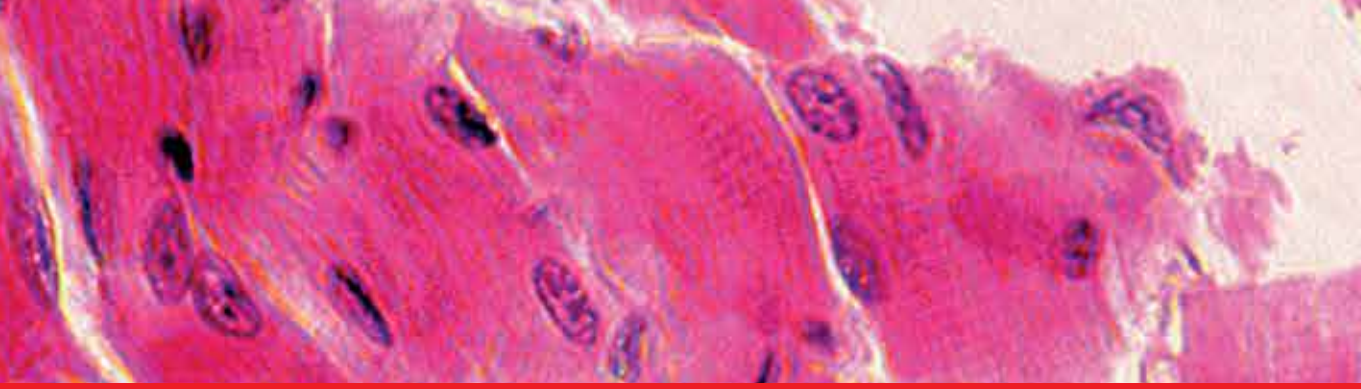

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Dystonia
Different Prospects

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DYSTONIA - DIFFERENT PROSPECTS

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Contributors

Nicolas Patricio Skármeta, Paula Andrea Espinoza-Mellado, Pedro Chana, Nikolina Semerdjieva, Ivan Milanov, Philippos Gourzis, Maria Skokou, Evangelia Eirini Tsermpini, Adamantia Giamarelou, Athanasios Gogos, Tamer Rizk

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Meet the editor

Tamer Rizk, MD, FRCPCH, HMPDip (UK), is a consultant pediatric neurologist in Saint John Regional Hospital, New Brunswick, Canada. He is an assistant professor of pediatric neurology. Tamer Rizk was born in Alexandria, Egypt, and graduated from Alexandria Medical University. He has a variety of publications and research interests, including general pediatric neurology, movement disorders, epilepsy, and cerebral palsy. Professor Rizk is author of 44 publications, including books such as: *Botulinum Toxin-A in Pediatric Spasticity* and *Epileptology: The Modern State of Science* published by InTech. He is a member of the British Paediatric Neurology Association, International Child Neurology Association, International Neurotoxin Association, and the Royal College of Paediatrics and Child Health; UK Consultation Panel with an interest in Community Child Health, Neurology, Neuro-Disability & Mental Health.

Contents

Preface

Dystonia is considered one of the most controversial diseases when it comes to diagnosis, classification, and evidence-based lines of management. Each case is different, and it can be quite challenging to get these movements under control.

Dystonia is a wide-spectrum disorder that affects all age groups. Management of dystonia is challenging, and specific goals should be identified. Dystonia is considered one of the most disabling conditions in the pediatric age group, which may remain until adulthood. Treatment is usually unsatisfactory, and patients will show limited response to pharmacotherapy.

Current treatment aims to help decrease the frequency of abnormal involuntary movements, improve posturing, and prevent the subsequent development of contractures. Many modalities are discussed in the management part, including pharmacotherapy, oral medications, cannabis, botulinum toxin injection, and surgical interventions like intrathecal baclofen pump and deep brain stimulation for patients with generalized dystonia who failed oral pharmacotherapies.

Bearing in mind the new classification, where the term “primary” is no longer recommended, and that in the majority of cases it resembles the new and more precise term “isolated”, both terms are used in this chapter. To be correct when providing information from the studies cited, it should be understood that time and effort are needed to replace completely the old terminology with the new one.

A full chapter was assigned to non-motor comorbidities encountered with dystonia, including sleep, psychiatric disorders, cognition, as well as pain and sensory symptoms, their pathophysiological and biochemical mechanisms, relations with symptomatic treating strategies for abnormal movements, and specific treatment for non-motor signs.

The book contains four chapters that discuss dystonia from new perspectives. The chapters have been written by different specialists from many countries. Dystonia may result from either diffuse or localized pathology of the cerebral cortex, brain stem, or spinal cord. Management of dystonia is challenging, and specific goals should be identified.

Meige’s syndrome, or "oromandibular dystonia," may be misdiagnosed as *temporomandibular joint* or psychogenic disorder, which will alter management and delay proper treatment. Dystonia with non-motor disorders includes sleep, cognitive, pain, sensory, and psychiatric disorders, and their pathophysiological and biochemical mechanisms and specific treatment are discussed.

This book will be of interest to GPs, neurologists, family physicians, and internal medicine specialists.

