

1 **Preventions of oral self-mutilation in** 2 **patients with Lesch-Nyhan syndrome**

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12 **ABSTRACT**

13 Lesch-Nyhan syndrome (LNS) is a rare genetic disorder linked to the X chromosome that implies an
14 inborn error of metabolism, due to deficiency in the purine metabolic pathway, affected individuals present
15 neurological symptoms, such as cognitive and motor impairment, besides behavioral changes such as self
16 and hetero-aggression. This characteristic aggressive behavior leads to insults and self-mutilation, thus
17 requiring methods of self-protection, some invasive and permanent, such as tooth extraction. Noninvasive
18 methods, such as the use of oral protectors, pharmacological therapies and botulinum toxin A applications,
19 are also employed to decrease discomfort and the implications of such behavior. We describe briefly the
20 methods of prevention against oral self-mutilation in patients with Lesch-Nyhan syndrome found in the
21 literature.

22 **INTRODUCTION**

23 First described in 1964, Lesch-Nyhan syndrome (LNS) is a rare disorder linked to the X chromosome,
24 that approximately one in 380,000 live births (Nyhan (1997)). It causes disturbance in the uric acid
25 metabolism and central nervous system (CNS)(Lesch and Nyhan (1964)) due to mutations in the gene
26 that codes for the hypoxanthine-guanine phosphoribosyltransferase enzyme (HPRT1), located between
27 Xq26 and Xq27, an important enzyme in the purine rescue route (Bell et al. (2016)). This results in
28 total or partial lack of HPRT activities and high level of uric acid concentration in urine (Dabrowski and
29 Medicine (2005)). The pathology may also be associated with dopaminergic activity deficits in the basal
30 ganglia (Visser et al. (2000)). The characteristic framework of LNS consists of a set of neurological
31 behaviors and symptoms, presenting a delay in the motor development and variable degrees of cognitive
32 impairment, self-injurious behavior (self-mutilation) that manifest during the first year of life (Bell et al.
33 (2016)). Patients are generally not able to sit independently and remain impassable throughout life, more
34 specifically, self-mutilation, which generally leads to the correct diagnosis of Lesch-Nyhan syndrome
35 (Christie et al. (1982); Schroeder et al. (2001)). According to Anderson and Ernst (1994), out of the 40
36 Lesch-Nyhan patients, the study found that 90% had permanent physical damage due to self-mutilation.
37 Patients are aware of their self-harming behavior and become agitated and afraid when their protective
38 and restrictive gear are removed (Lesch and Nyhan (1964)). The restriction method seems to be the
39 most suitable for controlling self-mutilation. Regarding the restrictions and nozzle protections used to
40 avoid self-mutilation, tooth extraction has been the most used method to reduce self-harming behavior
41 (Campolo González et al. (2018)). Even after tooth extraction, these edentulous patients turn to other
42 forms of self-mutilation, in many cases using their fingers to cause self-injury (Gutierrez et al. (2008)).
43 Other noninvasive methods include mild mouthguard use and psychiatric pharmacological therapy to
44 avoid further damage to soft perioral tissues. Recent treatments include the use of botulinum toxin type
45 A (BTX-A) injected into the bilateral masseters. BTX-A temporarily prevents presynaptic release of
46 acetylcholine, causing motor plaque dysfunction and muscle weakness (Dabrowski and Medicine (2005));

47 Zilli and Hasselmo (2008); Jeong et al. (2006); Olson and Houlihan (2000)). The focus of this work is to
48 present prevention methods against oral self-mutilation in patients with Lesch-Nyhan syndrome found in
49 literature.

