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Review

Corticosteroids and the Pharmacological Management of Autism—An Integrative Review

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Abstract: Autism spectrum disorder (ASD), or autism, is a lifelong neurodevelopmental condition typically detected during early childhood, for which no specific and efficient pharmacological management is currently available. No drugs have been developed specifically for the pharmacological management of autism. Thus, this approach often relies on various conventional psychotropic medications and, depending on the condition, other medications may also be used. Some studies available in the literature indicate that the adjunctive use of corticosteroids can help improve the quality of life of individuals with autism. Therefore, we conducted an integrative review using four databases, which were PubMed, Scopus, Web of Science, and Google Scholar, focusing on clinical trials and animal model studies involving corticosteroids related to autism. We analyzed the effects of treatment on core and associated autism symptoms, as well as adverse effects. Eight studies were selected and analyzed, seven involving humans and one using an animal model. These studies focused on the drugs pregnenolone (3), prednisolone (3), hydrocortisone (1), and betamethasone (1) in trials either alone or in combination with other medications (such as risperidone). We observed that corticosteroids safely and effectively reduced several symptoms, including stereotypical and social behaviors, hyperactivity, and irritability. Furthermore, no serious adverse effects were observed, although all selected studies were of short duration. Thus, corticosteroids are promising options to be included in the pharmacological management of autism, whether or not in combination with other medications, and further studies are needed to evaluate their long-term effectiveness.

Keywords: autism; corticosteroids; pharmacotherapy; integrative review

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1. Introduction

Autism spectrum disorder (ASD), or autism, is a lifelong neurological development condition typically detected during early childhood, for which there is no specific and efficient pharmacological management available to date. This condition is identified by impairment in social interactions and verbal and non-verbal communications, associated with stereotypical and repetitive behaviors [1].

Studies indicate that autism can arise due to several factors, such as premature birth, fetal exposure to psychotropic drugs, and exposure to pesticides, among others [2,3]. Its diagnosis remains, to a large extent, clinically subjective, although several scales developed have contributed to improving the evaluation process, providing a more accurate diagnosis over time [1].

Repetitive behaviors tend to contribute to social exclusion and limit children's abilities, causing significant distress for families [4]. A worrying fact is the increase in the prevalence of autism, which has practically quadrupled in recent decades [5]. This increase can be attributed to improved screening tools in children and adults, as well as more refined diagnostic criteria and more accurate behavioral and neuropsychological scales. Although this proportion is believed to be consistent across different racial, ethnic, and socioeconomic backgrounds, it is noteworthy that the prevalence in men can be up to five times higher than in women [6].

Currently, the management of autism mainly involves interventions with non-pharmacological interdisciplinary therapies, with teams made up of doctors, educational psychologists, speech therapists, occupational therapists, behavioral therapists, and psychologists. Interventions aim to promote improvements in language/communication skills, social interactions, parent training, and behavioral changes. Some of the best known include ABA (Applied Behavior Analysis), DIR (Developmental, Individual-differences, and Relationship-based Model) and the TEACCH Autism Program [1]. As for pharmacological management, to date, there are no drugs developed specifically for this condition. Thus, this approach ends up using several conventional psychotropic medications, such as atypical antipsychotics (especially risperidone and aripiprazole), selective inhibitors, and stimulants. Depending on the condition, other medications may also be used, such as anxiolytics. However, it is important to highlight that these medications are not specific and only aim to control inappropriate behaviors, such as psychomotor agitation, aggressiveness, and obsessive–compulsive symptoms [7–10]. This scenario highlights the importance of continuous research and effective approaches for diagnosing and improving the quality of life of autistic people, aiming to improve individuals' and their families' lives.

One topic that has been evaluated is the relationship, already established by clinical studies, of the hypothalamic–pituitary–adrenal (HPA) axis in autism. The body's response to stress is mediated by the HPA, playing a crucial role in adaptation to the environment. Abnormal HPA axis function in autistic children results in an irregular cortisol excretion rate, correlating with symptom severity [11].

Several studies have investigated the responsiveness of cortisol in autism, revealing a delay in the HPA axis when faced with physiological or physical manipulations. Furthermore, hyporesponsiveness was observed in stressful situations involving social components. However, it is important to note that hyperresponsiveness of the HPA axis has also been documented in contexts involving unpleasant stimuli or certain social contexts [11,12]. These findings highlight the complexity of HPA axis responses in ASD, opening the door for further investigation into how these responses contribute to symptoms.

Therefore, corticosteroids, known to have anti-inflammatory, immunomodulatory, and antineoplastic properties, have been studied for their potential use in the pharmacological management of autism. Studies have already demonstrated that some corticosteroids, alone or in combination with drugs from other therapeutic classes, led to positive effects on brain function related to language and behavioral performance [13–17]. Furthermore, the costs of these drugs are not high, which contributes to public health services, as well as public health, as they can be beneficial to countless individuals. Therefore, the use of corticosteroids, both alone and in combination with other treatments, may represent an effective approach to improving behavioral aspects in autistic people.

