

BUMETANIDE IN AUTISM SPECTRUM DISORDER

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ABSTRACT: Objectives: This study aimed to make a bibliographic update on the already published data on bumetanide, addressing the main information on its use in Autism Spectrum Disorder (ASD). Methods: This was an integrative narrative review in which the following databases were used: Web of Science, MEDLINE, ScienceDirect, and Scielo. The descriptors used were: Autism Spectrum Disorder, Autistic Disorder and Bumetanide. It was considered only articles published in English and French. Original articles, randomized clinical trials, case reports, and review articles were included. Results: The results show that the use of bumetanide alters regions of the brain linked to the positive development of language, improvement of visual contact, improvement in social interactions, among others. Studies are also concerned about the safety and efficacy of bumetanide in ASD since several adverse effects have been reported. The most frequent were hypokalemia, polyuria, and loss of appetite. Conclusion: Bumetanide has proven as effective in improving some important symptoms in ASD, especially linked to language and social interaction, however, studies with larger groups of patients and with longer treatment and observation time are needed to confirm the efficacy and clarify the safety profile in use for people with ASD.

KEYWORDS: Autism Spectrum Disorder; Bumetanide; Pharmacological treatment; Adverse effects.

BUMETANIDA NO TRANSTORNO DO ESPECTRO AUTISTA

RESUMO: Objetivo: O objetivo deste trabalho foi fazer uma atualização bibliográfica sobre os dados já publicados da bumetanida, abordando as principais informações sobre seu uso no Transtorno do Espectro Autista (TEA). Metodologia: Foi realizada uma revisão do tipo narrativa integrativa, da qual foram utilizadas as bases de dados: Web of Science, MEDLINE, ScienceDirect e Scielo, com a utilização dos seguintes descritores: Autism Spectrum Disorder, Autistic Disorder e Bumetanide. Foram considerados apenas artigos publicados nas línguas inglesa e francesa. Foram incluídos artigos originais, ensaios clínicos randomizados e relatos de caso. Foram excluídos artigos de revisão. Resultados: Os resultados mostram que o uso da bumetanida altera regiões do cérebro ligadas ao desenvolvimento positivo da linguagem, melhora do contato visual, melhora nas interações sociais, entre outros. Os estudos também se preocupam em relacionar a segurança e a eficácia da bumetanida no TEA, do qual foram relatados diversos efeitos adversos, sendo os mais frequentes a hipocalemia, a poliúria e a perda de apetite. Conclusão: A bumetanida mostrou ser eficaz na melhoria de alguns importantes sintomas no TEA, especialmente ligados à linguagem e interação social, entretanto, estudos com grupos maiores de pacientes e com maior tempo de tratamento e observação são necessários para confirmar a eficácia e esclarecer o perfil de segurança no uso para pessoas com TEA. **PALAVRAS-CHAVE:** Transtorno do Espectro Autista; Bumetanida; Tratamento farmacológico; Efeitos adversos.

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BUMETANIDA EN EL TRASTORNO DEL ESPECTRO AUTISTA

RESUMEN: Objetivos: Este estudio tuvo como objetivo realizar una actualización bibliográfica sobre los datos ya publicados sobre la bumetanida, abordando la principal información sobre su uso en el Trastorno del Espectro Autista (TEA). Métodos: Se trata de una revisión narrativa integradora en la que se utilizaron las siguientes bases de datos: Web of Science, MEDLINE, ScienceDirect y Scielo. Los descriptores utilizados fueron: Trastorno del Espectro Autista, Trastorno Autista y Bumetanida. Se consideraron sólo los artículos publicados en inglés y francés. Se incluyeron artículos originales, ensayos clínicos aleatorios, informes de casos y artículos de revisión. Resultados: Los resultados muestran que el uso de la bumetanida altera regiones del cerebro relacionadas con el desarrollo positivo del lenguaje, la mejora del contacto visual, la mejora de las interacciones sociales, entre otros. Los estudios también se preocupan por la seguridad y eficacia de la bumetanida en el TEA, ya que se han reportado varios efectos adversos. Los más frecuentes fueron la hipocalcemia, la poliuria y la pérdida de apetito. Conclusiones: La bumetanida ha demostrado ser eficaz en la mejora de algunos síntomas importantes en el TEA, especialmente vinculados al lenguaje y la interacción social, sin embargo, se necesitan estudios con grupos más grandes de pacientes y con mayor tiempo de tratamiento y observación para confirmar la eficacia y aclarar el perfil de seguridad en el uso para personas con TEA.