50 PREVENTIVE METHODS

51 Pharmacotherapy

52 Among the treatments used to alleviate the causes of this syndrome is the use of drugs aimed at inhibiting
53 the conversion of guanine and hypoxanthine to uric acid by HPRT. One of the most commonly used
54 drugs is allopurinol, treatment with allopurinol reduces serum levels of urate and uric acid and thus
55 prevents crystaluria, nephrolithiasis and gout. Some benzodiazepines and gamma-aminobutyric acid
56 inhibitors are used for the treatment of spasticity and dystonias, but due to the lack of knowledge about
57 neurological dysfunctions, useful therapies have not been found, and rehabilitation and muscle and
58 postural training programs are recommended. And for the control of self-mutilation, neuroleptics are used
59 to minimize this behavior. Benzodiazepines and carbamazepine are the most useful for decreasing anxiety
60 and suppressing harmful behavior (Zilli and Hasselmo (2008); Jeong et al. (2006)). Despite the numerous
61 benefits always reported to the use of these medications (Campolo González et al. (2018); Gutierrez et al.
62 (2008)). Buitelaar (1993), advises caution for many reasons. Primarily due to the sedative properties
63 induced by these drugs that prevent patients in both their cognitive functions and their physical abilities,
64 and secondly due long-term use side effects. In a case reported by Jeong et al. (2006), the patient was
65 receiving a daily dose of 2 mg diazepam to relieve the self-injurious action, but their success was limited.
66 After being submitted to a new psychiatric consultant, his medication was changed to sertraline 12.5 mg
67 and 0.25 mg risperidone, to control anxiety and self-injurious behavior. After seven days the dosages
68 of both drugs were doubled. After 15 days, the self-mutilation and shaking behavior was significantly
69 reduced and the interaction between the patient and his mother improved. According to the author within
70 1 month, the frequency of self-injurious behavior was limited to less than a single attempt per week, after
71 4 months of such pharmacotherapy resulted in the complete disappearance of self-injurious behavior
72 without any side effects.

73 Oral Device

74 The use of mouthguards is widely described in the technical literature . The use of mouth guards is
75 extensively described in the technical literature were described by Anderson and Ernst (1994); Jeong
76 et al. (2006). Scott and Ranalli (2005), mentions that the applications of oral protection devices are
77 many and varied, from the use as protector to the therapeutic one. Olson and Houlihan (2000), describe
78 the follow-up of a case, which the pediatric dentist build a two-piece acrylic mouth guard to fit firmly
79 on the patient's upper and lower teeth. In addition, there was a verbally reinforcing training for the
80 patient to keep the mouth guard in the correct mouth position. Jeong et al. (2006), emphasizes in his
81 case study the development of a soft mouthguard, which was fabricated and modeled using Biostar
82 (Scheu-Dental, Iserlohn, Germany). The upper dental arch was covered with a mouth guard made of soft
83 resin material. During the periodic dental monitoring phase, the patient appeared to be well adapted to
84 this soft mouthguard, and reduced frequency of general self-mutilation included fewer lip bites in the first
85 2 weeks of mouthguard use along with pharmacotherapy, according to the author's emphasis the treatment
86 results were very promising. The most commonly used oral device is a soft mouth guard (Dabrowski and
87 Medicine (2005); Jeong et al. (2006); Olson and Houlihan (2000)).

88

- 89 1. Bite-Blocks (Figure 1);
- 90
- 91 2. A combination of extraoral and intraoral orthodontic apparatus that covers the chin and is held in
92 place with a rubber band around the head or with a helmet on the neck-strap (Figure 2);
- 93
- 94 3. Acrylic trays intended to force the lower lip anteriorly onto the lower teeth (Figure 3B);
- 95
- 96 4. Various types of shields that protect the tongue and lips from direct injury (Figure 3A);
- 97
- 98 5. Labial bumpers welded onto orthodontic bands or stainless-steel crowns (Figure 4);