Considering the above, this work aimed to identify in the literature the potential for using corticosteroids as adjuvants to the current pharmacological management used for people with autism.

2. Methods

The present study is an integrative review to address in the literature the potential of using corticosteroids as adjuvants to the current pharmacological management used for people with autism.

Data collection was carried out from secondary sources through bibliographical research [18]. The following databases were used: PubMed/Medline, Scopus, Web of Science, and Google Scholar. To search for articles, several descriptors and their combinations in Portuguese and English were used. To screen studies in English, the following descriptors were used: "autism spectrum disorder" OR "autism pharmacotherapy" OR "autism treatment" OR "corticosteroids treatment autism spectrum disorder". In the selection of articles in Portuguese, the following descriptors were used: "transtorno do espectro do autismo" OR "tratamento para transtorno do espectro do autismo" OR "corticosteroides transtorno do espectro do autismo" OR "tratamento corticosteroide autismo". The research period covered publications up to the year 2023.

We used as inclusion criteria articles written in English and Portuguese which aimed to establish a relationship between the use of corticosteroids in the treatment of ASD. Studies could be conducted in animal models or in humans. Case studies, book chapters, comments, letters to the editor, and reviews, as well as articles published in non-indexed journals and articles with missing or incomplete data, were excluded.

The studies were retrieved from the databases and were checked to detect duplicates, which were properly removed. Next, the title and abstract were reviewed to identify studies that addressed the review question. The studies included at this stage had their full texts analyzed to verify the eligibility criteria.

Information for identification (main author, year of publication, country where the study was conducted), study objective, design, sample size, type of corticosteroid used, investigated outcomes, and main conclusions were extracted from the studies. Data were synthesized narratively to produce the review.

For the critical analysis of the included studies, we classified the levels of evidence according to Souza, da Silva, and Carvalho [18] as follows: Level 1: evidence resulting from the meta-analysis of multiple randomized controlled clinical studies; Level 2: evidence obtained in individual studies with an experimental design; Level 3: evidence from quasi-experimental studies; Level 4: evidence from descriptive (non-experimental) studies or with a qualitative approach; Level 5: evidence from case reports or experience (articles excluded); Level 6: evidence based on expert opinions (articles excluded).

3. Results and Discussion

A total of 620 articles that fit the descriptors used in the search were identified in the databases (Figure 1). After removing duplicate results, 173 articles remained, of which eight studies were included in the review.

The eight studies [13,16,17,19–23] that make up this review evaluated the use of corticosteroids in the pharmacological management of autism in a total of 400 patients. The sample sizes ranged from 12 to 148 participants, mostly composed of people with a mean age of 5.9 to 22.5 years and of both sexes. Participants' weights ranged from 20 to 45 kg (Table 1), except in one article that used a sheep model [23] (Table 2).