Professor Tamer Rizk, MD, FRCPCH, ProfDip HMPDip (UK)
Department of Pediatrics
Saint John Regional Hospital
New Brunswick, Canada

Introduction

Chapter 1

Introductory Chapter: Dystonia - Different Prospects

Tamer Rizk

Additional information is available at the end of the chapter

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1. Introduction

Movement disorders are considered one of the most controversial diseases when it comes to diagnosis, classification, and evidence-based lines of management, each case is different, and it can be quite challenging to get these movements under control [1].

Dystonia is a wide-spectrum disorder which affects all age groups. Etiology of dystonia is usually diverse; in some cases within the pediatric age group, the presence of spasticity can make the diagnosis more difficult. For example, cerebral palsy patients can suffer from dystonia and spasticity, though most of pediatric cases with cerebral palsy will suffer from spasticity alone. Dystonia may result from either diffuse or localized pathology of the cerebral cortex, brain stem, or spinal cord. Management of dystonia is challenging, and specific goals should be identified. Dystonia is considered one of the most disabling conditions in pediatric age group which may remain till adulthood, treatment is usually unsatisfactory, and patients will show limited response to pharmacotherapy [1].

Dystonia is a neurological disorder of patterned, involuntary, repetitive, or sustained contraction of antagonist group of muscles. This results in twisting movements and ends in abnormal posturing. Primary dystonia is considered the most common form of dystonia encountered through neurology practice. Isolated dystonia usually starts during childhood years or early adolescence. It usually runs a progressive course with marked disability and functional impairment. Recent advances in genetics elaborated more than the well-known monogenic forms of isolated dystonia due to DYT gene defects; the etiological spectrum is now widened with great variance in phenotype. Many genes which were thought to be responsible to cause certain disease were recently proven to be responsible for dystonia as well which results in more complex phenotype [2].

Current treatment aims to help decrease the frequency of abnormal involuntary movements, improve posturing, and prevent the subsequent development of contractures. This will reduce

pain and facilitate better quality of life. These include oral pharmacotherapy, e.g., trihexyphenidate (Level A Class I–II); botulinum toxin injection for cases of localized or segmental dystonia, e.g., cervical dystonia (Level A Class I–II); and surgical interventions like intrathecal baclofen pump; and deep brain stimulation (DBS) for cases with generalized dystonia who failed oral pharmacotherapies [3].

2. Management modalities

Intrathecal baclofen proved to be effective in progressive dystonia in selected cases. Deep brain stimulation is more effective in controlling primary generalized dystonia. Intracranial stimulation of the postero-latero-ventral region of the internal globus pallidus in patients with dystonia-choreoathetosis cerebral palsy significantly improved their level of functionality and motor abilities, reduces their pain, and improved their overall quality of life. Synergetic effect was proved to be highly effective in treating primary generalized dystonia where both surgical modalities were used and produced excellent control of dystonia. It can reach up to 97% improvement regarding hygiene, posturing, and daily life activities [3].

Medical cannabis have been explored in a variety of medical conditions which are not controlled with the current treatment modalities. Cannabidiol oil has been studied in pediatric cases with complex motor disorders; significant improvement in control of spasticity and dystonia was achieved; it was well tolerated and showed good effect on sleep pattern, pain, and overall quality of life [4].

3. Presentations

Dystonia has various forms of presentations; one of the popular forms is Meige's syndrome or "oromandibular dystonia"; it is considered as one of the most important forms of focal dystonia as it may be misdiagnosed as temporomandibular joint disorder or psychogenic disorder which will alter the management plan and delay proper treatment. That chapter describing oromandibular dystonia will cover its etiology, diagnosis, and available lines of management. Furthermore, the consensus update will be discussed, with recent classification of dystonia focusing on its clinical characteristics and etiology. The first focuses on the age of onset, body distribution, chronological pattern, coexistence of other movement disorders, and other neurological manifestations. The body distribution is classified to focal, segmental, multifocal, generalized, or hemi-dystonia. Associated features distinguish isolated dystonia in both genetic and idiopathic cases that are often resembled to as primary dystonia and combined dystonia. The second axis allows further division according to the presumed etiology.

Although dystonia is a rare condition in general population, the "pure," primary, and isolated dystonia is the third most common movement disorder, after essential tremor and Parkinson's disease; dystonia and associated disorders influenced a major impact on quality of life.

Concepts on phenomenology have also renewed with decades, considering dystonia to be a solely motor disorder to an increasing recognition of associated neurological or psychiatric features which indicate that the disorder is not purely motor. This resembles the growing knowledge on dystonia's pathophysiology where the recent insights from neurophysiologic studies identified functional abnormalities in the basal ganglia sensorimotor network and, more recently, the cerebellothalamocortical pathway. Besides the well-known lack of inhibition at different nervous system levels, dystonia is specifically characterized by abnormal sensory feedback, maladaptive plasticity in the sensorimotor cortex, and loss of cortical surround inhibition.

Bearing in mind the new classification, where the term "primary" is no more recommended, and the circumstance that in majority of cases it resembles the new and more precise term "isolated," both terms are used in this chapter, in order to be correct when providing information from the studies cited, fully understanding that some time and efforts are needed to replace completely the old terminology with the new one.

Dystonia with non-motor co-morbidities, including sleep and psychiatric disorders, cognition, as though as pain and sensory symptoms, their pathophysiological and biochemical mechanisms, relations with the symptomatic treating strategies for the abnormal movements, and specific treatment for the non-motor signs.

