Botulinum toxin (BoNT) is a very potent biological toxin produced by several species of the Clostridia bacteria family, such as Clostridium botulinum [1, 2].More recently, a large number of animal and clinical studies have shown that injections of BoNT-A into the masticatory muscles could produce several adverse events, such as muscle atrophy, alterations of the muscle's histological composition, replacement of contractile tissue with fatty tissue [30-32], muscle weakness [33], reduction in maximum bite force, decrease in masticatory performance [34], and reduction in mandibular bone volume and other bony structural changes mainly in the mandible's head and alveolar region [35, 36].Some of the proposed analgesic effects of BoNT-A are: (1) suppression of the peripheral and central release of transport neurotransmitters (such as glutamate, calcitonin gene related peptide (CGRP), and substance P (SP)) to sensory regions of the trigeminal ganglia; (2) regulation of the pain modulation system by influencing the gamma-aminobutyric acid (GABA) and opioid-ergic systems; (3) reduction of microglia activation; and (4) modulation of ion channels [transient receptor potential vanilloid 1 (TRPV1), calcium (C+), and sodium (Na+)] [6, 9-12].Results from well conducted randomized placebo-controlled clinical trials (RCTs) on the effects of BoNT-A on persistent M-TMD differ, but those showing positive effects of BoNT-A indicate improvements in pain levels, somatosensory alterations, muscle tenderness, jaw mobility, and psychological well-being [23-29].Thus, due to its analgesic properties, BoNT-A is used as a treatment approach for chronic pain conditions such as chronic migraine (on-label), but also other pain conditions such as neuropathic, back, pelvic, and myogenous temporomandibular disorder (TMD) pain (M-TMD) (off-label) [13-16].M-TMD is the most common (45%) diagnosis among the TMD diagnoses and is characterized by regional pain and increased tenderness in the masticatory muscles, diminished masticatory performance, and restricted jaw movements [17].Initially, the analgesic effect in neuromuscular disorders and musculoskeletal pain was attributed to the muscle relaxant effect, until the anti-hyperalgesic effect in non-muscular pain models was unequivocally demonstrated in human and animal models [6, 7].