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CRITICAL REVIEW

Sedation and its Potential Risks in Children with Autism Spectrum Due to Drug Overlaps: A Critical Review

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ABSTRACT

Objective: To analyse pharmacological overlap in patients with autism spectrum disorder (ASD) under conscious sedation in a dental office environment, identifying any potential risks and complications. **Material and Methods:** A critical review was conducted by selecting articles from online databases (Pubmed and Lilacs), using a search algorithm and eligibility criteria. The Medscape® platform was used to verify interactions between drugs commonly used by patients with ASD and medications used for sedation in paediatric dentistry. **Results:** Due to their polydrug use, children with ASD are at risk of complications, namely Serotonin Syndrome (SS), Neuroleptic Malignant Syndrome (NMS), increase or decrease of the QT interval (QTi) and Torsade de Pointes (TdP), due to pre-existence of metabolic syndrome, deepening the sedation level or even leading to a decrease in the sedative capacity of the drugs used. **Conclusion:** It is essential to assess better drug interaction in ASD patients submitted to sedation. The severity of the disorder and the need for sedation for dental treatment are directly proportional. However, increases in sedative doses tend to increase risks and complications in children with ASD.

Keywords: Mental Health; Autistic Disorder; Child Development; Pharmacology; Child.

Introduction

Autism Spectrum Disorder (ASD) is an inherited and highly heterogeneous neurodevelopmental disorder with a prevalence of 1 in 59 children in the United States [1]. Diagnosis involves clinical observation and grouping of social and behavioural symptoms [2]. The behavioural disorders most associated with ASD are irritability, self-aggressive behaviour, tantrums, anxiety, phobias, attention deficit hyperactivity disorder (ADHD), psychosis, bipolar disorder, and mood disorder, which often need to be controlled for better social interaction [1,3]. Therefore, due to its complexity, diagnosis and treatment of ASD frequently require an interprofessional team [2].

Treatment of the disorder involves a range of drug and non-drug therapies, respecting the particularities of the child with ASD and family adherence [1]. The inclusion of a pharmacological routine for these children is related to the severity of the disorder and its correlated symptoms, as well as the difficulty in accessing nonpharmacological therapy services [1,4]. Pharmacological protocols worldwide are focused on symptoms and individuality, i.e., restoring quality of life [3]. A wide range of medications is used to control behaviours, such as anxiolytics, antipsychotics, serotonin reuptake inhibitors, GABA-modulating agents, or even stimulants and hormone therapies [3,4].

The innate management and behavioural characteristics of patients with ASD permeate through the inability to adhere to new routines and to environments considered hostile, as dental offices are often referred to[1]. Therefore, the management of nonpharmacological behaviour in these environments frequently fails. Thus, conscious sedation or even general anaesthesia tends to be a viable alternative for the successful execution of dental treatments [1,5]. Considering that patients with ASD tend to be considered polypharmacological patients, the addition of sedative agents may generate risks of increasing the effects of drugs, leading children to a deep sedation condition, being at risk of medical complications such as vomiting, laryngospasm, cardiorespiratory depression, and risk of death [4,6].

A critical analysis of drug overlap in patients with autistic spectrum disorder submitted to conscious sedation in a dental setting is necessary. To this end, the main drug interactions for the management of ASD and sedative agents commonly used in paediatric dentistry will be discussed, addressing their risks and complications.

Material and Methods

This present review was based on the following guiding question: To which potential risks and complications are children with ASD subjected when submitted to conscious sedation in paediatric dentistry?

As inclusion criteria, original scientific research and review articles published in full that answered the guiding question were adopted, as well as manuals and guidelines highlighting protocols regarding the pharmacological management of children with ASD. There were no language or publication period restrictions. Duplicate results on different search platforms, editorials, letters to the editor, abstracts published in conference proceedings, theses, and dissertations were excluded from this review.

The bibliographic search was conducted from February to August 2023, using the Latin American and Caribbean Literature in Health Sciences (Lilacs) and US National Library of Medicine (PubMed) databases. The electronic search combined MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors) descriptors interspersed by Boolean operators. The publication period of eligible studies was not limited. To further capture studies on the topic, a broad search strategy was used in the PubMed and Lilacs databases,

respectively: (Autism Spectrum Disorder) AND (Psychopharmacology); (Autism Spectrum Disorder) AND (Psychopharmacology).

The total number of articles found on both search platforms was 270. The results were analyzed according to title, abstract, and keywords. Articles that did not answer the guiding question of this study were excluded (n = 262), and the others were read in full. Thus, the works carried out by Aishworiya et al. [7], Eissa et al. [8], Howes et al. [3], and Persico et al. [9] on the pharmacological treatment of ASD were used as references to establish the drugs used in the treatment of ASD and its related symptoms and the drugs commonly used for moderate sedation in children were taken from the books edited by Malamed [10] and Dock [11].

In order to draw a parallel between these drugs, the Medscape® [12] platform was used to verify the existence of drug interactions, as well as any potential complications and risks.

