 2013; Epstein & Loren, 2013). As

such, there has been debate and uncertainty as to whether improvements in behaviours of concern with ADHD medications are due to improvements in ADHD that previously could not be diagnosed with ASD, or whether improvements in behaviours of concern associated with ASD are being observed.

The exact mechanism of action of methylphenidate remains unclear (Arnsten & Dudley, 2005). ASD has been associated with abnormalities in the dopaminergic system. Dopamine plays an important role in planning, motor and motivational processes which are abnormal in people with ADHD (Marinho et al., 2018; Wu et al., 2012). ADHD stimulants are thought to increase the availability of dopamine and noradrenaline neurotransmitters in the prefrontal cortex, the area of the brain that regulates attention, learning and memory (Brown et al., 2018; Ranjbar-Slamloo & Fazlali, 2020; Storebo et al., 2015).

Similarly, the non-stimulants of atomoxetine, clonidine and guanfacine increase neurotransmitters in the prefrontal cortex to reduce the symptoms of hyperactivity and inattention associated with ADHD. Guanfacine and clonidine are selective α-2A adrenergic agonists that act on receptors primarily located in the prefrontal cortex, resulting in increased activation of the noradrenergic system (Levin et al., 2019). The exact mechanism of action of the non-stimulant atomoxetine is unclear (Clemow & Bushe, 2015). Atomoxetine is a norepinephrine (noradrenaline) uptake inhibitor which inhibits presynaptic norepinephrine transporters (Clemow & Bushe, 2015) leading to increased noradrenaline and dopamine in the prefrontal cortex (Volkow & Swanson, 2013).

This systematic review on the effectiveness of ADHD-related medications for behaviours of concern and associated risk of adverse effects is part of a larger systematic review investigating all types of pharmacological interventions for people with ASD and behaviours of concern.

Objectives

To determine the effectiveness of ADHD-related medications 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 ADHD-related medications increases the risk of these adverse effects.

Methods

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

Inclusion criteria

All randomised controlled trials (RCTs) of ADHD-related medications 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 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 involving 548 participants were included in the analysis. Eight trials (366 participants) compared ADHD-related non-stimulants (atomoxetine, clonidine, and guanfacine) to a placebo whilst three trials (182 participants) compared a stimulant (methylphenidate) to placebo. All participants were aged between 5 and 17 years. All trials reporting behaviours of concern or adverse effects were short-term (3 months or less).

Behaviours of concern

Irritability

Nine trials involving 442 participants provided data for the outcome of irritability. ADHD-related medications were associated with a significant reduction in irritability in the short-term (nine trials, 11 datasets, 442 participants, SMD -0.24; 95% CI -0.43 to -0.04).

When stimulant ADHD-related medications were compared to non-stimulant ADHD-related medications, the stimulant methylphenidate had a significant effect on irritability (two trials, 116 participants, SMD -0.50, 95% CI: -0.01 to -0.08). This indicates a 35% reduction in irritability scores in the stimulant (methylphenidate) groups compared to placebo groups.

The non-stimulants, atomoxetine, guanfacine and clonidine, did not have an effect on irritability SMD (seven trials, 326 participants, SMD -0.17, 95% CI -0.38 to 0.05).

Improvement and Relapse

No included trials reported this outcome.

Aggression

No included trials reported this outcome.

Self-injurious behaviour

No included trials reported this outcome.

Quality of life

One trial involving 54 participants provided data for the outcome of quality of life. ADHD-related medications (atomoxetine) did not have an effect on quality of life (mean difference 2.00, 95% CI -3.03 to 7.03).

Adverse effects

The types of adverse effects reported include gastrointestinal, metabolic and neurological. These adverse effects are similar in type and associated risk to those reported in Cochrane systematic reviews of stimulant and non-stimulant ADHD-related drugs for participants with ADHD (Osland et al., 2018; Storebo et al., 2015).

Gastrointestinal adverse effects

Stomach or abdominal discomfort

ADHD-related medications were associated with a more than 2-fold increase in stomach or abdominal discomfort compared to placebo (five trials, 670 participants, RR 2.32; 95% CI 1.31 to 4.11).

Constipation

ADHD-related medications were associated with a 5-fold increase in constipation compared to placebo (three trials, 250 participants, RR 5.00; 95% CI 2.87 to 8.70).

Metabolic adverse effects

Decreased appetite

ADHD-related medications were associated with more than 2-fold greater risk of decreased appetite compared to placebo (six trials, 731 participants, RR 2.37; 95% CI 1.62 to 3.47).

Neurological adverse effects

Fatigue

ADHD-related medications were associated with a 4-fold increase in fatigue compared to placebo (three trial, 219 participants, RR 4.01, 95% CI 1.92 to 8.34).

Insomnia

ADHD-related medications were associated with a nearly 2-fold increased risk in insomnia compared to placebo (five trials, 631 participants, RR 1.79, 95% CI 1.18 to 2.70).

Emotional / tearful

ADHD-related medications were associated with a more than 4-fold increase in emotions or being tearful (two trials, 310 participants, RR 4.49, 95% CI 1.74 to 11.60).