PALABRAS CLAVE: Trastorno del Espectro Autista; Bumetanida; Tratamiento farmacológico; Efectos adversos.

1. INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition that manifests itself throughout life and is characterized by social interaction and communication deficits, and by the presence of repetitive behaviors. These deficits are known as core symptoms of ASD (APA, 2014).

Its etiology is still unknown. However, the current tendency is to consider it as a syndrome of multicausal origin that encompasses genetic, neurological, and social factors of the child (PINTO et al., 2016). Moreover, the evidence-based pharmacology of ASD is currently limited to the treatment of behavior or diagnosis of concomitant symptoms, that is, there is no drug treatment for ASD.

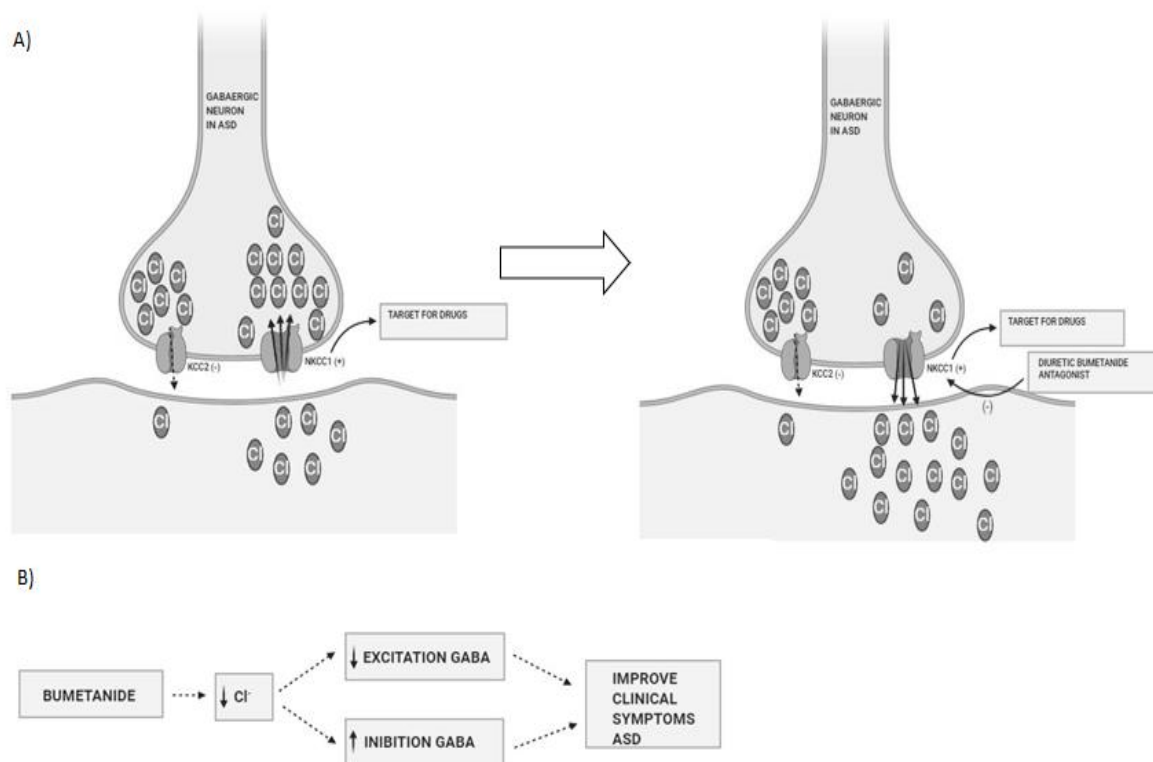
Bumetanide is a loop diuretic used to control hypertension, bronchopulmonary dysplasia, nephritic syndromes, or cardiac congestions (LEMONNIER et al., 2012), that has been studied as a therapeutic resource on the control of some ASD symptoms (JAMES; GALES ; GALES , 2019). The inhibitory effect of γ -aminobutyric acid (GABA) is profoundly altered in patients with ASD since there is an excessive accumulation of chloride in neurons which transforms this GABA-ergic, a naturally inhibitory, into an excitatory signaling (LEMONNIER et al., 2010).