Results

Among the main medications used for sedation in paediatric dentistry, it was found that benzodiazepines (Diazepam and Midazolam) and first-generation antihistamines (Promethazine, Hydroxyzine, and Diphenhydramine) are the most commonly used classes of drugs. However, as this was a population with ASD, about 40 medications were listed. Studies verified that, due to pre-existing metabolic syndrome and their polydrug use, children with ASD have increased risks of complications, namely increased effects of sedation or lower sedative capacity of the drugs used, serotonin syndrome, as well as neuroleptic malignant syndrome, increase or decrease of the QT interval (QTi) and Torsade de Pointes (TdP).

The interaction between antidepressants and benzodiazepines usually leads to increased sedation or more significant effects of these sedatives, as seen in the interaction between Fluvoxamine and Midazolam. The interaction between antidepressants and first-generation antihistamines often leads to changes in QTc. In addition to changing the QTc, cyclic antidepressants cause increased sedation and anticholinergic effects, as observed through the interaction between Nortriptyline and Promethazine (Table 1).

The interaction between antipsychotics and benzodiazepines commonly causes an increase in the effect of depressants in the central nervous system, especially considering the joint action of Clozapine and Diazepam, which deepens sedation levels. Besides increasing the level of sedation, the interaction between first-generation antipsychotics and antihistamines, namely the association between Clozapine and Hydroxyzine, increases the risk of SS and NMS, causing changes in QTc. In turn, the association between antipsychotics, glutamatergic antagonists, and Diphenhydramine commonly causes anticholinergic effects and hypoglycaemia, besides increasing the level of sedation (Table 2).

The interaction between anticonvulsants and sedatives decreases the effects of benzodiazepines and prevents interaction with antihistamines, except for Topiramate, which increases the sedative effect of drugs (Table 3).

The combined use of stimulants, alpha-adrenergic agonists, and sedatives, namely the association between methylphenidate and Promethazine, usually presents cardiovascular effects and increases the level of sedation, leading to an increased risk of arrhythmia or sudden death (Table 4).

Other drugs can also increase the sedation effect when used in combination with antihistamines or benzodiazepines, such as melatonin and cannabidiol. On the other hand, the combined use of acetylcholinesterase inhibitors and antihistamines often alters QTc and cholinergic transmission. However, no effect is reported with benzodiazepines (Table 5).

Table 1. Main interactions and repercussions derived from drug interaction between drugs used for sedation, cyclic antidepressants, and reuptake inhibitors.

Drugs	Diazepam	Midazolam	Promethazine	Hydroxyzine	Diphenhydramine
SSRI					
Citalopram [3,9]	No interactions	No interactions	Both increase serotonin levels. Risk of SS and NMS-like reactions.	Hydroxyzine increases Citalopram toxicity by QTc. TdP risk.	No interactions
Fluoxetine [3,8,9]	Fluoxetine increases the level/effect of Diazepam.	No interactions	Fluoxetine increases the level/effect of Promethazine. Both increase QTc.	Same as Citalopram.	Diphenhydramine increases the level/effect of Fluoxetine.
Escitalopram [8,9]	No interactions	No interactions	No interactions	Both increase QTc.	No interactions
Paroxetine [8,9]	No interactions	No interactions	Same as Fluoxetine	Same as Escitalopram	Same as Fluoxetine
Sertraline [8,9]	No interactions	No interactions	Same as Fluoxetine, except for: Both decrease QTc.	Same as Escitalopram	No interactions
Fluvoxamine [3,8,9]	Fluvoxamine increases the level/effect of Diazepam.	Fluvoxamine increases level/effect of midazolam. Risk of hypoventilation, airway obstruction, or apnoea and profound and/or prolonged drug effect.	Both increase QTc.	Same as Escitalopram	No interactions
Venlafaxine [8,9]	No interactions	No interactions	Same as Fluoxetine	Both decrease QTc.	No interactions
sNRI					
Atomoxetine [3,7,9]	No interactions	No interactions	No interactions	Both increase QTc.	Diphenhydramine increases the level/effect of Atomoxetine.
Cyclic antidepressants					
Nortriptyline [8,9]	Both increase sedation.	Both increase sedation.	Both increase QTc. Both increase sedation. One increases the level of the other—additive anticholinergic effects.	Both increase QTc. Both increase sedation.	Diphenhydramine increases the level/effect of Nortriptyline. Both decrease cholinergic effects/transmission. Both increase sedation.
Clomipramine [3,8,9]	Same as Nortriptyline	Same as Nortriptyline	Same as Nortriptyline	Same as Nortriptyline	Same as Nortriptyline
Desipramine [8,9]	Same as Nortriptyline	Same as Nortriptyline	Same as Nortriptyline	Same as Nortriptyline	Same as Nortriptyline
Mirtazapine [9]	Same as Nortriptyline	Same as Nortriptyline	Both decrease QTc. Both increase sedation.	Same as Nortriptyline	Both increase sedation.
Trazodone [9]	Same as Nortriptyline	Same as Nortriptyline	Same as Nortriptyline, except for: One increases the toxicity of the other. Additive hypotensive effects.	Same as Nortriptyline	Both increase sedation. Both decrease cholinergic effects/transmission.