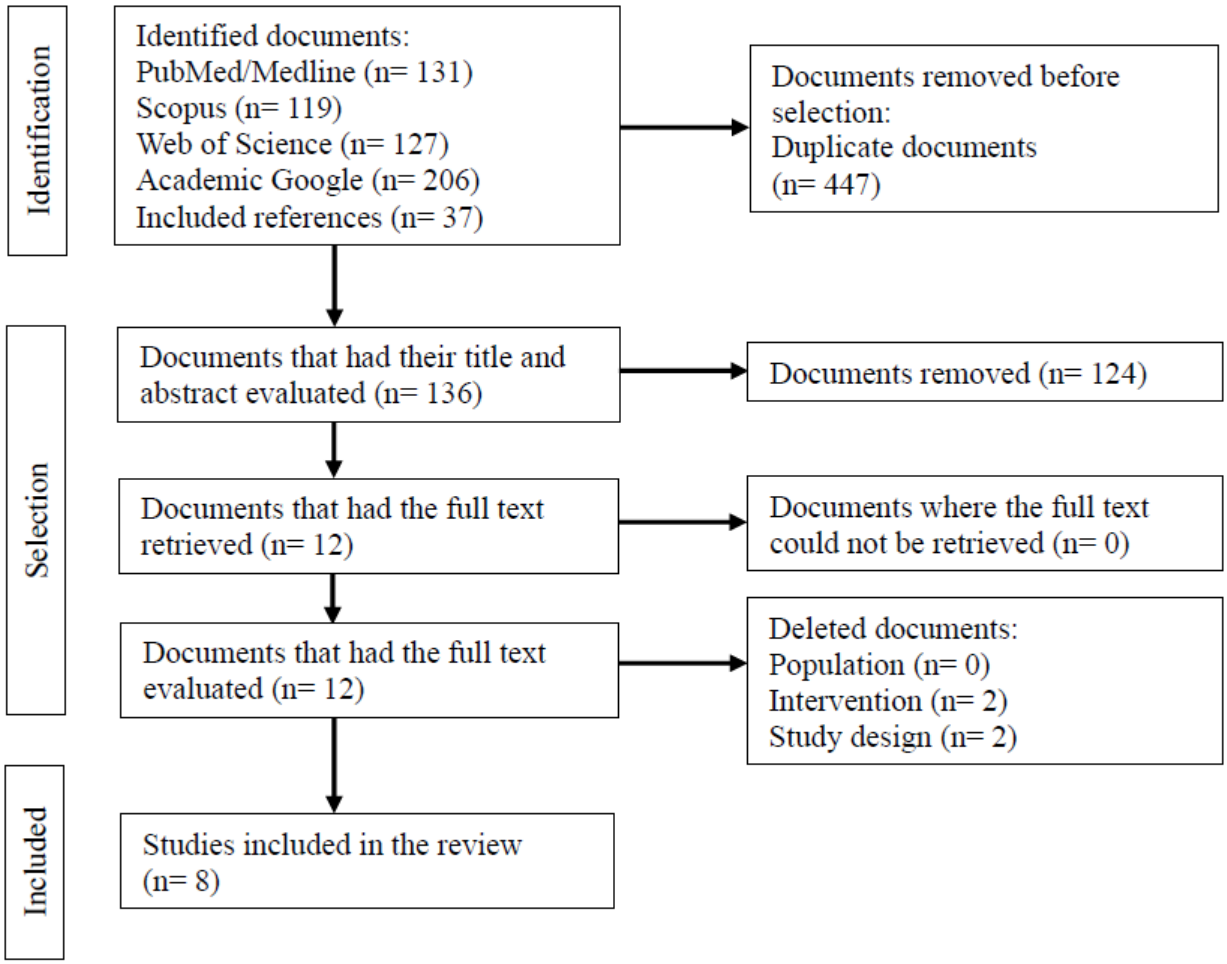

Figure 1. Study selection flowchart.

Table 1. Studies selected for the integrative review on the use of corticosteroids in the pharmacological management of autism.

References	Design/Number of Patients	Mean Age	Sex	Objective	Investigated Drug
Majewska et al. [19]	Cohort n = 148	5.9 ± 3.5 years	Men: 79 Women: 69	To evaluate the potential of steroid hormones in autism.	Pregnenolone
Fung et al. [20]	Prospective n = 12	22.5 ± 5.8 years	Men: 10 Women: 2	To evaluate the tolerability and efficacy of pregnenolone in reducing irritability in autistic adults.	Pregnenolone
Duffy et al. [13]	Retrospective n = 44	4.5 ± 2.2 years	Men: 36 Women: 8	To evaluate the effects of corticosteroids in autistic children on the 4 Hz frequency-modulated auditory-evoked response (FMAER) originating from the language cortex of the superior temporal gyrus, EEG language, and behavior.	Prednisolone

Table 1. *Cont.*

References	Design/Number of Patients	Mean Age	Sex	Objective	Investigated Drug
Corbett et al. [21]	Experimental n = 25	9.7 ± 1.9 years	Men: 22 Women: 3	To evaluate the relationship between cortisol and oxytocin in autistic children under baseline and physiological stress conditions (hydrocortisone challenge).	Hydrocortisone
Ayatollahi et al. [22]	Experimental n = 59	13.31 ± 2.12 years	Men: 36 Women: 23	To evaluate the efficacy and safety of the combination of pregnenolone and risperidone in autistic adolescents.	Pregnenolone
Brito et al. [17]	Experimental n = 38	4.8 ± 1.3	Men: 38	To describe the effect of prednisolone on language in autistic children.	Prednisolone
Malek et al. [16]	Experimental n = 26	6.34 ± 2.07	Men: 25 Women: 1	To evaluate the efficacy and safety of prednisolone as an adjuvant treatment to risperidone in children with regressive autism.	Prednisolone

Table 2. Study in an animal model selected for the integrative review on the use of corticosteroids in the pharmacological management of autism.

References	Design/Number of Animals	Objective	Investigated Drug
Kuypers et al. [23]	Experimental n = 37	To evaluate the effect of prenatal glucocorticoids in modulating brain inflammation in an animal model.	Betamethasone

Although there are many corticosteroids, among the studies that met the selection criteria, the evaluation of only three representatives can be observed, including prednisone (3), hydrocortisone (1), and betamethasone (1). Three other studies evaluated the use of pregnenolone, an endogenous corticosteroid precursor, and derivatives.

Of the studies with prednisolone, two present Level 2 evidence [16,17], which stands out because it was possible to check the improvement of core and associated symptoms, as well as development and language parameters, both individually [17] and in association with risperidone [16] (Tables 1 and 2). The selected articles identified that the use of corticosteroids in autistic people is effective and safe for both sexes, leading to a significant improvement in several parameters, such as irritability, stereotypical behavior, language, and social behavior (Table 3). Furthermore, the beneficial effects of these medications can be enhanced by combining other therapies. The most common adverse effects were dizziness, abdominal pain, headache, insomnia, and increased appetite, with no more serious adverse effects observed.

Table 3. Outcomes of the studies included in the integrative review on the use of corticosteroids in the pharmacological management of autism.