Many antipsychotic drugs have been used to control these comorbid conditions. Neuroleptics caused variety of intolerable side effects, among which drug-induced movement disorders could be seriously problematic. Tardive syndromes, represented by tardive dyskinesia and tardive dystonia, still remain challenging in many respects.

"Dystonia tarda" was a term firstly used in 1973 to define a dystonia which appeared as a delayed undesirable effect in patients exposed to neuroleptic drugs. Case descriptions appear in the literature even earlier, but a definition of the term "tardive dystonia" came from Burke et al. [5] who also implemented criteria for the diagnosis. The syndrome consists of involuntary, sustained muscle contractions, usually slow, often painful, affecting the face, neck, limbs, or trunk. The involuntary muscle contraction(s) often cause abnormal postures and twisting movements, which are often disfiguring and socially awkward.

Tardive syndromes manifest in a variety of persistent motor and sensory syndromes, manifesting as an adverse reaction from antidopaminergic agents or, less often, by other types of drugs. Tardive dyskinesia was the first to be observed, in the 1950s, typically comprising rhythmic, repetitive oro-buccal-lingual involuntary movements, which however can also appear in the trunk, limbs, and pelvis. Later, it was also described as a distinct, frequently co-occurring, or independently manifesting condition. Although the term "tardive" implicates a long exposure and delayed onset, tardive syndromes can actually show up even days after administration of the offending agent, notwithstanding that risk increases with longer exposure durations. Another important feature is their persistent nature, meaning that they persist or even worsen following discontinuation of the offending drug.

Researchers have difficulties to deal with it separately. Moreover, there is often some confusion in the literature, as authors may sometimes use the term tardive dyskinesia in order to

refer to a variety of tardive syndromes. Much work examines tardive syndromes in general, and it is difficult to extract data referring specifically to tardive dystonia. Still, the distinction and separate examination are important, because it differs from tardive dyskinesia in respects of presentation, course, prognosis, and treatment; it is frequently more debilitating and treatment resistant; it is associated with poorer quality of life, reduced treatment compliance, and psychiatric morbidity. Another task is to differentiate tardive dystonia from acute dystonia, emerging acutely and within days after the initial administration of anti-D2 agents, in young males, as well as from other types of dystonia.

In their pioneering work, Adityanjee et al. [6] had hoped that tardive dystonia together with tardive dyskinesia would in the future be a matter of historical interest, thanks to the advent of new, better antipsychotics. Twenty years later, these movement disorders are not at all lost, not yet forgotten. Continuing to be a serious burden, they call for better understanding, prompt recognition, prevention, and better treatment.

Author details

Tamer Rizk

Address all correspondence to: drtamergaber@gmail.com

Dalhousie Medical School, Saint John, NB, Canada

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Oromandibular Dystonia (OMD)

Chapter 2

Orofacial Dystonia and Other Oromandibular Movement Disorders

Nicolás Patricio Skármeta,
Paula Espinoza-Mellado and Pedro Chana

Additional information is available at the end of the chapter

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Abstract

Orofacial movement disorders (OMD) are a group of conditions that affect the motor aspect of the trigeminal, facial, and hypoglossal cranial nerves. These alterations are produced by pathologic disorders affecting the central nervous system, manifesting as isolated or combined hyperkinetic dysfunctional activities on the masticatory, facial mimic, or tongue musculatures. A comprehensive understanding of orofacial dystonias is essential to identify different variants of OMD that could be easily mislabeled or misdiagnosed. In this chapter, the authors focus on different aspects of the pathophysiology, epidemiology, clinical features, and management of orofacial dystonias and other movement disorders that are poorly recognized but not uncommon presentations of OMD, such as orofacial dyskinesias, drug-induced orofacial reactions, tardive orofacial syndromes, and bruxism.

Keywords: oromandibular dystonia, orofacial dystonias, orofacial dyskinesias, tardive dyskinesias, drug-induced extrapyramidal reactions, sleep bruxism/awake bruxism

1. Introduction

The first written medical description of OMD was made in 1910 in Dr. Meige's paper entitled "Le convulsion de la Face, une forme clinique de convulsione faciale Bilateral et Mediane." However, the clinical features outlined by Dr. Meige were not the first description of the phenomena, some pictorial representations dating from the sixteenth century were the first recorded description of OMD. Meige's description summarized the clinical signs featured in orofacial dystonia, differentiating them from other movement disorders that affect the lower half of the face. He also emphasized relevant details such as the involvement of different

structures of the lower face, the description of specific precipitating factors, maneuvers that tended to milden and restrained the involuntary movement disorders, or their complete remission during sleep. Almost half a century later, OMD started to gain attention again [1].

Oromandibular dystonias (OMDy) are focal dystonias affecting the motor aspects of trigeminal, facial, and hypoglossal cranial nerves. Most OMDy are diagnostically challenging, mainly because they may have numerous presentations and severities, triggers may be hard to recognize, and orofacial movements may be quiescence during periods being often primary or idiopathic [2]. Consequently, OMDy may be commonly mistaken with temporomandibular disorders, spontaneous condylar dislocation, hemimasticatory or hemifacial spasm, and psychogenic disorders [3–7]. In this chapter, the authors focus on different aspects of the pathophysiology, epidemiology, clinical features, and management of OMDy that may be useful to identify them from other movement disorders that are poorly recognized but not uncommon, such as orofacial dyskinesias, tardive orofacial syndromes, and bruxism.