QTc: Corrected QT Interval; TdP: Torsade de Pointes; SS: Serotonin Syndrome; NMS: Neuroleptic Malignant Syndrome; SSRI: Selective Serotonin Reuptake Inhibitor; sNRI: Selective Norepinephrine Reuptake Inhibitor.

Table 2. Main interactions and repercussions derived from drug interaction between drugs used for sedation, antipsychotics, and glutamatergic antagonists.

Drugs	Diazepam	Midazolam	Promethazine	Hydroxyzine	Diphenhydramine
1st Generation Antipsychotic					
Loxapine [9]	Both increase sedation.	Both increase sedation.	Risk of SS and NMS. Both increase antidopaminergic effects, including extrapyramidal symptoms and NMS. Both increase sedation.	Both increase sedation.	Diphenhydramine decreases Loxapine levels. Loxapine increases the effects of Diphenhydramine. Additive anticholinergic effects, possible hypoglycaemia. Both increase sedation.
Haloperidol [9]	Same as Loxapine	Same as Loxapine	Same as Loxapine, plus: Both increase the QTc. Haloperidol increases the level/effect of Promethazine.	Same as Loxapine, plus: Both increase the QTc.	Same as Loxapine, plus: Diphenhydramine increases the level/effect of Haloperidol.
2nd Generation Antipsychotics					
Aripiprazole [3,8,9]	Both increase sedation.	Both increase sedation.	Risk of SS and NMS. Both increase antidopaminergic effects, including extrapyramidal symptoms and NMS. Both increase sedation.	Both increase QTc. Both increase sedation.	Diphenhydramine decreases Aripiprazole levels. Aripiprazole enhances the effects of Diphenhydramine. Additive anticholinergic effects, possible hypoglycaemia. Both increase sedation. Diphenhydramine increases the level/effect of Aripiprazole.
Risperidone [3,8,9]	Same as Aripiprazole	Same as Aripiprazole	Same as Aripiprazole, plus: Both increase QTc.	Same as Aripiprazole	Same as Aripiprazole
Olanzapine [9]	Same as Aripiprazole	Same as Aripiprazole	Same as Aripiprazole, plus: Both decrease QTc.	Same as Aripiprazole	Diphenhydramine decreases levels of Olanzapine. Olanzapine increases the effects of Diphenhydramine. Additive anticholinergic effects, possible hypoglycaemia. Both increase sedation.
Lurasidone [9]	One increases the toxicity of the other. Potential for greater CNS depressant effects when used simultaneously.	One increases the toxicity of the other. Potential for greater CNS depressant effects when used simultaneously.	Risk of SS and NMS. Lurasidone increases the effects of Promethazine. Increased risk of hypotension with concurrent use.	One increases the toxicity of the other. Potential for greater CNS depressant effects when used simultaneously.	One increases the toxicity of the other. Potential for greater CNS depressant effects when used simultaneously.

			Potential for additive effects on the CNS.		
Clozapine [8,9]	Same as Aripiprazole, plus: Potential risk of cardiorespiratory collapse.	Same as Aripiprazole	Same as Aripiprazole	Hydroxyzine increases Clozapine toxicity by QTc. TdP risk. Both increase sedation.	Same as Aripiprazole
Quetiapine [9]	Same as Aripiprazole	Same as Aripiprazole	Same as Aripiprazole	Same as Clozapine	Same as Olanzapine
Ziprasidone [9]	Same as Aripiprazole	Same as Aripiprazole	Same as Risperidone	Same as Clozapine	Same as Olanzapine
Paliperidone [9]	Same as Aripiprazole	Same as Aripiprazole	Same as Risperidone	Same as Aripiprazole	Same as Olanzapine
Amisulpride [9]	No interactions	No interactions	Both increase QTc.	Both increase QTc.	No interactions
Glutamatergic antagonist					
Amantadine [3,8,9]	No interactions	No interactions	No interactions	No interactions	Increased potential for anticholinergic adverse effects.

QTc: Corrected QT Interval; TdP: Torsade de Pointes; SS: Serotonin Syndrome; NMS: Neuroleptic Malignant Syndrome; CNS: Central Nervous System.

Table 3. Main interactions and repercussions derived from drug interaction between drugs used for sedation, anticonvulsants, and GABAergic agonists.