The increase of internal $[Cl^-]$ in the pathology has a double origin: an internalization of the exporter of chloride KCC2, which leads to a failure of the neurons to export the excess chloride out of the cell, and persistent or increased activity of the importer of chloride NKCC1, leading to exaggerated accumulation of chloride inside the neuron. KCC2 is considered an unlikely target for pharmacological treatments because it is not stable, it is in the internalized form, and there are currently no selective agonists available. In contrast, NKCC1 has been studied as a likely

pharmacological target due to its stability. Some antagonists of this receptor have been identified, for example, some diuretics, among them, bumetanide (HADJIKHANI et al., 2015).

The effect observed in neurons after the use of bumetanide is the reduction of internal chloride concentrations, since this diuretic induces a significant elimination of sodium and chlorine associated with a proportionally lower elimination of potassium (HAJRI et al., 2019) which interrupts the abnormal GABAergic excitation, thus initiating the process of GABAergic inhibition, and may thus reduce the clinical symptoms of ASD, such as hyperactivity and improved social integration (FENG et al., 2020). In addition, it was observed that the dose and treatment time of bumetanide are important variables for its therapeutic efficacy in ASD (HAJRI et al., 2019). Figure 1 illustrates schematically the effect of GABAergic modulation of bumetanide on neurons (A) and its implications on ASD (B).

Figure 1. GABAergic signaling in patients with ASD and the function of bumetanide.



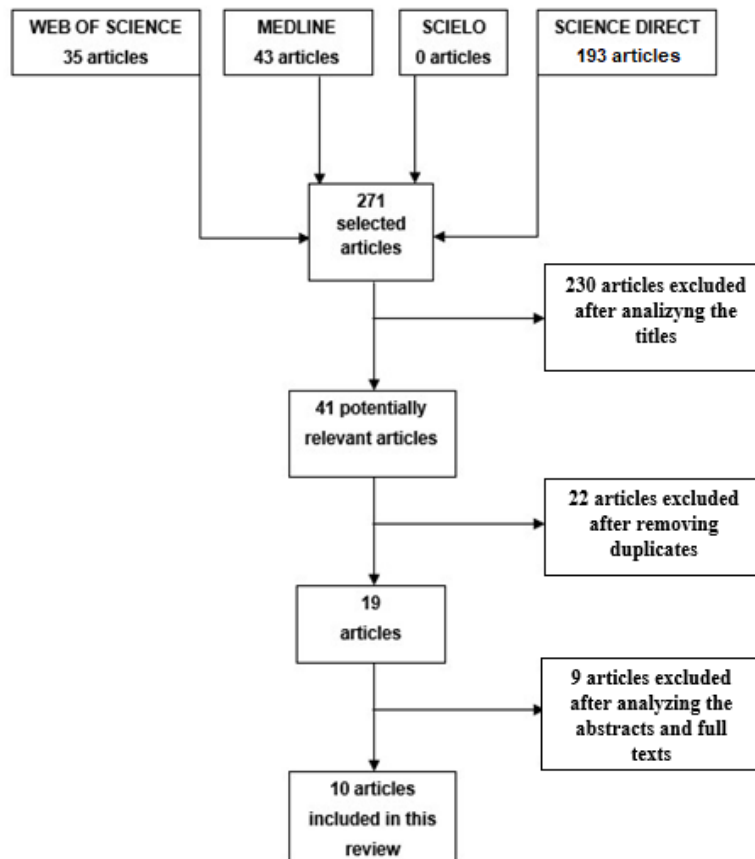
Thus, the purpose of this review was to conduct a survey of articles published chronologically between January 2010 and July 2020 on bumetanide used as a therapeutic option for the control of the core symptoms of ASD and to evaluate the risk-benefit of this drug.