2. Oromandibular dystonia

2.1. Definition and clinical presentation

Oromandibular dystonia is an infrequent form of focal dystonia, which affects the lower half of the face and mandible [8]. It manifests like sustained or intermittent, involuntary muscle contractions, which can cause repetitive movements of the lower facial, masticatory or tongue muscles or sustained abnormal postures in the lower face [9]. Dystonic oromandibular movements may present as isolated or combined movements, affecting an isolated group of mandibular muscles (e.g., symmetric contraction of the elevators of the mandible, producing jaw closing dystonia) or various groups of muscles (asymmetric or alternated contraction of jaw depressors and elevators resulting in mandibular tremor or jaw deviating dystonia) [9].

Because clinical presentations are not uniform, focal OMDy can be characterized phenomenologically by the functional motor activity involved in the oromandibular movement. Consequently, OMDy can be subdivided into different subtypes: jaw-opening dystonia, jaw-closing dystonia, jaw-deviating oromandibular dystonia, perioral dystonias, and/or lingual oromandibular dystonia [10]. When OMDy occurs together with blepharospasm, it is usually called cranial dystonia or Meige syndrome [11]. Toloza and Marti suggested that most cases of OMDy occur in combination with blepharospasm, only manifesting independently in 2–23% of the cases [12]. Isolated jaw-closing dystonia seems to be the more prevalent form of OMD and is less likely to be associated with other craniocervical dystonias. Approximately 32% of jaw OMDy are associated with facial grimacing, lip pursing, or other facial contortions [13]. Spontaneous remission is uncommon but may occur within the first 5 years [11]. Morning benefit (milder symptoms during morning) and overflown phenomenon (aberrant muscle activation during certain tasks) are also relatively common in OMDy patients [14].

The dystonic muscle contractions may interfere with several orofacial motor activities like mastication, swallowing, and verbal and non-verbal communication, explained probably by the uncoordinated and deviated muscle masticatory activity with antagonist cocontractions

found in electromyographic studies [15]. Also, depending on the subtype of OMDy, patients may present trismus, dental wear, uncontrollable tooth clenching or grinding, frequent oral ulcers, forceful involuntary closures, jaw dislocation, dental restorations damage or fractures, temporomandibular joint overload, facial contortions, lip sucking or smacking, lip pursing, chewing-like movements, mouth retraction, and platysma contractions [13, 16–18]. Generally, the masticatory spams disappear during sleep [19].

OMDy can be triggered by mandibular activities, such as talking, yawning, chewing, or swallowing, often causing severe social impairment, reduced quality of life, and weight loss [20–22]. Also, patients frequently report exacerbating factors such as emotional stress and other daily activities like driving, reading, praying, looking upward/downward, or chewing [11]. Jaw and facial pain is also frequent and can often mislead the clinician, especially because OMDy are rare, may have remittance periods, and triggers are usually hard to identify [23]. Sensory trick ("geste antagonistique") may ameliorate OMDy symptoms temporarily, being more effective in jaw-opening dystonia more than jaw-closing dystonia [24, 25].

2.2. Epidemiology

The prevalence of the dystonic oromandibular movements varies within the different reports. In the United States, the estimated prevalence has been reported from 0.52 to 30 cases per 100,000 [26–28]. Other studies have reported a prevalence of 6.9 cases per 100,000 and an incidence of 3.3 cases per million [26, 29]. Women seem to be more affected than men, in a female: male ratio of 3:1, typically with adult age onset near the sixth decade of life (more prevalent between 45 and 75 years) [9, 29]. A recent multicentric study featuring centers from the United States, Canada, Germany, Australia, England, France, and Italy reported that from all forms focal dystonia, OMDy had a prevalence of 8.7%, being one of the less prevalent subtypes of focal dystonia [30] (**Table 1**).

2.3. Etiology

The etiology of OMDy may be primary (idiopathic) or secondary. The primary form is the most common form of OMDy, not involving any central nervous system pathology, brain lesion, or tumor. Studies by Tan and Jankovic reported that most of OMDy were primary, accounting for 63% of the cases reported [31]. The pathophysiology of OMDy is currently

	Number of cases	%
Primary	11	44
Neurodegenerative diseases (Parkinson's disease, Huntington's disease, other)	9	36
Secondary neuroleptic	3	12
Functional	2	8

Table 1. Prevalence and etiology OMD from Movement Disorders Tertiary Center, Centro de Trastornos de Movimientos (CETRAM), Chile, January 2014–October 2015.

unknown, but several pathophysiological explanations have been pondered as probable causes, such as basal ganglia dysfunction, hyperexcitability of motor neurons interneurons related to signaling pathways, loss of inhibition, aberrant dopamine signaling, monoaminergic dysfunction, abnormal plasticity, and abnormal sensory function [32–34].

The most common cause of secondary dystonia is tardive dystonia (drug-induced) reported in 22.8% of the cases. Other causes described are peripheral-induced OMDy in 9.3% of the cases, postanoxic states OMDy representing 2.5% of the cases, neurodegenerative disorders 1.8%, and head injury-associated OMDy accounting for 0.9% of the cases [13].

Tardive OMDy produced by haloperidol, thioridazine, and metoclopramide accounts for the majority of the reports of drug-induced cases. Also, calcium channel blockers antivertiginous drugs such as flunarizine and cinnarizine have also been associated with OMDy [35].