Study	Interventions	Outcome	Conclusion	Level of Evidence
Majewska et al. [19]	Pregnenolone (plus derivatives) vs. dehydroepiandrosterone—DHEA vs. androstenediol vs. androstenedione (plus derivatives)	The association between autism and high levels of several steroid hormones in the saliva of prepubertal children was found in both sexes.	Steroid levels could potentially serve as biomarkers of autism for all prepubertal children; it favors treatment with this class of drugs.	II
Fung et al. [20]	Pregnenolone vs. placebo	Pregnenolone improved the parameters assessed on the ABC-I scale after 12 weeks of treatment, as well as the variables of lethargy and social withdrawal.	Pregnenolone is effective, safe, and well tolerated. It reduces irritability, improves social functioning, and alleviates sensory dysfunctions. Adverse effects are milder compared to other medications.	II
Duffy et al. [13]	Prednisolone vs. placebo	Steroid therapy improved electrophysiological indicators of language-specific brain function. Furthermore, there was an improvement in language and behavioral performance.	Prednisone treatment is effective in treating the symptoms of autism, specifically language-related symptoms.	I
Corbett et al. [21]	Hydrocortisone vs. placebo	There was a significant increase in oxytocin during the experimental condition. The results demonstrated that oxytocin reduced stress levels during hydrocortisone administration. Therefore, it interacted with the social capacity of autistic children. The diminished moderating effect of oxytocin on cortisol also played a contributory role in the increased stress often observed in autistic children.	Hydrocortisone treatment modulates the effects of oxytocin on social behavior, as well as on functional interaction and stress modulation.	II
Ayatollahi et al. [22]	Pregnenolone vs. placebo	Pregnenolone treatment significantly improved irritability, stereotypy, and hyperactivity scales. There were no serious adverse effects between the groups.	The administration of pregnenolone has proved effective in the pharmacological management of autistic adolescents.	II
Brito et al. [17]	Prednisolone vs. placebo	The treatment increased the global Assessment of Language Development score. The total number of communicative acts was also positive. Adverse effects were mild.	Prednisolone generates positive effects even at low doses.	II

Table 3. *Cont.*

Study	Interventions	Outcome	Conclusion	Level of Evidence
Malek et al. [16]	Risperidone + prednisolone vs. risperidone + placebo	The treatment was able to improve irritability, lethargy, stereotypy, and hyperactivity subscale scores. Likewise, a significant decline for all inflammatory markers assessed was induced.	Pharmacological management with prednisolone is effective for both behavior and molecular parameters.	II
Kuypers et al. [23] (obs: animal model)	Control vs. lipopolysaccharide (LPS) vs. betamethasone vs. pre-betamethasone + LPS	Treatment with antenatal glucocorticoids administered before LPS reduced the effects of intrauterine inflammation in the fetal brain. The results demonstrate that betamethasone before LPS can prevent inflammatory effects.	Antenatal betamethasone administered before intra-amniotic inflammation reduced the cerebral inflammatory response after intra-amniotic LPS and prevented hippocampal and white matter lesions in the fetal brain.	II

Corticosteroids are a class of steroid hormones secreted by the adrenal gland in response to stress. Since their discovery in the 1940s, these substances have been used in particular due to their immunosuppressive and/or anti-inflammatory effects [23]. These medications inhibit apoptosis and the demargination of neutrophils and inhibit NF-Kappa B and other inflammatory transcription factors. Phospholipase A2 is also inhibited, leading to a decrease in the formation of arachidonic acid derivatives. Finally, they also promote the expression of anti-inflammatory genes, such as interleukin-10 [24].

Studies using both animal models and humans also suggest that corticosteroids can modulate the activation of microglia, indicating their ability to modulate brain activity [25]. Furthermore, it has been observed that these substances can increase the number of natural killer cells [26] and reduce blood levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), in the first weeks of administration.

Some studies suggest that its use could contribute to reducing autism symptoms. In our integrative review, the included studies suggest an improvement in parameters such as irritability, stereotypical behavior, language, and social behavior, with common adverse effects.

The study by Duffy et al. [13], despite presenting a lower level of evidence, reinforces the potential for improvement in language development parameters. The results observed also indicated that autistic children may present dysfunctions in the HPA axis, evidenced by an irregular pattern of cortisol excretion correlated with the severity of symptoms [11]. In this context, Duffy et al. [13] associated improvements in specific indicators of electrophysiological brain functions related to language, measured by the frequency-modulated auditory-evoked response (FMAER), as well as behavioral performance [13]. It has also been observed that the use of prednisone over time results in significant improvements in language skills, expression, and social behavior in autistic children [17]. Furthermore, prednisolone combined with risperidone has been demonstrated to improve irritability, hyperactivity, lethargy, and stereotypical behavior in children with regressive autism [16].