2. METHODS

The present study is a narrative bibliographic research which was carried out using the following databases: Web of Science, MEDLINE, ScienceDirect, and Scielo; and the descriptors:

"Autism Spectrum Disorder", "Autistic Disorder" and "Bumetanide". Articles published in English, French and Portuguese were selected. There was no publishing year limitation for the selection of articles. It was included only original articles, randomized clinical trials, case reports, and review articles. All selected studies were conducted on humans. Articles that did not fit the hypothesis of this work or were outside the inclusion criteria were excluded. The search period for articles was from June 24th to July 28th of 2020. Figure 2 shows the steps for the search and selection of the articles.

Figure 2. Diagram with steps for the search and selection of the article



3. RESULTS AND DISCUSSION

This integrative review was carried out starting from the inclusion of a total of 10 articles that served as a foundation for this work. The choice of articles was made to seek a correlation between bumetanide and therapeutic application in autistic spectrum disorder, also focusing on the safety profile. Next, we will discuss in chronological order these works on the advances in research involving the use of bumetanide for ASD. Table 1 briefly describes the main findings of these papers.

TABLE 1. Main data from the methodological designs of the researches using bumetanide in ASD.

Article	Number of patients	Age of patients (years)	Treatment time (days)	Dose (mg/dat)	Symptoms / Benefits
Lemonnier and Ben-Ari, 2010	05	03 - 11	90	1	Improvement in cognitive regulation and social interaction / Reduction of hyperactivity and stereotyped movements
Lemonnier et al., 2012	60	03 - 11	90	1	Improvement in eye contact, verbal and nonverbal communication, social participation and reduction of hyperactivity
Hadjikhani et al., 2013	07	14 - 28	300	1	Improvement in emotional recognition, description of own emotions
Grandgeorge et al., 2014	01	10	540	2	Improvement in sensory behaviors and social interactions
Lin Du et al., 2015	60	02 - 06	90	1	Reduction of hyperactivity and anxiety/ Improvement of social and emotional perception
Lemonnier et al., 2017	88	02 - 18	90	1, 2 ou 4	Improvement in the visual recognition of emotional figures, media and restricted interests
Hadjikhani et al., 2018	09	14 - 28	300	1	Improvement in social-emotional understanding and increase in eye contact
Hajri et al., 2019	29	05 - 16	364	1, 1.5 ou 2	Improvement in social interaction, use of objects, verbal and non-verbal communication
Zhang et al., 2020	83	03 - 06	90	1	Improvement in social emotion stimuli and social interaction / Reduction of stereotyped movements and bizarre use of body movement
Feng et al., 2020	01	02	30	1	Positive language development and reduced hyperactivity

Lemonnier and Ben-Ari (2010) conducted a study testing the effects of bumetanide 1 mg per day in five autistic babies for three months. An improvement in cognitive regulation of these children was observed, such as improvement in social interaction and the reduction of stereotyped movements. This evolution was reported by the children's parents, demonstrating that bumetanide can help improve behavioral aspects in patients with ASD. Although it was a pilot study, clinical surveillance was performed on the patients once a month, such as dehydration, asthenia, and diarrhea research and monitoring of sodium and potassium levels in the blood after the end of each evaluation, and no adverse effects were reported.