Drugs	Diazepam	Midazolam	Promethazine	Hydroxyzine	Diphenhydramine
Anticonvulsant and mood stabiliser					
Topiramate [9]	Topiramate increases the level/effect of Diazepam. Both increase sedation.	Topiramate increases the level/effect of Midazolam. Both increase sedation.	Both increase sedation.	Both increase sedation.	Both increase sedation.
Phenytoin [9]	Phenytoin decreases the level/effect of Diazepam.	Phenytoin decreases the level/effect of Midazolam.	No interactions	No interactions	No interactions
Carbamazepine [9]	Same as Phenytoin, plus: Diazepam increases Carbamazepine levels. Carbamazepine decreases Diazepam levels.	Same as Phenytoin	No interactions	No interactions	No interactions
Oxcarbazepine [9]	Same as Phenytoin, plus: Oxcarbazepine increases the level/effect of Diazepam.	Same as Phenytoin	No interactions	No interactions	No interactions
Lithium [9]	No interactions	No interactions	Risk of neurotoxicity. Multiple mechanisms are involved.	Both increase QTc.	No interactions
GABAergic Agonist					
Arbaclofen/Baclofen [3,7]	Both increase sedation.	Both increase sedation.	Both increase sedation.	Both increase sedation.	Both increase sedation.

Corrected QT Interval.

Table 4. Main interactions and repercussions derived from drug interaction between drugs used for sedation, stimulants, and alpha-adrenergic agonists.

Drugs	Diazepam	Midazolam	Promethazine	Hydroxyzine	Diphenhydramine
Stimulant					
Methylphenidate [3,7–9]	No interactions	No interactions	Risk of cardiac arrhythmia or sudden death.	No interactions	No interactions
Alpha-adrenergic agonist					
Clonidine [3,7–9]	One increases the toxicity of the other. Coadministration increases CNS depressant effects.	No interactions	Additive hypotensive effects; possible delirium.	One increases the toxicity of the other. Coadministration increases CNS depressant effects.	No interactions
Guanfacine [3,7–9]	No interactions	No interactions	Same as clonidine	No interactions	No interactions
Lofexidine [3]	Both increase sedation.	Both increase sedation.	Both increase sedation.	Both increase QTc. Both increase sedation.	Both increase sedation.

QTc: Corrected QT Interval; CNS: Central Nervous System.

Table 5. Main interactions and repercussions derived from drug interaction between drugs used for sedation and various drugs of interest to the autistic patient.

Drugs	Diazepam	Midazolam	Promethazine	Hydroxyzine	Diphenhydramine
Neurohormone					
Melatonin [3,8]	Both increase sedation.	Both increase sedation.	Both increase sedation.	Both increase sedation.	Both increase sedation.
AChEi					
Donepezil [8]	No interactions	No interactions	Both decrease QTc.	Both increase QTc.	Donepezil increases, and Diphenhydramine decreases cholinergic transmission/effects. Donepezil decreases the effects of Diphenhydramine. Diphenhydramine increases the level/effect of Donepezil.
Galantamine [8]	No interactions	No interactions	No interactions	No interactions	Same as Donepezil
Other					
Cannabidiol [7]	Cannabidiol increases the level/effect of Diazepam.	No interactions	No interactions	No interactions	No interactions
Metformin [7]	No interactions	No interactions	Promethazine decreases the effects of Metformin. Risk of hypoglycaemia.	No interactions	No interactions

QTc: Corrected QT Interval; AChEi: Acetylcholinesterase Inhibitor.

Discussion

Conscious sedation in the dental office, especially for children with autistic spectrum disorder (ASD), aims at better managing behavioural and movement patterns, ensuring the safety and completion of treatment [5]. Such a procedure may also prevent co-occurrences, such as aggressiveness, anxiety, tantrums, inattention, phobias, hyperactivity, and irritability [1].

The choice of drugs administered to induce conscious sedation in the dental office may be influenced by pre-existing factors, such as the induction or inhibition of enzymes responsible for the metabolism of drugs, i.e., the metabolization of drugs in the body can be modulated accidentally or deliberately by modifying the number of enzymes responsible for processing a given substance [13,14], in particular, due to competition with the cytochrome P450 enzyme. Thus, a specific drug may have its action increased or decreased due to the induction or inhibition of a second drug. When planning sedation procedures in patients with ASD, health professionals may encounter children using more than one modulating drug, which may generate, aggravate or prolong complications by deepening the sedation (or anaesthetic) level, serotonin syndrome, neuroleptic malignant syndrome, increased or decreased QTc and Torsade de Pointes, or even by not obtaining any clinically satisfactory level of sedation.

The singularity of conscious sedation in children with autism spectrum disorder (ASD) is mainly a result of the interaction between daily and sedative drugs, both in the CNS and in peripheral systems or key organs for maintaining homeostasis, namely the cardiovascular system, respiratory system, liver, and skeletal muscles. Communication and reaction to stimuli are necessary to assess sedation levels due to the risk of cardiorespiratory complications. However, in patients with ASD, both communication and the reaction to stimuli may be impaired and inadequate to evaluate the severity of loss of consciousness.

ASD patients are more likely to develop metabolic syndrome, which is characterised by hyperglycaemia, type 2 diabetes mellitus, hypertension, and obesity [15]. In these patients, obesity is a recurrent condition. However, reduced doses of sedatives are recommended [5], as when calculating doses based on the weight of a patient with an elevated body mass index (BMI), the amount administered will be more significant than necessary [16]. In addition, benzodiazepines, drugs commonly used for sedation in these patients, are liposoluble and accumulate in subjects with larger amounts of fat tissue. Therefore, predictability must be assured, as administration of a larger volume of sedatives may lead to loss of the protective reflexes of airways [5].