Other adverse effects

There was no difference between the ADHD stimulant or non-stimulant groups and placebo in the rates of reported cardiovascular, Immune, psychological, respiratory, skin and urinary adverse effects.

Risk of Bias

The review found low-level evidence that stimulant ADHD-related medications resulted in a significant reduction in irritability for intervals of up to three months. Evidence was considered low-level as this effect may have been due to only two trials of the stimulant methylphenidate. In addition, the potential inclusion of participants with ADHD may mean that a decrease in irritability could be related to symptoms of ADHD.

Discussion

There is low-level evidence that stimulant ADHD-related medications decrease irritability in people with autism. However, non-stimulant ADHD-related medications did not significantly decrease irritability. Although the decreases associated with stimulants were marked (around 35%), these findings are limited by potential biases in trial design and the small overall sample sizes. In addition, there were no data to assess the effects of ADHD-related medications on aggression or self-injury in people with autism.

In addition, some of the included trials were published in or prior to 2005, meaning that participants were likely to have had undiagnosed ADHD as well as ASD. As such, it is difficult

to determine if the improvements observed following ADHD medication was due to improvements in ASD related behaviours of concern or improvement in ADHD symptoms.

Furthermore, given that all trials were short-term treatment trials of less than three months, it is unclear whether the apparent effects seen would be maintained over a longer period. These results and level of evidence are similar to other systematic reviews on the use of ADHD-related medication for autism (Patra et al., 2019; Sturman et al., 2017).

We are not able to make any clear conclusions about the benefits and harms of ADHD-related medication use in adults with ASD as the clear majority of participants in these trails 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 a larger analysis of the long-term effectiveness and adverse effects associated with ADHD-related medications.

In particular, population-based studies are needed to identify the effectiveness and long-term health effects of the use of ADHD-related medications such as methylphenidate in people with ASD and people with ASD and diagnosed comorbid ADHD now that the DSM-5 permits this comorbidity.

Implications for practice

Based on data from all identified trials that compared ADHD-related medications to placebo, stimulant ADHD medications (methylphenidate) appear to reduce irritability by approximately 35%. Non-stimulant ADHD-related medications did not have an effect on irritability when compared to placebo. There was also considerable evidence of significant adverse effects associated with ADHD-related medications in the short-term that needs to be considered.

Providers can support participants with behaviours of concern to ensure they 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 ADHD-related medications can be discussed with the person and other support persons such a family members.

If participants are receiving ADHD-related medications to manage behaviours of concern, providers can support them to ensure they are regularly reviewed 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.

Antshel K. M., Zhang-James, Y., & Faraone, S. V. (2013). The comorbidity of ADHD and Autism Spectrum Disorder. *Expert Review of Neurotherapeutics*, *13*(10), 1117–1128. https://doi.org/10.1586/14737175.2013.840417

Arnsten, A., & Dudley, A. G. (2005). Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. *Behavioral and Brain Functions*, 1 (2): 1-9. doi:10.1186/1744-9081-1-2

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 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

Brown, K., Samuel, S., & Patel, D. R. (2018). Pharmacologic management of attention deficit hyperactivity disorder in children and adolescents: a review for practitioners. *Translational Pediatrics*, *7*(1), 36–47. https://doi.org/10.21037/tp.2017.08.02

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.

Clemow, D., & Bushe, C. J. (2015). Atomoxetine in patients with ADHD: A clinical and pharmacological review of the onset, trajectory, duration of response and implications for patients. *Journal of Psychopharmacology*, *29*(12), 1221–1230. https://doi.org/10.1177/0269881115602489

Cortese, S. Castelnau, P., Morcillo, C., Roux, S., & Bonnet-Brilhault, F. (2012). Psychostimulants for ADHD-like symptoms in individuals with autism spectrum disorders. *Expert Review of Neurotherapeutics*, *12*(4), 461–473. https://doi.org/10.1586/ern.12.23

Deeks, J. J., Higgins J. P. T., & Altman, D. G. (2020). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M, J., Welch, V. A., (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1 (Updated September 2020). Available from www.training.cochrane.org/handbook

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., Kiernan, C., Alborz, A., Reeves, D., Mason, H., Swarbrick, R., Mason, L., & Hatton, C. (2001). The prevalence of challenging behaviors: A total population study. *Research in Developmental Disabilities*, *22*(1), 77–93. https://doi.org/10.1016/S0891-4222(00)00061-5

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

Epstein J., & Loren, R. E. (2013). Changes in the definition of ADHD in DSM-5: Subtle but important. *Neuropsychiatry* 3 (5): 455-58. doi:10.2217/npy.13.59

Hanson E, Cerban B. M., Slater C. M., Caccamo L. M., Bacic, J., Chan, E. (2013). Brief report: prevalence of attention deficit/ Hyperactivity disorder among individuals with an autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *43*(6), 1459–1464. https://doi.org/10.1007/s10803-012-1677-7