In general, studies indicated a beneficial effect of prednisolone compared to a placebo [13,16,17], especially in reducing irritability, lethargy, stereotypical behavior, and/or hyperactivity in children. These findings suggest prednisone is potentially useful in pharmacological management, although more research is needed to fully understand its effects and underlying mechanisms.

The work of Corbett et al. [21] evaluated oxytocin and cortisol, both key neuromodulators of biological and behavioral responses and which have a synergistic effect. They

have already been implicated in autism but are rarely investigated together. The results showed that hydrocortisone, a corticosteroid used mainly as a topical anti-inflammatory medication, modulates the effects of oxytocin on social behavior, as well as functional interaction and stress modulation. These results not only help to evaluate the potential of corticosteroids as potentially useful in pharmacological management, but also increase the understanding of how oxytocin acts as a stress-modulating agent in individuals. Oxytocin receptor agonists have already been developed and studied as potential new drugs for the pharmacological management of autism [27].

Studies with pregnenolone, a precursor of steroid hormones synthesized in various tissues, including the brain and lymphocytes, proved to be very interesting. This precursor can be classified as a neurosteroid and can also exert rapid actions on the cell membrane through allosteric interactions with the GABA-A receptor. Its ability to act as an anti-inflammatory and/or immunoregulatory agent in several neuro-inflammatory pathologies is recognized [28,29]. Aggelakopoulou et al. [30] proposed that this substance is capable of suppressing the pro-inflammatory activation of microglial cells in humans and animal models. Furthermore, it is also the precursor to a variety of other corticosteroids, such as allopregnanolone and pregnenolone sulfate [31], the latter being a modulator of N-methyl-D-aspartate (NMDA) receptors [32]. Allopregnanolone also regulates GABA-A receptors [31] and, subsequently, the sulfated form of pregnenolone proved to modulate NMDA receptors [32]. These receptors may be related to the development of autism, as they are critical for synaptic plasticity in the central nervous system [33].

Studies have suggested multiple pathways through which these substances may influence core and associated symptoms of autism. Majewska et al. [19], in this sense, identified an association with high levels of several steroid hormones in the saliva of prepubertal children, pointing to the potential of these hormonal levels as biomarkers of autism, which, in turn, favors treatment with this class of medicines. This suggests a more targeted and personalized approach to management based on hormonal profiles.

Autism in adults has gained increasing attention in psychiatric settings [34]. Notwithstanding, the study by Fung et al. [20] was the only one in which the effect of corticosteroids in this population was evaluated. The results showed that pregnenolone is also effective, safe, and well tolerated by autistic adults, reducing irritability, improving social functioning, and alleviating sensory dysfunctions. Unfortunately, the number of patients was the lowest among the studies (n = 12).

The study by Malek et al. [16] was the only one to evaluate the association of a corticosteroid with risperidone, one of only two drugs approved by the FDA for the pharmacological management of autism [22]. In this randomized placebo-controlled study, 59 autistic children and adolescents were randomly allocated to treatment with risperidone and a placebo (n = 29) or risperidone and pregnenolone (n = 30) for 10 weeks. Throughout treatment, individuals who received risperidone and pregnenolone showed improvements in irritability, stereotypical behavior, and hyperactivity compared to those who received risperidone and a placebo. Pregnenolone demonstrated a favorable safety profile and was well tolerated, with mild-to-moderate side effects, including changes in appetite, rash, headache, or abdominal pain.

The improvement in symptoms observed with the oral administration of pregnenolone may be associated with greater excitability in the neuronal circuits responsible for the limbic system [35]. Compared to the placebo, allopregnanolone (measured after pregnenolone ingestion) was associated with increased activity in the dorsomedial prefrontal cortex and its connectivity with the amygdala. This increase in connectivity resulted in a reduction in anxiety symptoms. It is noteworthy that pregnenolone has demonstrated positive effects in the treatment of several psychiatric disorders, as evidenced in previous studies [36–38]. Understanding the impact of pregnenolone on the central nervous system opens up interesting perspectives for potential applications.

In addition to human studies, the study with animals (sheep) carried out by Kuypers et al. [23] demonstrated the prevention of inflammatory effects in the brain of

animals by using betamethasone. These data provide a comprehensive view of the results obtained in the reviewed studies and suggest the effectiveness of the use of corticosteroids in different therapeutic approaches. This is in line with other animal studies that have also indicated that corticosteroids can prevent inflammatory effects in the brain [26,38,39].

Taken together, these findings suggest that pharmacological treatment with corticosteroids may provide benefits for autistic individuals, especially children, offering promising perspectives for therapeutic interventions. However, it is important to note that the studies reviewed focus on short-term adverse effects. Autism treatment, however, requires the chronic use of medications, which is a serious issue for corticosteroids, as their use can cause a range of adverse effects, mainly influenced by dose and duration. High doses are linked to severe issues, such as life-threatening infections, while even low-to-moderate doses over time can result in significant side effects. Common side effects include skin thinning and weight gain, while others, such as myopathy, metabolic disorders, cardiac disorders, and osteoporosis, are associated with prolonged use. Osteoporosis, for instance, affects about 40% of users within the first year of use. Adverse effects can be further aggravated by other medications used concurrently or by pre-existing conditions, such as acute lymphoblastic leukemia [25].