Paradoxically, even in the possibility of desaturation and apnoea, conscious sedation of children with autism and high BMI may require higher doses of sedatives. Acoustic hypersensitivity, increased amounts of serum glutamate, and abnormalities of the GABAergic system elucidate, in part, the increased need for sedatives [17,18]. The severity of the disorder, anxiety, hyperphobia, and combativeness endorse the need for a higher dosage of sedatives to ensure successful dental treatment in children with autism [19].

Increased sedation can be achieved through the interaction between the central nervous system and depressant drugs such as benzodiazepines, barbiturates, first-generation antihistamines, and opioid analgesics [6]. With this, sedation levels may deepen loss of consciousness (a consequence of the inhibition of the ascending reticular activating system), loss of the protective reflexes of the upper airways, and decrease in respiratory rate (a consequence of the inhibition of brainstem respiratory nuclei) [20,21]. Such increased sedation may be remarkably delicate in paediatric patients with ASD who do not have the expected reactions of a neurotypical patient to auditory, tactile, and pain stimuli, which are often required to evaluate the patient's sedation level [5]. Moreover, most of the sedation assessment scales commonly used need to be revised for this population group.

Thus, such parameters rely on subjective criteria for sedating patients, generating risks due to their empirical essence.

Clonidine and Guanfacine are effective drugs for the treatment of ADHD and hypertension in children and adolescents [22]. The hypotensive effect of both medicines may be amplified by administrating Promethazine, and the sedative side effect may degenerate into central depression in the interaction between Clonidine and Diazepam or Hydroxyzine. This may cause an unplanned increased level of sedation, bringing risks to the treatment of children with ASD. On the other hand, the sedative effect may be diminished due to competition for enzymes related to cytochrome P450, such as in cases of concomitant use of anticonvulsants and mood stabilizers with Midazolam and Diazepam, namely Topiramate, Phenytoin, Carbamazepine, and Oxcarbazepine.

Patients with ASD may be predisposed to developing serotonin syndrome (SS), which is characterized by supraphysiological stimulation of serotonin receptors or in serotonin-acting regions, either by increased production of the neurotransmitter, reuptake inhibition, increased release, degradation inhibition, 5HTR stimulating substances or a combination of these causes. This condition may be related to the presence of neuropsychiatric symptoms (such as mood elevation and confusion), neuromuscular symptoms (such as tremors, myoclonus, hyperreflexia, and akathisia), and neurovegetative symptoms (such as tachycardia, tachypnoea, fever, and sweating) [23].

Conscious sedation in paediatric dentistry can be carried out with first-generation antihistamines [11,24]. Although their affinity for 5HT1a and 5HT2a is slight when compared to histamine receptors, Promethazine and Diphenhydramine act on serotonergic neurotransmission [25,26] and, when associated with drugs with known action on this pathway, such as second-generation neuroleptics [27] used to treat anxiety, aggressiveness, and irritability in children with autism, may trigger SS symptoms. In addition, the diagnosis of SS is difficult in ASD patients due to communication difficulties [28].

Neuroleptic Malignant Syndrome (NMS) is a pharmacogenic clinical condition of incomplete pathophysiological elucidation that presents symptoms ranging from variation in mental status to generalised rigidity, hyperthermia, diaphoresis, autonomic activation, creatine kinase (CK) elevation, parkinsonism and respiratory arrest [29,30]. The most accepted theory on the pathophysiology of NMS is related to the hyporregulation of dopaminergic transmission and its central and systemic effects. This may be a result of direct action on the dopaminergic system through antagonism of dopaminergic receptors [29,31], the sudden decrease of antiparkinsonian drugs [30], and drug modulation in the dopaminergic system, such as antidepressants [32,33]. A second etiological pathway for SNM is associated with indirect modulation of the dopaminergic system by drugs with anticholinergic effects [34,35] and interference with GABAergic transmission [36,37]. It is also worth noting that interactions between direct and indirect action on the dopaminergic system may also occur [38].

Conscious sedation requires administering drugs that alter dopaminergic neurotransmission by interfering with the cholinergic and GABAergic systems. In addition, patients with autism use antipsychotics, which are the drugs most often related to the onset of NMS. This deleterious interaction can be explained by the neuroleptic derivation of some antihistamines, such as Promethazine, which have greater affinity with H1R, generating more significant levels of sedation, but still with antidopaminergic activity that, although reduced, may increase the action of typical and atypical neuroleptics. Nevertheless, both autism and NMS are entities whose pathophysiology is not entirely defined, requiring greater care when planning the treatment of autistic patients to avoid NMS complications.