Secondary OMDy can be caused by brainstem lesions, cerebrovascular disease, traumatic brain injury, and neurodegenerative disorders including multiple system atrophy, progressive supranuclear palsy, Huntington's disease, and neuroacanthocytosis. OMDy secondary to neurodegenerative disorders often present coexisting symptoms, such as chorea, seizures, amyotrophy, or subcortical dementia [19].

Peripheral trauma is a known to be causative or predisposing factors in several neurological disorders. Despite that most reports relating orofacial or dental trauma/procedures to OMDy are mostly anecdotal, the precise relation of peripheral trigeminal trauma and the onset of OMDy is still unclear [36].

Traumatic injuries, fractures, surgeries, and peripheral trigeminal nerve deafferentation or amputation have been associated with the onset of OMDy [37]. Also, numerous ambulatory dental procedures have been described as possible causative or predisposing factors of OMDy [38]. Ill-fitting dentures, endodontic treatments, gingivectomy, tooth extraction, apicectomy, prosthodontics, TMJ arthroscopy, and dental implants had been reported in dental and neurological literature [8, 39–44].

Sankhla et al., in a review of 9083 patients, reported that of a total 197 patients diagnosed with OMDy, 27 cases had a history of facial trauma prior the onset of the dystonia [45]. Jankovic and Van der Linden noticed that 65% of the dystonia and tremors were associated with trauma-induced events [37]. Causation, however, is scarce as dental interventions are widespread while OMDy is very infrequent [29].

Eleven gene mutations have been identified as putative causes of dystonia. Of those, DYT6/THAP1 gene variations have been involved in early-onset, progressive craniocervical dystonia (OMDy, spasmodic dysphonia, and cervical dystonia) [46].

2.4. Treatment approaches

The treatment of OMDy is challenging and often requires multidisciplinary evaluation. Proper dental and oral evaluation is needed to assess orofacial and oropharyngeal function [29]. Triggers (especially relevant to sensory tricks) and the subtype of OMDy should be carefully identified.

Audiovisual recordings may be helpful in analyzing both. Adequate nutrition must be maintained when OMDy interferes with nutrition [29].

Physical therapy or speech therapy can be helpful sometimes. Peripheral afferent blocks targeted to the muscles with 5–10 ml 0.5% lidocaine solutions seem to improve unless temporarily OMDy, suggesting that somatosensory input may be relevant in the pathogenesis of dystonia [47].

Sensory tricks (geste antagoniste) do not seem to provide adequate long-term relief and many times requires actions that interfere with normal functional activities [29]. Reports indicate that sensory tricks like pressing the teeth or lips with the fingers, placing objects in the mouth (cigarettes, gum, or object between the molars or chin), singing, or humming may be helpful in one-third of the patients [24, 25, 45]. Oral appliances have shown to be useful in some cases [24, 42], especially when they successfully mimic the patient's sensory tricks. Singer and Papapetropoulus suggested that sensory tricks worked better for jaw-opening dystonia rather than in jaw closing dystonia [16].

A recent study by Yoshida et al. found that older patients with intraoral sensory tricks were more likely to respond to an oral appliance treatment compared to patients who do not have sensory tricks. Also, the authors reported that splint therapy was more effective in patients with jaw-closing dystonia who reported sensory tricks that involved mastication [14].

Deep brain stimulation targeting the externus globus pallidus has shown some continued efficacy, reporting interesting result in patients with Meige syndrome, but the evidence is still preliminary [48–50].

Pharmacological treatment of dystonia is mostly based on empirical experience rather than supported by rationale scientific evidence [51]. Oral medications are rarely beneficial in improving dystonic symptoms and may include anticholinergic drugs, baclofen, dopaminergic drugs, and benzodiazepines [52]. Tetrabenazine reported benefits in the treatment of the symptoms in 26 to 60% of OMDy patients but is frequently associated with important side effects like parkinsonism and suicidal ideation [7, 53]. Zolpidem in doses ranging from 5 to 20 mg has shown some promising results, but since these findings are only in a relatively small number of cases, prospective clinical trials are needed to determine its effectiveness [54, 55].

Chemodenervation with botulinum toxin (BT) is considered by most to be the first line of treatment. However, there are no high-level clinical trials to support this claim, and the evidence is mainly based on small series of cases [56]. Hallett et al. in an evidence-based review concluded that abobotulinumtoxin A and onabotulinumtoxin A have level C recommendation according to American Academy of Neurology Classification for the Quality of Evidence (AANC) and level U for incobotulinumtoxin A and rimabotulinumtoxin B (inadequate data or treatment still unproven) [57]. As expected, a recent systematic review that intended to evaluate the effectiveness of BT in OMDy concluded that due to the variability of the outcomes there is insufficient evidence to recommend or refute BT as a treatment option [58]. Nonetheless the scarce data, empirical experience over past 20 years has shown that BT is an effective and safe approach in the treatment of OMDy [59]. Because OMDy encompasses a broad range of musculature, it is among the most challenging forms of focal dystonias to treat

with BT [60]. The outcome of the injection depends critically on proper muscle identification, dose selection, and managing patient's expectations [29].

2.5. Subtypes of OMDy, muscle selection, and botulinum toxin application technique

2.5.1. Jaw-closing dystonia

The muscles responsible for jaw closing are the masseters, temporalis muscles, and medial pterygoid muscles. In jaw-closing dystonia, the masseter and temporalis are the primary targeted muscles, mainly because BT application is percutaneously and relatively easy to perform.