Houghton, R., Ong, R., & Bolognani, F. (2017). Psychiatric comorbidities and use of psychotropic medications in people with autism spectrum disorder in the United States. *Autism Research, 10*(12), 2037–2047. https://doi.org/10.1002/aur.1848

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

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

Levin, H., Troyanskaya, M., Petrie, J., Wilde, E. A., Hunter, J. V., Abildskov, T. J., & Scheibel, R. S. (2019). Methylphenidate treatment of cognitive dysfunction in adults after mild to moderate traumatic brain injury: Rationale, efficacy, and neural mechanisms. *Frontiers in Neurology*, *10*, 925–925. https://doi.org/10.3389/fneur.2019.00925

Madden, J. M., Lakoma, M. D., Lynch, F. L., Rusinak, D., Owen-Smith, A. A., Coleman, K. J., Quinn, V. P., Yau, V. M., Qian, Y. X., & Croen, L. A. (2017). Psychotropic medication use among insured children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *47*(1), 144–154. https://doi.org/10.1007/s10803-016-2946-7

Marinho, V., Oliveira, T., Rocha, K., Ribeiro, J., Magalhães, F., Bento, T., Pinto, G. R., Velasques, B., Ribeiro, P., Di Giorgio, L., Orsini, M., Gupta, D. S., Bittencourt, J., Bastos, V. H., & Teixeira, S. (2018). The dopaminergic system dynamic in the time perception: A review of the evidence. *International Journal of Neuroscience*, *128*(3), 262–282. https://doi.org/10.1080/00207454.2017.1385614

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

Mikami, A., Miller, M., & Lerner, M. D. (2019). Social functioning in youth with attention-deficit/hyperactivity disorder and autism spectrum disorder: Transdiagnostic commonalities and differences. *Clinical Psychology Review*, *68*, 54–70. https://doi.org/10.1016/j.cpr.2018.12.005

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

Osland S., Steeves T., & Pringsheim T. (2018). Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (Review). Cochrane database of systematic reviews, issue 6 (Art no. CD007990). https://doi.org/10.1002/14651858.CD007990.pub2

Patra, S., Nebhinani, N., Viswanathan, A., & Kirubakaran, R. (2019). Atomoxetine for attention deficit hyperactivity disorder in children and adolescents with autism: A systematic review and meta-analysis. *Autism Research*, *12*(4), 542–552. https://doi.org/10.1002/aur.2059

Ranjbar-Slamloo, Y., & Fazlali, Z. (2020). Dopamine and noradrenaline in the brain; Overlapping or dissociate functions? *Frontiers in Molecular Neuroscience*, *12*, 334–334. https://doi.org/10.3389/fnmol.2019.00334

Rasmussen, L., Pratt, N., Roughead, E., & Moffat, A. (2018). Prevalence of psychotropic medicine use in Australian children with autism spectrum disorder: A drug utilization study based on children enrolled in the longitudinal study of Australian children. *Journal of Autism and Developmental Disorders*, *49*(1), 227–235. https://doi.org/10.1007/s10803-018-3718-3

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

Rosello, B., Berenguer, C., Baixauli, I., Colomer, C., & Miranda, A. (2018). ADHD symptoms and learning behaviors in children with ASD without intellectual disability. A mediation analysis of executive functions. *PloS One*, *13*(11), e0207286–e0207286. https://doi.org/10.1371/journal.pone.0207286

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

Sokolova, E., Sluiter-Oerlemans, A. M., Rommelse, N. N., Groot, P., Hartman, C. A., Glennon, J. C., Claassen, T., Heskes, T., & Buitelaar, J.K. (2017). A Causal and mediation analysis of the comorbidity between attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). *Journal of Autism and Developmental Disorders*, *47*(6), 1595–1604. https://doi.org/10.1007/s10803-017-3083-7

Storebo O. J., Ramstad, E., Krogh, H. B., Nilausen, T. D., Skoog, M., Holmskov, M., Rosendal, S., Groth, C., Magnusson, F. L., Moreira-Maia, C. R., Gillies, D., Buch Rasmussen, K., Gauci, D., Zwi, M., Kirubakaran, R., Forsbol, B., Simonsen, E., & Gludd, C. (2015). Methylphenidate for children and adolescents with attention deficit disorder (ADHD) (Review). *Cochrane Database of Systematic Reviews*, Issue 11. doi: 10.1002/14651858.CD009885.pub2.

Sturman, N., Deckx, L., & van Driel, M. L. (2017). Methylphenidate for children and adolescents with autism spectrum disorder. *Cochrane Database of Systematic Reviews, Issue 11.* Art. No.: CD011144. doi 10.1002/14651858.CD011144.pub2.

Volkow, N., & Swanson, J. M. (2013). Adult attention deficit–hyperactivity disorder. *The New England Journal of Medicine*, *369*(20), 1935–1944. https://doi.org/10.1056/NEJMcp1212625

Wu, J., Xiao, H., Sun, H., Zou, L., & Zhu, L.-Q. (2012). Role of dopamine receptors in ADHD: A systematic meta-analysis. *Molecular Neurobiology*, *45*(3), 605–620. https://doi.org/10.1007/s12035-012-8278-5