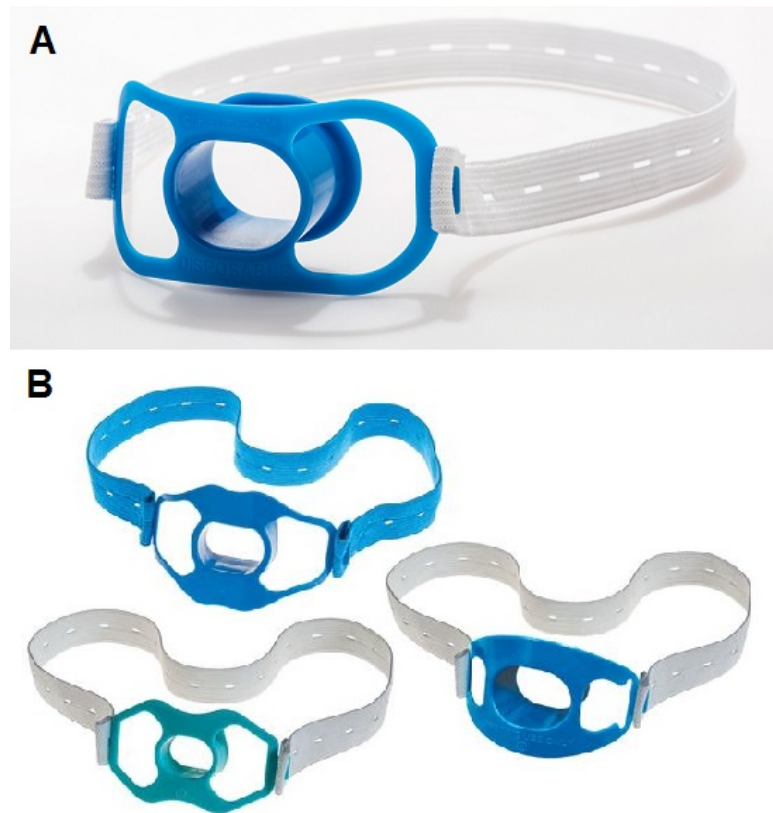


Figure 1. Models of Bite Blocks. (A) Endoscopic Bite Blocks by Choice, (B) ScopeValet™ - Endoscopic Bite Blocks by Healthcare (2018).

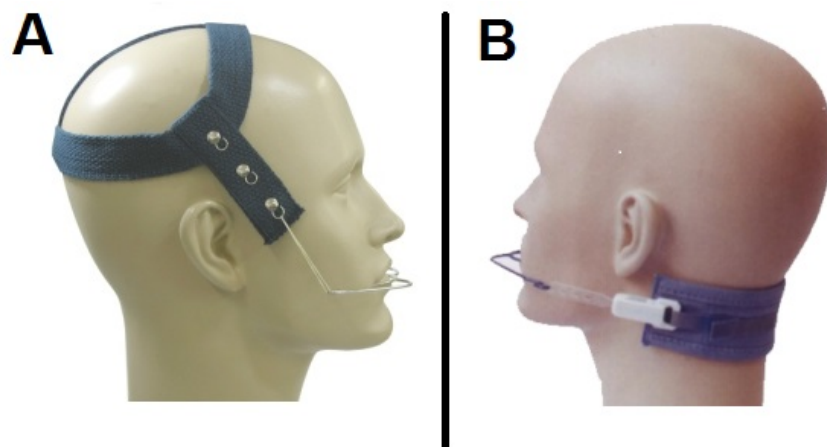


Figure 2. Models of helmet on the neck-strap. (A) Extra Oral Supplies by Biodental (2018), (B) Extraoral Supplies by JJORTHO and Tencent (2018).