Lemonnier et al., (2012) designed and carried out a new study with two groups: placebo and bumetanide. Initially conducted with sixty children, this analysis used 1 mg of bumetanide per day for three months. Soon after the beginning, there were two withdrawals related to the use of bumetanide, one for enuresis and another for hypokalemia. The results of this study showed that behaviors such as low language ability, high level of stereotyping, low social interaction, and hyperactivity gave way to better social participation, improved verbal and nonverbal communication and reduced hyperactivity. However, among the patients who continued the treatment, it is noteworthy that hypokalemia was present in six patients, which was corrected with potassium supplementation so that the values were within normal standards. With the placebo-controlled study and the use of a larger number of patients, it was possible to notice that the effects of bumetanide were related to the improvement of some symptoms of ASD, such as behavioral aspects of patients and social interactions. However, the study was conducted with only one dose of bumetanide (1mg/day), and the ideal dose was questioned.

Hadjikhani et al., (2013), in a pilot study, sought to observe magnetic resonance imaging to determine the effects of bumetanide treatment, conducting a study with seven autistic patients for ten months at a dosage of 1 mg per day. This study showed that the regions of the brain involved in social and emotional perception were activated during the treatment. Therefore, it improved the ability to identify and describe one's own emotions, demonstrating the possible effectiveness of using bumetanide as a treatment for ASD. However, hypokalemia was observed in one of the patients who was treated with potassium supplementation and a frequent increase in urinary output was also observed, but without monitoring for signs of dehydration, weight loss or increased sodium levels in the patient.

Grandgeorge et al. (2014) published a case report in which they used the treatment of bumetanide at a dose of 2 mg per day in a ten-year-old Asperger's patient for ten months. It was reported improvements in a wide range of sensory behaviors, including auditory, vestibular, tactile, multisensory, and oral sensory processing. Moreover, improvements were observed even after 3

months of treatment, considering that most studies are conducted in this short period and show similar improvements, such as increased social interaction and reduction of hyperactivity, showing no clinical abnormalities during treatment. In this work, although it was carried out with only one patient, it was observed a possible effectiveness of bumetanide as a long-term treatment regarding the improvement of sensory behavior in patients with ASD.

In a pilot study, conducted by Du et al., (2015), they used a double-blind controlled method to follow sixty autistic children, using the combination of ABA (Applied Behavior Analysis) treatment (FOXX, 2008) with bumetanide and a control group using only the ABA method to find significant improvements in ASD comorbidities. During three months, the CARS (Childhood Autism Rating Scale) scores, a behavior assessment scale used to evaluate the presence and severity of ASD (RELLINI et al., 2004) were significantly reduced in matters of hyperactivity, emotional response and anxiety. During the monitoring, one patient interrupted the treatment due to polyuria. However, in the other individuals, there were no abnormal changes in routine blood tests, routine urine tests, liver function tests, kidney function tests, blood electrolytes, blood glucose tests or electrocardiograms (Du et al., 2015). This study, although it is the first to use this combination, proves to be relevant, for the ABA treatment, which is also a tool used to understand autistic behavior in combination with bumetanide, may have a promising future in the treatment of some manifestations of ASD.

Continuing his studies, Lemonnier et al., (2017) published a placebo-controlled study with eighty-eight patients with ASD, separating them into subgroups, this time receiving different doses of bumetanide (0.5 mg, 1 mg and 2 mg, twice a day). The treatment with two daily doses allowed to increase the patient's exposure to bumetanide due to the short half-life of the drug (about 40 - 90 minutes). Among the main symptoms which showed improvement were: progress in communication, reduction of restricted interests and repetitive behavior. However, eleven patients interrupted the treatment due to adverse effects, five due to hypokalemia and four related to diuresis. The study group in which better results were observed was the group of patients who received bumetanide at a dose of 2 mg twice a day, which was higher than 10 points on the CARS scale compared to the other groups. However, they were the group in which more adverse effects were reported such as hypokalemia (16), loss of appetite (9), polyuria (8), dehydration (6), vomiting (5), fatigue (4), asthenia (3), weight loss (3), abdominal pain (2), polydipsia (2) and hyperuricemia (1).