Even low doses of corticosteroids can cause serious adverse effects if used long-term. Palmowski et al. [40], in a systematic review and meta-analysis, observed that long-term low doses can reduce the occurrence of certain adverse effects but increase the risk of infections by 40% in patients with rheumatoid arthritis, a condition in which these medications are commonly used. Warrington and Bostwick [41] also found that severe psychiatric reactions can occur in nearly 6% of patients, while mild-to-moderate reactions may occur in about 28%, depending on the dose used. These symptoms primarily include issues such as sleep disturbances, euphoria, hypomania, and depression. Given the nature of autism, it is not advisable to simply include medications that may worsen existing symptoms or introduce new ones.

However, it is essential to conduct further research to strengthen the evidence on the utility of corticosteroids in the treatment of autism and thus better understand the mechanisms underlying the positive effects described and how the dose is related to these effects.

4. Conclusions

This integrative review makes a significant contribution to the field of complementary treatment for autism by highlighting that the use of corticosteroids may offer a safer, more efficient, and higher-quality approach. The findings suggest that corticosteroids, whether as a monotherapy or in combination with other medications, represent a promising approach to the pharmacological management of core and associated symptoms of autism. In addition to demonstrating the treatment's safety and efficacy, the results encourage the development of new corticosteroid-combined therapies for clinical practice. These advances pave the way for more personalized interventions based on specific biomarker profiles, offering more effective and targeted treatments. However, future research is essential to elucidate the underlying mechanisms, optimize dosages, and minimize potential side effects, especially those already known to be associated with prolonged use of this drug class, ensuring safe and effective interventions for individuals with autism.