2.5.1.1. Masseter muscle

The masseter muscle is one of the major muscles of the mastication, with a thick quadrilateral muscle disposition. It is primarily involved in the elevation of the jaw and the deviation during its ipsilateral activity. The anterior two-thirds (superficial Masseter) originates from the lower border of the zygomatic arch and the lateral surface of the ascending mandibular ramus, projecting downward and posterior to the lateral aspect of the lower border of the ramus (near the second molar in its anterior border) and mandibular angle (posterior border). The last third has a more posterior origin in the zygomatic arch projecting in a vertical direction towards the central part of the ramus [61, 62] (**Figure 1**).

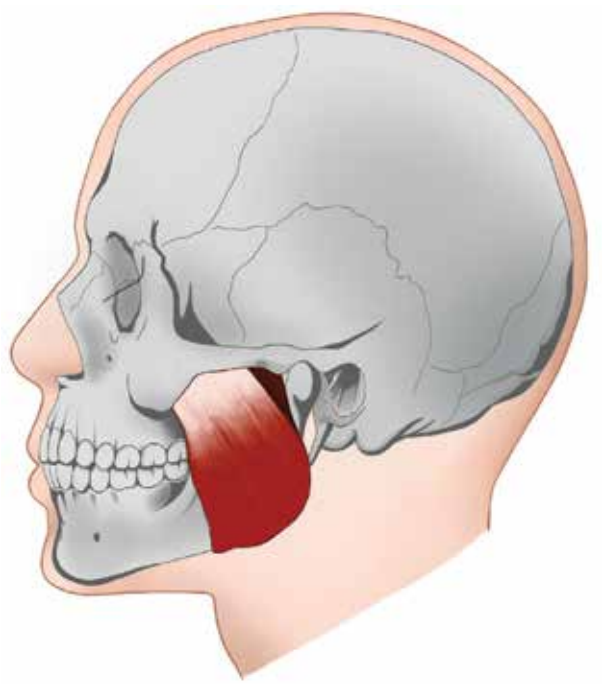

Figure 1. Masseter muscle anatomy.

The alignment of masseter muscle fibers is mostly oriented to give a biomechanical advantage towards performing jaw closing and elevation, also having some importance in lateral deviation and protrusion of the mandible. Hence it is of primary importance in the treatment of jaw-closing dystonia.

The application of botulinum toxin must be individualized for each patient. Usually, 2–3 points of injection are recommended since the masseter is a superficial muscle, clinically palpable the technique can be performed without EMG guidance. The muscle is usually approached by inserting the needle injection 1 cm anterior to the posterior border of the ramus and is easily palpable by making the patient clench. If EMG is used, the EMG discharges will ensure that the needle is in the masseter and not in the parotid gland [19] (**Figure 2**).

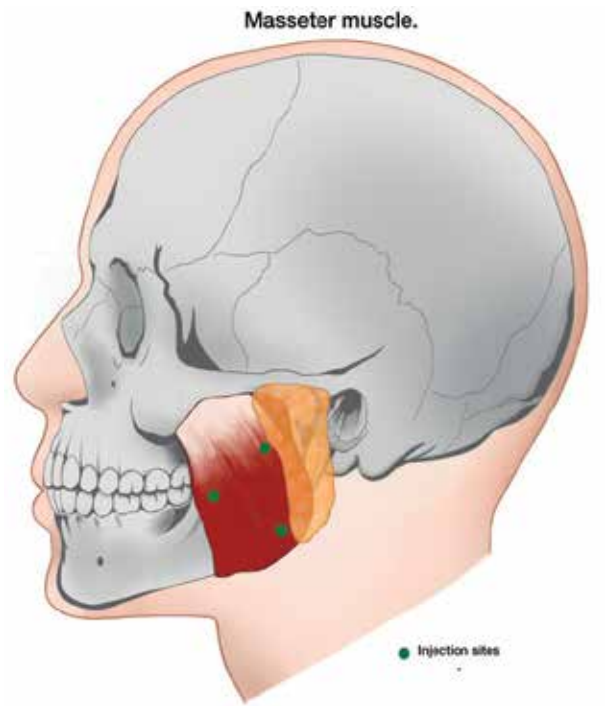

Figure 2. Masseter muscle recommended injection sites.

2.5.1.2. Temporalis muscle

The temporalis muscle is also one of the major mandibular elevators, consisting of three separate muscular fascicles with different vectorial orientations, displaying a distinctive fun shape and occupying almost the entire temporal fossa (conformed by the parietal, sphenoid, temporal, and zygomatic bones) on the lateral aspect of the skull.

It has three different fascicles (anterior, middle, and posterior) that merge into one sole muscle coursing inferiorly and medially to the zygomatic arch, where they converge in the temporalis tendon to insert in the coronoid process.

The three fascicles are aligned in a different disposition. The anterior fibers are oriented vertically, the middle fibers are disposed on a diagonal orientation, and the posterior fibers possess a more horizontal disposition. The three fascicles functioning altogether are involved in mandibular vertical closure. Anterior and the middle fibers are primarily involved in jaw-closing activities. The posterior fibers involved in jaw closure, but also are influential in promoting the settlement of the temporomandibular joint condylar disc complex into the glenoid fossa and helping retrusion of the mandible after it is protruded. Lastly, it is described that the ipsilateral three fascicles may be relevant in stabilizing the jaw during lateral excursive movements [61, 62] (**Figure 3**).