In this study, Lemonnier et al., (2017) concluded that the frequency and incidence of adverse effects were directly correlated to the dosage of bumetanide administered. Thus, considering the abstinence rate and the severity of the observed adverse effects, the dosage of 1 mg twice a day seemed to be the best option considering safety and efficacy. Thus, the use of bumetanide in higher dosages requires caution, since there is also the risk of developing a greater number of adverse

reactions.

In a work published for Hadjikhani et al., (2018) they worked on the hypothesis that bumetanide modulates amygdala activation, which can be overactivated in individuals with ASD. In the protocol used by them, after ten months of treatment with bumetanide in nine patients at a dose of 1 mg per day, it was observed some normalization of amygdala activation in response to eye contact, which is important in improving social understanding in individuals with ASD since restricted eye contact in ASD is a frequent symptom. There was no informed report in the study on the appearance of side effects.

Still, regarding this study Hadjikhani et al., (2018), the authors discuss that concerning amygdala activation, at birth, babies instinctively attend the 'protofaces', through the subcortical facial processing system. The protofaces and faces activate a path that goes from the upper collar to the pulvinar nucleus of the thalamus and the amygdala. In ASD, this pathway becomes overconnected due to the excitatory and inhibitory imbalance. Subsequently, eye contact activates the subcortical system and assists in the normal maturation of the cortical facial processing in neurotypicals, but in ASD, the eyes overactivate the system, in particular, the amygdala and cause overexcitement, resulting in an aversion to eye contact and reduced experience with eyes and faces, which ends up leading to abnormal maturation of the brain. Bumetanide supposedly restores this excitatory and inhibitory balance, since it acts on the importer of NKCC1 chloride, and the amount of amygdala activation in response to restricted eye contact in autism is significantly reduced, which has consequently induced autists to increase the time spent spontaneously making eye contact after treatment.

Hajri et al., (2019) conducted a study with twenty-nine autistic patients, starting the protocol with bumetanide at a dose of 1 mg per day, gradually increasing the dose, until reaching 2 mg per day. Among the withdrawals during the treatment, five children were excluded due to side effects such as hypokalemia (2), pruritus (2) and polyuria (1). In the remaining patients, no adverse effects related to bumetanide were reported, and no significant differences in clinical benefits were observed among children who received 1 mg per day and 2 mg per day. In both dosages, improvements in social interaction, nonverbal communication, and visual response were observed, symptoms that are present in a large part of the patients with ASD and that impair their social integration.

Based on previous studies that worked only on the hypothesis that bumetanide restores the excitatory-inhibitory balance of the brain in patients with ASD, Zhang et al., (2020) used magnetic resonance spectroscopy (MRS) to determine whether bumetanide can regulate the GABA/Glutamate ratio in autists' brains. To do so, he conducted a placebo-controlled clinical trial with eighty-three patients, administering 1 mg per day for three months and observing, through brain imaging, the main

regions of the brain that would be altered with the administration of bumetanide. The findings suggest the hypothesis that bumetanide can restore the balance of GABA in the autistic brain since evidence from neuroimages has shown that the GABA/Glutamate ratio has decreased both in the visual and insular cortex. Throughout the treatment, an improvement in sensory integration and a decrease in stereotyped movements and nonsocial movements were observed. However, some side effects were registered in the patients such as polyuria (15), hypokalemia (4), loss of appetite (4), fatigue (1), and hyperuricemia (1).

Also, Feng et al., (2020) published a case report involving a thirty-month-old female child, who started treatment with vitamin D and after 6 months supplementation was interrupted due to lack of efficacy. After that, the treatment with bumetanide was initiated, being administered twice a day, at a dose of 0.5 mg for thirty days. The patient presented social and communication difficulties, she did not follow instructions, she avoided eye contact, she had no verbal communication and she presented hyperactivity. Soon after a week of bumetanide use, there was a positive development on language, she spoke voluntarily and had her hyperactivity reduced, developing her scenario of improvement until the end of her treatment, which showed improvements in social interaction and reduction of stereotyped behaviors without presenting clinical abnormalities in blood or urine.