Another risk factor of interest for ASD patients undergoing sedation involves any changes in the QT interval (QTi). In particular, the QTi is the time of ventricular electrical activity represented electrocardiographically by the QRS complex, which is the depolarization of the ventricles, and the T wave, which is the repolarization of the ventricles. Physiologically, this interval lies approximately between 360ms and 450ms [39,40]. The time of ventricular electrical activity may increase to around 500ms by genetic inheritance or in an acquired manner, such as drug action. An increased QTi can lead to Torsade de Pointes, which is ventricular tachycardia, ventricular fibrillation, and sudden death [41,42]. Paradoxically, the reduction of QTi to values of less than 360ms is also associated with arrhythmias, ventricular fibrillation, and sudden death. Similarly, it can also be inherited or pharmacologically induced [40,43].

Hereditary alteration of QTi may be associated with syndromic forms of autism, as altered ion channels also affect those in the CNS [43,44]. The origin or pharmacological amplification of this complication takes place by the deregulation of ion channels responsible for cardiac electrical activity [45-47]. Both antidepressants and antipsychotics, antiparkinsonians and antihistamines, alter the QTi in different intensities and increase the risk of sinus rhythm loss, seizures, and sudden death [40,48] in psychiatric patients [46] and in children [40]. The greater likelihood of drug interactions between daily use drugs (such as antidepressants and antipsychotics) and the drugs administered for this procedure [49] (such as Hydroxyzine) highlights greater care to prevent cardiovascular events in patients with autism in the context of moderate sedation [45,50,51].

Conclusion

It is essential to carefully assess any drug interactions in patients with ASD submitted to sedation. The severity of the disorder and the need for sedation for dental treatment are directly proportional. Nonetheless, any increase in sedative doses tends to lead to more significant risks and complications in children with ASD.

Authors' Contributions

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All authors declare that they contributed to a critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

References

[1] Hyman SL, Levy SE, Myers SM; Council on Children with Disabilities, Section on Developmental and Behavioral Pediatrics. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics 2020; 145(1):e20193447. https://doi.org/10.1542/peds.2019-3447

[2] Autism spectrum disorder in under 19s: recognition, referral and diagnosis. London: National Institute for Health and Care Excellence (NICE); 2017. 45 p. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553265/pdf/Bookshelf_NBK553265.pdf [Accessed on June 30, 2021].
[3] Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, et al. Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. J Psychopharmacol 2018; 32(1):3-29. https://doi.org/10.1177/0269881117741766
[4] Lamy M, Erickson CA. Pharmacological management of behavioral disturbances in children and adolescents with autism spectrum disorders. Curr Probl Pediatr Adolesc Health Care 2018; 48(10):250-264. https://doi.org/10.1016/j.cppeds.2018.08.015
[5] Coté CJ, Wilson S; American Academy of Pediatrics; American Academy of Pediatric Dentistry. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures. Pediatrics 2019; 143(6):e20191000. https://doi.org/10.1542/peds.2019-1000
[6] Miyake RS, Reis AG, Grisi S. Sedação e analgesia em crianças. Rev Assoc Med Bras 1998; 44(1):56-64. https://doi.org/10.1590/s0104-42301998000100012 [In Portuguese].
[7] Aishworiya R, Valica T, Hagerman R, Restrepo B. An update on psychopharmacological treatment of autism spectrum disorder. Neurotherapeutics 2022; 19(1):248-262. https://doi.org/10.1007/s13311-022-01183-1