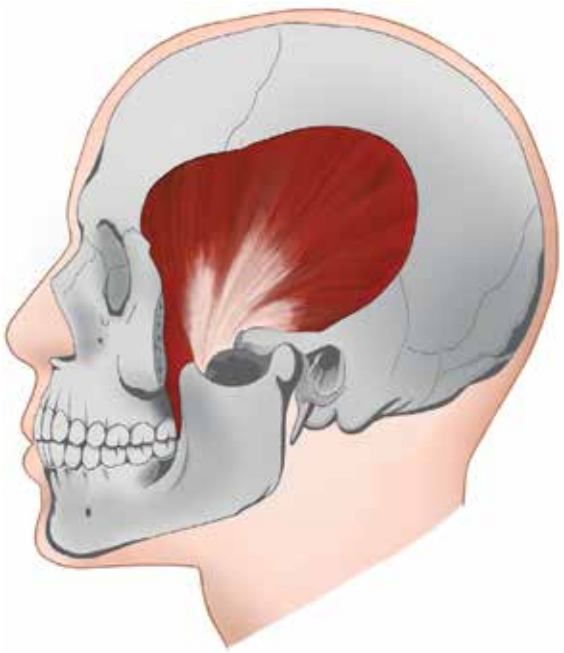

Figure 3. Temporalis muscle anatomy.

The injection technique should be performing at least one point per fascicle. Identification of the anterior portion of the temporalis muscle can be challenging in certain occasions. An easy way to rapidly identify this fascicle is to ask the patient to perform opening, closing, and clench movements repeatedly. This maneuver will contract the anterior temporalis fibers and will help identify the puncture points. The muscle is approached perpendicular to its plane and as highly possible in the temporal fossa. Because of this wide radiating pattern, it is best to give 3–4 injections into the muscle [19] (**Figure 4**).

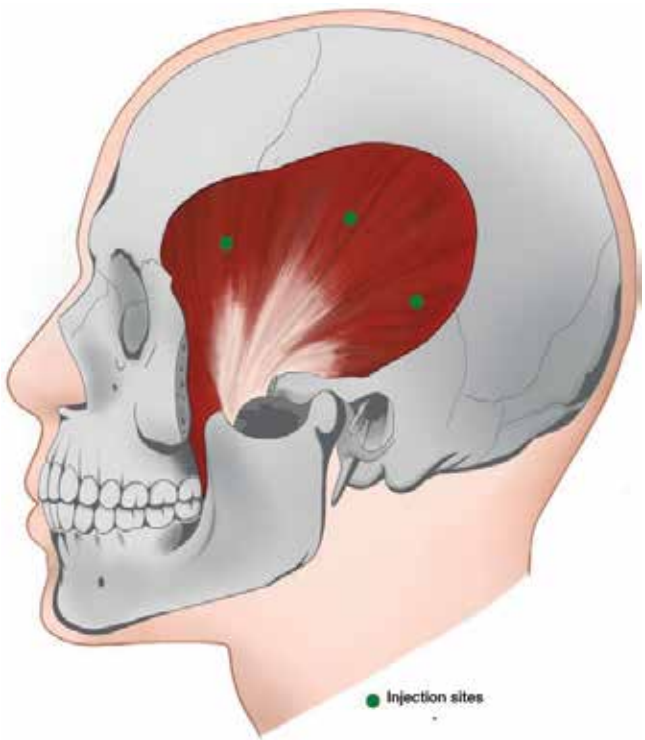

Figure 4. Temporalis muscle recommended injection sites.

2.5.1.3. Medial pterygoid muscle

The medial pterygoid muscle or internal pterygoid muscle is a deep quadrilateral muscle of mastication, primarily involved in the elevation of the mandible. It has two distinct points of origin: first, the "deep head" emerging from the medial surface of the lateral pterygoid plate of the sphenoid. The second point, the "superficial head" arises from the maxillary tuberosity and the pyramidal process of the palatine bone. Both heads orientate in a posterior and inferior direction, inserting at the medial surface of the ramus and mandibular angle via a shared tendinous insertion [62] (**Figure 5**).

The function of the medial pterygoid muscle is primary jaw closure and is considered a functional analog of the masseter muscle. During contralateral mandibular deviation, it acts in conjunction with the ipsilateral inferior head of the lateral pterygoid muscle producing contralateral translatory movement of the mandible and ipsilateral translation of the mandibular condyle. The bilateral activity of these muscles in conjunction with the bilateral activity of the inferior head of the lateral pterygoids results in jaw protrusion [63].

As the lateral pterygoid muscle, the medial pterygoid botulinum toxin application can be performed using an intraoral or extraoral approach.