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References

1. Lord, C.; Elsabbagh, M.; Baird, G.; Veenstra-Vanderweele, J. Autism spectrum disorder. *Lancet* **2018**, *392*, 508–520. [CrossRef] [PubMed]
2. Sharma, S.R.; Gonda, X.; Tarazi, F.I. Autism spectrum disorder: Classification, diagnosis and therapy. *Pharmacol. Ther.* **2018**, *190*, 91–104. [CrossRef] [PubMed]
3. Biosca-Brull, J.; Pérez-Fernández, C.; Mora, S.; Carrillo, B.; Pinos, H.; Conejo, N.M.; Collado, P.; Arias, J.L.; Martín-Sánchez, F.; Sánchez-Santed, F.; et al. Relationship between autism spectrum disorder and pesticides: A systematic review of human and preclinical models. *Int. J. Environ. Res. Public Health* **2021**, *18*, 5190. [CrossRef] [PubMed]
4. Adler, B.A.; Wink, L.K.; Early, M.; Shaffer, R.; Minshawi, N.; McDougle, C.J.; Erickson, C.A. Drug-refractory aggression, self-injurious behavior, and severe tantrums in autism spectrum disorders: A chart review study. *Autism* **2015**, *19*, 102–106. [CrossRef]
5. Zablotsky, B.; Black, L.I.; Blumberg, S.J. Estimated prevalence of children with diagnosed developmental disabilities in the United States, 2014–2016. *NCHS Data Brief* **2017**, *291*, 1–8.
6. Christensen, D.L.; Baio, J.; Van Naarden Braun, K.; Bilder, D.; Charles, J.; Constantino, J.N.; Daniels, J.; Durkin, M.S.; Fitzgerald, R.T.; Kurzius-Spencer, M.; et al. Prevalence and characteristics of Autism Spectrum Disorder among children aged 8 Years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2012. *MMWR Surveill. Summ.* **2018**, *65*, 1–23. [CrossRef]
7. Canitano, R.; Scandurra, V. Risperidone in the treatment of behavioral disorders associated with autism in children and adolescents. *Neuropsychiatr. Dis. Treat.* **2008**, *4*, 723–730. [CrossRef]
8. Stachnik, J.; Gabay, M. Emerging role of aripiprazole for treatment of irritability associated with autistic disorder in children and adolescents. *Adolesc. Health Med. Ther.* **2010**, *15*, 105–114. [CrossRef]
9. Wink, L.K.; Plawecki, M.H.; Erickson, C.A.; Stigler, K.A.; McDougle, C.J. Emerging drugs for the treatment of symptoms associated with autism spectrum disorders. *Expert Opin. Emerg. Drugs* **2010**, *15*, 481–494. [CrossRef]
10. Hurwitz, R.; Blackmore, R.; Hazell, P.; Williams, K.; Woolfenden, S. Tricyclic antidepressants for autism spectrum disorders (ASD) in children and adolescents. *Cochrane Database Syst. Rev.* **2012**, *3*, 1–16. [CrossRef]
11. Priya, M.D.L.; Geetha, A.; Suganya, V.; Sujatha, S. Abnormal circadian rhythm and cortisol excretion in autistic children: A clinical study. *Croat. Med. J.* **2010**, *54*, 33–41. [CrossRef] [PubMed]
12. Taylor, J.L.; Corbett, B.A. A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders. *Psychoneuroendocrinology* **2014**, *49*, 207–228. [CrossRef]
13. Duffy, F.H.; Shankardass, A.; McAnulty, G.B.; Eksioglu, Y.Z.; Coulter, D.; Rotenberg, A.; Als, H. Corticosteroid therapy in regressive autism: A retrospective study of effects on the Frequency Modulated Auditory Evoked Response (FMAER), language, and behavior. *BMC Neurol.* **2014**, *14*, 70. [CrossRef] [PubMed]
14. Wan, E.S.; Qiu, W.; Baccarelli, A.; Carey, V.J.; Bacherman, H.; Rennard, S.I.; Agustí, A.; Anderson, W.H.; Lomas, D.A.; DeMeo, D.L. Systemic steroid exposure is associated with differential methylation in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2012**, *186*, 1248–1255. [CrossRef]
15. Golla, S.; Sweeney, J.A. Corticosteroid therapy in regressive autism: Preliminary findings from a retrospective study. *BMC Med.* **2014**, *12*, 79. [CrossRef] [PubMed]
16. Malek, M.; Ashraf-Ganjouei, A.; Moradi, K.; Bagheri, S.; Mohammadi, M.R.; Akhondzadeh, S. Prednisolone as adjunctive treatment to risperidone in children with regressive type of Autism Spectrum Disorder: A randomized, placebo-controlled trial. *Clin. Neuropharmacol.* **2020**, *43*, 39–45. [CrossRef] [PubMed]
17. Brito, A.R.; Vairo, G.P.T.; Dias, A.P.B.H.; Olej, B.; Nascimento, O.J.M.; Vasconcelos, M.M. Effect of prednisolone on language function in children with autistic spectrum disorder: A randomized clinical trial. *J. Pediatr.* **2021**, *97*, 22–29. [CrossRef]
18. Souza, M.T.; da Silva, M.D.; de Carvalho, R. Integrative review: What is it? How to do it? *Einstein* **2010**, *8*, 102–106. [CrossRef]
19. Majewska, M.D.; Hill, M.; Urbanowicz, E.; Rok-Bujko, P.; Bieńkowski, P.; Namysłowska, I.; Mierzejewski, P. Marked elevation of adrenal steroids, especially androgens, in saliva of prepubertal autistic children. *Eur. Child Adolesc. Psychiatry* **2014**, *23*, 485–498. [CrossRef]
20. Fung, L.K.; Libove, R.A.; Phillips, J.; Haddad, F.; Hardan, A.Y. Brief report: An open-label study of the neurosteroid pregnenolone in adults with autism spectrum disorder. *J. Autism Dev. Disord.* **2014**, *44*, 2971–2977. [CrossRef]
21. Corbett, B.A.; Bales, K.L.; Swain, D.; Sanders, K.; Weinstein, T.A.; Muglia, L.J. Comparing oxytocin and cortisol regulation in a double-blind, placebo-controlled, hydrocortisone challenge pilot study in children with autism and typical development. *J. Neurodev. Disord.* **2016**, *8*, 32. [CrossRef] [PubMed]
22. Ayatollahi, A.; Bagheri, S.; Ashraf-Ganjouei, A.; Moradi, K.; Mohammadi, M.R.; Akhondzadeh, S. Does pregnenolone adjunct to risperidone ameliorate irritable behavior in adolescents with Autism Spectrum Disorder: A randomized, double-blind, placebo-controlled clinical trial? *Clin. Neuropharmacol.* **2020**, *43*, 139–145. [CrossRef] [PubMed]
23. Kuypers, E.; Jellema, R.K.; Ophelders, D.R.; Dudink, J.; Nikiforou, M.; Wolfs, T.G.; Nitsos, I.; Pillow, J.J.; Polglase, G.R.; Kemp, M.W.; et al. Effects of intra-amniotic lipopolysaccharide and maternal betamethasone on brain inflammation in fetal sheep. *PLoS ONE* **2013**, *8*, e81644. [CrossRef] [PubMed]
24. Williams, D.M. Clinical pharmacology of corticosteroids. *Respir. Care* **2018**, *63*, 655–670. [CrossRef] [PubMed]