[8] Eissa N, Al-Houqani M, Sadeq A, Ojha SK, Sasse A, Sadek B. Current enlightenment about etiology and pharmacological treatment of autism spectrum disorder. Front Neurosci 2018; 12:304. https://doi.org/10.3389/fnins.2018.00304
[9] Persico AM, Ricciardello A, Lamberti M, Turriziani L, Cucinotta F, Brogna C, et al. The pediatric psychopharmacology of autism spectrum disorder: A systematic review - Part I: The past and the present. Prog Neuropsychopharmacol Biol Psychiatry 2021; 110:110326. https://doi.org/10.1016/j.pnpbp.2021.110326
[10] Malamed SF. Sedação Oral. Sedação na Odontologia. 5th ed. Rio de Janeiro: Elsevier; 2012. p. 95-118. [In Portuguese].
[11] Dock M. Abordagem Farmacológica do Comportamento do Paciente. In: Dean JA, Avery DR, McDonald RE, editors. McDonald e Avery Odontopediatria para Crianças e Adolescentes. 9th ed. Rio de Janeiro: Elsevier; 2011. p. 249-72. [In Portuguese].
[12] Drug Interaction Checker. New York: Medscape Reference; 1995. Available from: https://reference.medscape.com/drug-interactionchecker [Accessed on September 24, 2022].
[13] Taniguchi C, Guengerich FP. Metabolismo dos fármacos. In: Golan DE, Tashjian Junior AH, Armstrong EJ, Armstrong AW, editors. Princípios de Farmacologia: A Base Fisiopatológica da Farmacoterapia. 2nd ed. Rio de Janeiro: Guanabara-Koogan; 2009. p. 46–57. [In Portuguese].
[14] Taniguchi CM, Armstrong SR, Green LC, Golan DE, Tashjian Jr. AH. Toxicidade dos fármacos. In: Golan DE, Tashjian Junior AHAEJ, Armstrong AW, editors. Princípios de farmacologia: A base fisiopatológica da farmacoterapia. 2nd ed. Rio de Janeiro: Guanabara Koogan; 2009. p. 58-68. [In Portuguese].
[15] Chieh AY, Bryant BM, Kim JW, Li L. Systematic review investigating the relationship between autism spectrum disorder and metabolic dysfunction. Res Autism Spectr Disord 2021; 86:101821. https://doi.org/10.1016/j.rasd.2021.101821
[16] Midazolam [package insert]. Sabará, MG: Hipolabor Farmacêutica Ltda.; 2022. [In Portuguese].
[17] Asahi Y, Kubota K, Omichi S. Dose requirements for propofol anaesthesia for dental treatment for autistic patients compared with intellectually impaired patients. Anaesth Intensive Care 2009; 37(1):70-73. https://doi.org/10.1177/0310057X0903700101
[18] Seo KH, Jung HS, Kang EG, Kim CJ, Rhee HY, Jeon YS. Sedation using 5% lidocaine patches, Midazolam and propofol in a combative, obese adolescent with severe autistic disorder undergoing brain magnetic resonance imaging: a case report. Korean J Anesthesiol 2014; 67(6):421-424. https://doi.org/10.4097/kjae.2014.67.6.421
[19] Berkenbosch JW, Nguyen T-Q, Emmanouil D, Hardan AY. Special considerations during sedation of the child with autism spectrum disorder. In: Mason KP, editor. Pediatric Sedation Outside of the Operating Room. 3rd ed. Cham: Springer; 2021. p. 545-560.
[20] Ashley P, Anand P, Andersson K. Best clinical practice guidance for conscious sedation of children undergoing dental treatment: an EAPD policy document. Eur Arch Paediatr Dent 2021; 22(6):989-1002. https://doi.org/10.1007/s40368-021-00660-z
[21] Malamed SF. Condutas emergenciais. Sedação na Odontologia. 5th. ed. Rio de Janeiro: Elsevier; 2012. p. 446-481. [In Portuguese].
[22] Posey DJ, McDougle CJ. Guanfacine and guanfacine extended release: treatment for ADHD and related disorders. CNS Drug Rev 2007; 13(4):465-474. https://doi.org/10.1111/j.1527-3458.2007.00026.x
[23] Cintra P, Ramos A. Síndrome serotoninérgico: Manifestações clínicas, diagnóstico e terapêutica. Psilogos 2008; 5(1-2):88-96. https://doi.org/10.25752/psi.4088 [In Portuguese].
[24] Relia S, Ekambaram V. Pharmacological approach to sleep disturbances in autism spectrum disorders with psychiatric comorbidities: A literature review. Med Sci 2018; 6(4):95. https://doi.org/10.3390/medsci6040095
[25] Birmes P, Coppin D, Schmitt L, Lauque D. Serotonin syndrome: A brief review. CMAJ 2003; 168(11):1439-1442. Available from: https://www.cmaj.ca/content/cmaj/168/11/1439.full.pdf [Accessed on September 24, 2022].