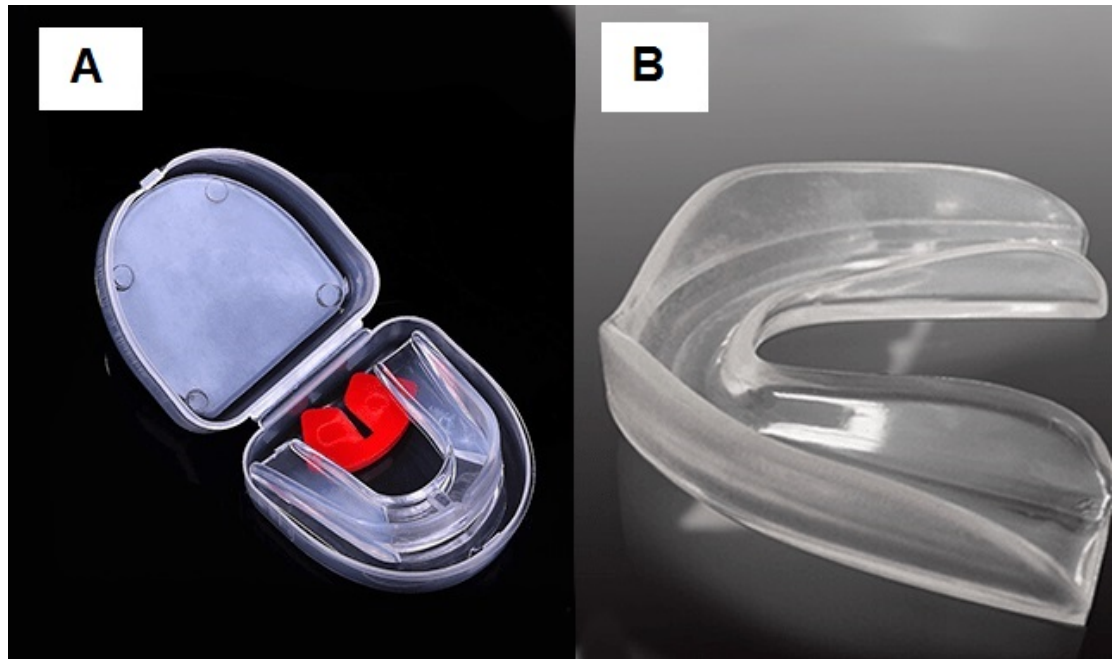


Figure 3. Mouthguard double model (A) that is used at the bottom and top and mouthpiece singular model (B) with single format for upper teeth. Source: Fighter (2018).



Figure 4. (A) Intraoral occlusal view with hard arc labial bumpers (Jacob et al. (2014)). (B and C) Lip Bumpers Models (Care (2018)).

99

100 **Botulinum Toxin Type-A**

101 Dabrowski and Medicine (2005), present a case of an LNS patient who underwent botulinum toxin A
102 (BTX-A) treatment injected into the bilateral masseters. The active principle of BTX-A is to temporarily
103 prevent presynaptic release of acetylcholine, causing motor plaque dysfunction and muscle weakness. As
104 reported, the treatment resulted in a significant reduction in self-injurious behavior and healing of the
105 patient's local lesions. This work suggested a biological mechanism of action of BTX-A in the central
106 and peripheral nervous system, which results in a reversal of this behavioral pathway. In the treatment
107 of the mentioned study, BTX-A was administered in both masseter muscles, with 20 units of BTX-A
108 being injected at each site, meaning a total of 40 units per muscle group. The toxin was reconstituted with
109 1cm³ of saline solution; its application was performed using a 27-gauge needle and 1cm³ syringe. These
110 applications were repeated every 3 months for a series of three visits. BTX-A was well tolerated, and
111 benefits lasted up to 10 weeks, when at last the behavior returned, requiring the use of restrictions. During
112 this treatment the patient was able to return to school, his wounds on his hands, lips and tongue healed
113 completely, his speech ability improved, although he continued to be abnormal. According to the authors,
114 no impact was observed on the ability to eat or swallow, which contributed to the patient's physiology. The
115 family emphasized a decrease in self-harm behavior as well as hostility. The conclusion of the treatment
116 suggested that BTX-A may be more active, either directly on the peripheral nervous system or indirectly
117 on the central nervous system, interfering with the pathway of behavior that causes self-mutilation to
118 occur in the LNS. Other study carried out by Gutierrez et al. (2008), reports the application of BTX-A on
119 the muscles of a 30-year-old male patient. According to Gutierrez, the application of BTX-A in muscles
120 instead of masseters is due to the patient having his lesions mainly on the lips. The author of the study also
121 points out that the other method employed by Dabrowski and Medicine (2005) requires significant doses
122 of BTX-A and may have spread to the pharyngeal muscles, thus affecting dysphagia. In this methodology
123 2 sessions were applied every 3 months, the injections in the both zygomatic muscles, in the lower part of
124 the orbicularis oculi muscle and lower upper eyelid of the lip. During applications, there was a significant
125 drop in oral self-mutilations. This study reinforces the results of the therapeutic approach of BTX-A,
126 reporting a decrease in harmful behavior, improvement of patient's tissues and no adverse side effects.
127 Despite the limitations of these studies, because it is applied in only two invidious, it is a safe and effective
128 alternative therapeutic treatment for the decrease or elimination of the self-mutilations in LNS(Dabrowski
129 and Medicine (2005); Gutierrez et al. (2008)).

130 **FINAL CONSIDERATIONS**

131 The technical literature concludes that there are no specific references methods for the prevention of this
132 type self-mutilation, methods need to be developed and applied according to the needs of each patient. As
133 an alternative to dental extraction, it is suggested a combination psychiatric therapy, pharmacological,
134 dental treatment, personalized mouthguard and, in extreme cases, the application of treatment based
135 on botulinum toxin type-A is a viable option in reducing, decreasing and in eliminating self-injurious
136 behavior involving the oral pathways.

137 **AUTHOR CONTRIBUTIONS**

138 All authors contributed equally to the elaboration, revision and approval of the final article.

139 **COMPETING INTERESTS**

140 No competing interests were disclosed.

141 **GRANT INFORMATION**

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