In the research carried out for this study, it was observed that bumetanide presents a series of adverse effects. Table 2 shows the main information on the most prevalent adverse effects mentioned in the studies. The information on this table refers to 343 patients, which was the sum of all patients in the articles. Although there is a wide range of reactions, these do not seem to be of greater severity for patients, considering that the most common effects such as hypokalemia, polyuria, and loss of appetite, were dose-dependent and could be reversed or attenuated with supplementation and follow-up of electrolytes, avoiding dehydration and loss of important micronutrients.

TABLE 2. Integrative data from studies showing the main adverse effects of bumetanide on ASD.

Adverse effect	Amount of notifications	(%)*	Dose (mg/kg) per number of patients
Hipocalemia	44	12,8	1 mg (12); 2 mg (16); 4 mg (16)
Polyuria	38	11	1 mg (18); 2 mg (9); 4 mg (11)
Loss of appetite	20	5,8	1 mg (4); 2 mg (7); 4 mg (9)
Dehydration	09	2,6	2 mg (3); 4 mg (6)
Asthenia	07	2	1 mg (2); 2 mg (2); 4 mg (3)
Fatigue	06	1,7	1 mg (1); 2 mg (1); 4 mg (4)
Hyperuricaemia	06	1,7	1 mg (2); 2 mg (3); 4 mg (1)
Vomit	06	1,7	2 mg (1); 4 mg (5)
Weight loss	06	1,7	2 mg (3); 4 mg (3)
Polydipsia	05	1,4	1 mg (1); 2 mg (2); 4 mg (2)
Abdominal pain	04	1,1	1 mg (1); 2 mg (1); 4 mg (2)
Enurese	02	0,5	1 mg (2)
Diarrhea	02	0,5	2 mg (2)
Pruritus	02	0,5	2 mg (2)

In this study, research of existing data on the use of bumetanide in ASD was carried out, and all selected studies demonstrated significant clinical improvements in its use, such as improved verbal communication, reduced hyperactivity, positive language development, among other common symptoms in autism. Bumetanide, being a diuretic and antihypertensive, becomes more accessible to the population and expands the possibility of new treatments for autism, since only aripiprazole and risperidone have been legally authorized by the Food and Drug Administration (FDA) for the treatment of autism. However, different dosages of the drug were used in the studies, ranging from 0.5 mg to 2 mg per day, therefore, studies still need to be carried out in order to identify the most effective dosage for this treatment.

Over the last 10 years, we have observed an increase in publications which aim to use bumetanide in ASD. Although they are still very few, it became evident that these studies differed greatly in their characteristics, varying from case report to randomized controlled trial, double-blind study and even the use of spectroscopy to better evaluate the results obtained. The results of these studies show that the use of bumetanide can be safe, as long as it is accompanied by clinical and biological surveillance of the patients.

As main limitations found in this work, we can list the scarce number of published articles reporting the use of the drug in ASD and the low number of patients that the studies present, since some studies describe only one case report. Moreover, most studies have established a 90-day observation period, which is considered short to determine positive responses in patients. At the moment, it is not possible to claim that bumetanide will act in the entire autistic population, since it is a very heterogeneous group, with different levels of severity, symptoms and comorbidities.

4. CONCLUSION

In conclusion, it is believed that bumetanide, or some future successor molecule, may present itself as a drug that can act in the treatment of some of the main symptoms of ASD. Currently, there is a need for treatment strategies that are focused on early atypical development of the autistic brain which can attenuate the symptoms of ASD so that the side effects do not have a high risk to the patient, with bumetanide being a promising choice.

INTEREST CONFLICTS

The authors declare that there is no conflict of interest.

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