[26] Khan S, Saud S, Khan I, Asif M, Ismail O, Salam A, et al. Serotonin syndrome presenting with concomitant tramadol and diphenhydramine use: A case report of an unlikely side-effect. Cureus 2018; 10(4):e2421. https://doi.org/10.7759/cureus.2421
[27] Racz R, Soldatos TG, Jackson D, Burkhart K. Association between serotonin syndrome and second-generation antipsychotics via pharmacological target-adverse event analysis. Clin Transl Sci 2018; 11(3):322-329. https://doi.org/10.1111/cts.12543
[28] Direk MÇ, Yıldırım V, Güneş S, Bozlu G, Okuyaz Ç. Serotonin syndrome after clomipramine overdose in a child. Clin Psychopharmacol Neurosci 2016; 14(4):388-390. https://doi.org/10.9758/cpn.2016.14.4.388
[29] American Psychiatric Association (APA). DSM-5: Manual Diagnóstico e Estatístico de Transtornos Mentais. 5th. ed. Porto Alegre: Artmed; 2014. p. 709-711. [In Portuguese].
[30] Souza RAP, Silva MAF, Coelho DM, Galvão MLS, Souza NAC, Picão AP. Síndrome neuroléptica maligna. Rev Bras Clin Med 2012; 10(5):440-445. [In Portuguese].
[31] Berloffa S, Dosi C, Tascini B, Fossati B, Lupetti I, Masi G. Neuroleptic malignant syndrome in children with Autism Spectrum Disorder (ASD): A case report and brief review of recent literature. Children 2021; 8(12):1201. https://doi.org/10.3390/children8121201
[32] Pytliak M, Vargová V, Mechírová V, Felšöci M. Serotonin receptors - From molecular biology to clinical applications. Physiol Res 2011; 60(1):15-25. https://doi.org/10.33549/physiolres.931903
[33] Richelson E. Pharmacology of antidepressants. Mayo Clin Proc 2001; 76(5):511-527. https://doi.org/10.4065/76.5.511
[34] Standaert DG, Galanter JM. Farmacologia da Neurotransmissão Dopaminérgica. In: Golan DE, Tashjian Junior AH, Armstrong EJ, Armstrong AW, editors. Princípios de Farmacologia: a Base Fisiopatológica da Farmacoterapia. 2nd ed. Rio de Janeiro: Guanabara Koogan; 2009. p. 166-185. [In Portuguese].
[35] Criado PR, Criado RF, Maruta CW, Machado Filho Cd. Histamina, receptores de histamina e anti-histamínicos: Novos conceitos. An Bras Dermatol 2010; 85(2):195-210. https://doi.org/10.1590/s0365-05962010000200010 [In Portuguese].
[36] Griffin Jr. EA, Lowenstein DH. Farmacologia da neurotransmissão elétrica anormal no sistema nervoso central. In: Golan DE, Tashjian Junior AH, Armstrong EJ, Armstrong AW, editors. Princípios de Farmacologia: A Base Fisiopatológica da Farmacoterapia. 2nd ed. Rio de Janeiro: Guanabara Koogan; 2009. p. 203-216. [In Portuguese].
[37] Borroto-Escuela DO, Ambrogini P, Narvaez M, Di Liberto V, Beggiato S, Ferraro L, et al. Serotonin heteroreceptor complexes and their integration of signals in neurons and astroglia-relevance for mental diseases. Cells 2021; 10(8):1902. https://doi.org/10.3390/cells10081902
[38] Ishii T, Kimura Y, Ichise M, Takahata K, Kitamura S, Moriguchi S, et al. Anatomical relationships between serotonin 5-HT2A and dopamine D2 receptors in living human brain [published correction appears in PLoS One 2018; 13(5):e0197201]. PLoS One 2017; 12(12):e0189318. https://doi.org/10.1371/journal.pone.0189318
[39] Vo LC, Snyder C, McCracken C, McDougle CJ, McCracken JT, Aman MG, et al. No apparent cardiac conduction effects of acute treatment with risperidone in children with autism spectrum disorder. J Child Adolesc Psychopharmacol 2016; 26(10):900-908. https://doi.org/10.1089/cap.2016.0090
[40] Shah RR. Drug-induced QT interval shortening: Potential harbinger of proarrhythmia and regulatory perspectives. Br J Pharmacol 2010; 159(1):58-69. https://doi.org/10.1111/j.1476-5381.2009.00191.x
[41] Ribeiro S. Síndrome de QT Longo. Rev Cardiopulmonar 2006; 17(1):43-49. [In Portuguese].
[42] Martins JM, Figueiredo TP, Costa SC, Reis AMM. Medicamentos que podem induzir prolongamento do intervalo QT utilizados por idosos em domicílio. Rev Ciênc Farm Básica Apl 2015; 36(2):297-305. [In Portuguese].
[43] Endres D, Decher N, Röhr I, Vowinkel K, Domschke K, Komlosi K, et al. New Cav1.2 channelopathy with high-functioning autism, affective disorder, severe dental enamel defects, a short QT Interval, and a novel CACNA1C loss-of-function mutation. Int J Mol Sci 2020; 21(22):8611. https://doi.org/10.3390/ijms21228611
[44] Timothy Syndrome. Danbury (CT): National Organization for Rare Disorders (NORD); c2005-2020 [updated 2020]. Available from: https://rarediseases.org/rare-diseases/timothy-syndrome/ [Accessed on May 16, 2022].
[45] Husain Z, Hussain K, Nair R, Steinman R. Diphenhydramine induced QT prolongation and torsade de pointes: An uncommon effect of a common drug. Cardiol J 2010; 17(5):509-511.
[46] Timour Q, Frassati D, Descotes J, Chevalier P, Christé G, Chahine M. Sudden death of cardiac origin and psychotropic drugs. Front Pharmacol 2012; 3:76. https://doi.org/10.3389/fphar.2012.00076
[47] Staikou C, Stamelos M, Stavroulakis E. Impact of anaesthetic drugs and adjuvants on ECG markers of torsadogenicity. Br J Anaesth 2014; 112(2):217-230. https://doi.org/10.1093/bja/aet412
[48] Höcht C, Opezzo JAW, Taira CA. Intervalo QT prolongado inducido por fármacos desde el punto de vista de un farmacólogo. Rev Argent Cardiol 2004; 72(6):474-480. [In Spanish].
[49] Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs: Most patients have easily identifiable risk factors. Medicine 2003; 82(4):282-290. https://doi.org/10.1097/01.md.0000085057.63483.9b
[50] Carvalho MVH, Carvalho VN, Falani FS. Alterações eletrocardiográficas em crianças e jovens assistidos pela Associação dos Pais e Amigos dos Excepcionais (APAE). Rev Med UFPR 2017; 4(1):11-16. [In Portuguese].
[51] Hidroxizina [package insert]. Juiz de Fora, MG: Nativita Indústria e Comércio Ltda.; 2022. [In Portuguese].