25. Yasir, M.; Goyal, A.; Sonthalia, S. Corticosteroid adverse effects. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK531462/ (accessed on 10 November 2024).
26. Sugama, S.; Takenouchi, T.; Fujita, M.; Kitani, H.; Conti, B.; Hashimoto, M. Corticosteroids limit microglial activation occurring during acute stress. *Neuroscience* **2013**, *232*, 13–20. [CrossRef]
27. Eddy, J.L.; Krukowski, K.; Janusek, L.; Mathews, H.L. Glucocorticoids regulate natural killer cell function epigenetically. *Cell Immunol.* **2014**, *290*, 120–130. [CrossRef]
28. Frantz, M.; Pellissier, L.P.; Pflimlin, E.; Loison, S.; Gandía, J.; Marsol, C.; Durroux, T.; Mouillac, B.; Becker, J.A.; Le Merrer, J.; et al. LIT-001, the first nonpeptide oxytocin receptor agonist that improves social interaction in a mouse model of autism. *J. Med. Chem.* **2018**, *61*, 8670–8692. [CrossRef]
29. Murugan, S.; Jakka, P.; Namani, S.; Mujumdar, V.; Radhakrishnan, G. The neurosteroid pregnenolone promotes degradation of key proteins in the innate immune signaling to suppress inflammation. *J. Biol. Chem.* **2019**, *294*, 4596–4607. [CrossRef]
30. Aggelakopoulou, M.; Kourepini, E.; Paschalidis, N.; Simoes, D.C.; Kalavrizioti, D.; Dimisianos, N.; Papathanasopoulos, P.; Mouzaki, A.; Panoutsakopoulou, V. ERβ-dependent direct suppression of human and murine Th17 cells and treatment of established central nervous system autoimmunity by a neurosteroid. *J. Immunol.* **2016**, *197*, 2598–2609. [CrossRef]
31. Hosie, A.M.; Wilkins, M.E.; da Silva, H.M.; Smart, T.G. Endogenous neurosteroids regulate GABAA receptors through two discrete transmembrane sites. *Nature* **2006**, *444*, 486–490. [CrossRef]
32. Kostakis, E.; Smith, C.; Jang, M.K.; Martin, S.C.; Richards, K.G.; Russek, S.J.; Gibbs, T.T.; Farb, D.H. The neuroactive steroid pregnenolone sulfate stimulates trafficking of functional N-methyl D-aspartate receptors to the cell surface via a noncanonical, G protein, and Ca^{2+}-dependent mechanism. *Mol. Pharmacol.* **2013**, *84*, 261–274. [CrossRef] [PubMed]
33. Lee, K.; Mills, Z.; Cheung, P.; Cheyne, J.E.; Montgomery, J.M. The role of zinc and NMDA receptors in Autism Spectrum Disorders. *Pharmaceuticals* **2023**, *16*, 1. [CrossRef] [PubMed]
34. Nyrenius, J.; Waern, M.; Eberhard, J.; Ghaziuddin, M.; Gillberg, C.; Billstedt, E. Autism in adult psychiatric out-patients: Self-reported suicidal ideation, suicide attempts and non-suicidal self-injury. *BJPsych Open* **2023**, *9*, e167. [CrossRef] [PubMed]
35. Marx, C.E.; Keefe, R.S.; Buchanan, R.W.; Hamer, R.M.; Kilts, J.D.; Bradford, D.W.; Strauss, J.L.; Naylor, J.C.; Payne, V.M.; Lieberman, J.A.; et al. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. *Neuropsychopharmacology* **2009**, *34*, 1885–1903. [CrossRef]
36. Osuji, I.J.; Vera-Bolaños, E.; Carmody, T.J.; Brown, E.S. Pregnenolone for cognition and mood in dual diagnosis patients. *Psychiatry Res.* **2010**, *178*, 309–312. [CrossRef]
37. Ritsner, M.S.; Gibel, A.; Shleifer, T.; Boguslavsky, I.; Zayed, A.; Maayan, R.; Weizman, A.; Lerner, V. Pregnenolone and dehydroepiandrosterone as an adjunctive treatment in schizophrenia and schizoaffective disorder: An 8-week, double-blind, randomized, controlled, 2-center, parallel-group trial. *J. Clin. Psychiatry* **2010**, *71*, 1351–1362. [CrossRef]
38. Wang, X.; Sun, Z.; Yang, T.; Lin, F.; Ye, S.; Yan, J.; Li, T.; Chen, J. Sodium butyrate facilitates CRHR2 expression to alleviate HPA axis hyperactivity in autism-like rats induced by prenatal lipopolysaccharides through histone deacetylase inhibition. *mSystems* **2023**, *8*, e0041523. [CrossRef]
39. Kirsten, T.B.; Lippi, L.L.; Bevilacqua, E.; Bernardi, M.M. LPS exposure increases maternal corticosterone levels, causes placental injury and increases IL-1B levels in adult rat offspring: Relevance to autism. *PLoS ONE* **2013**, *8*, e82244. [CrossRef]
40. Palmowski, A.; Nielsen, S.M.; Boyadzhieva, Z.; Schneider, A.; Pankow, A.; Hartman, L.; Da Silva, J.A.; Kirwan, J.; Wassenberg, S.; Dejaco, C.; et al. Safety and Efficacy Associated with long-term low-dose glucocorticoids in rheumatoid arthritis: A systematic review and meta-analysis. *Rheumatology* **2023**, *62*, 2652–2660. [CrossRef]
41. Warrington, T.P.; Bostwick, J.M. Psychiatric adverse effects of corticosteroids. *Mayo Clin. Proc.* **2006**, *81*, 1361–1367. [CrossRef]