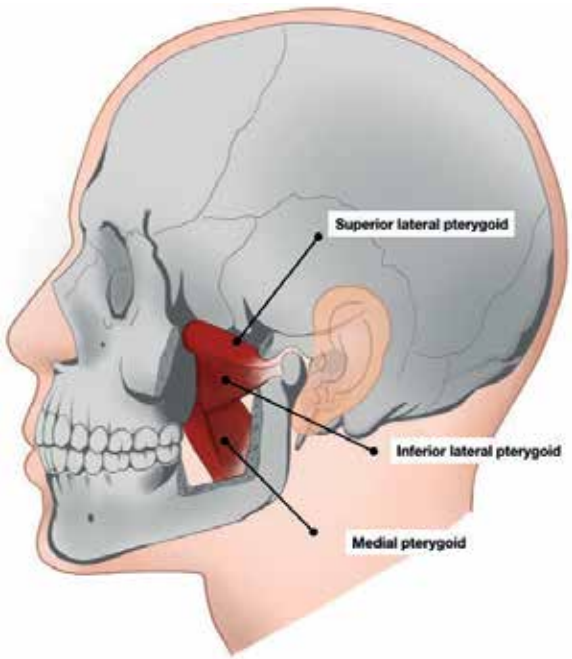

Figure 5. Medial and lateral pterygoid muscle anatomy.

There are two different forms of performing the extraoral injection into the medial pterygoid muscle. From below, inserting the EMG electrode about 0.5–1 cm anterior to the angle of the mandible along the interior aspect of the mandible and angled perpendicularly to the ascending mandibular ramus, the adequate positioning of the electrode should be verified by asking the patient to clench. While performing this approach, the clinician should be careful in avoiding the facial artery [19] (**Figure 6**).

The other approach is more technically complex because the electrode must traverse deep through an extensive amount of tissues and network of vessels (the pterygoid venous plexus). This extraoral approach requires to position the patient in a supine position with the mouth open wide. The punction site should be selected in the window bounded by the lower border of the zygomatic arch, the mandibular notch, the mandibular condyle, and the coronoid process. Then, the needle electrode is directed caudally towards the medial pterygoid muscle [64].

The intraoral technique is easier to perform, especially for those who are more familiar with intraoral injections. The technique must be executed by palping the muscle intraorally and inserting the needle electrode through the pharyngeal wall until the muscle is reached [64].

2.5.2. Jaw-opening dystonia

The muscles involved in jaw opening are the inferior lateral pterygoids and the submental complex (which includes the digastrics, mylohyoid, and geniohyoid muscles). The primary in promoting jaw opening is the inferior lateral pterygoid. The submental complex has a secondary role in promoting jaw opening, primarily assisting jaw opening at the beginning of the aperture.

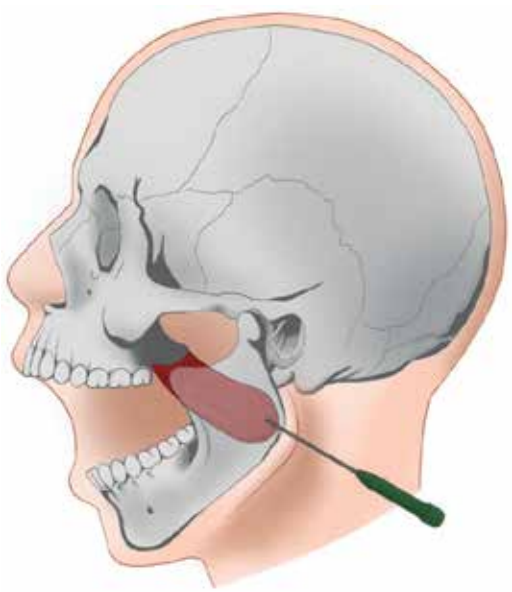

Figure 6. Medial pterygoid muscle extraoral botulinum toxin application technique.

2.5.2.1. Lateral pterygoid muscle

The lateral pterygoid muscle is a nonpalpable masticatory muscle located in the lateral portion of the infratemporal region, primarily involved in both jaw closure and opening. Lateral pterygoid muscle consists of two independent "heads" or "belies" (superior and inferior) that have two separate functional roles. The superior head has his origin in the greater wing of the sphenoid bone. The fibers of the superior head primarily insert in the articular fovea of the mandibular condylar head (accounting 60–70% of the times). A less frequent anatomic variant is the insertion at the temporomandibular joint disc and capsular complex (30–40% of the times). Functionally, the superior head of the lateral pterygoid muscle acts as an active stabilizer of the condyle during the closure [62].

The inferior head of the lateral pterygoid has less diverse anatomic variations, having its origin in the outer surface of the pterygoid plate and inserting in the lower part of the anterior fovea of the condyle and condylar neck. When acting bilaterally, the inferior head of the pterygoid muscle produces jaw protrusion and jaw opening when it acts in conjunction with the suprahyoid muscles. During these activities, the superior head of the pterygoid muscle is inhibited, giving this muscle a unique role in mandibular movement depending on which part of the muscle is activated. Conversely, when the inferior head of the muscle is activated unilaterally, a contralateral deviation of the jaw is produced [63]. Therefore, the inferior head of lateral pterygoid is one of the main targets in jaw-opening dystonia and jaw-deviating dystonia (**Figure 5**).

The access to the lateral pterygoid is complicated and can be performed intraorally or extraorally. Both approaches (intraoral or extraoral) require the use of electromyographic guidance to ensure intramuscular injection.

In the intraoral injection, the patient should be semi-reclined with his/her mouth slightly open and deviated to the contralaterally to the side of the procedure. The insertion of the needle electrode is above the second molar mucobuccal fold. The electrode is directed inward, upward, and backward sliding close to the tuberosity until hitting the pterygoid plate (to inject the inferior head) [65]. The direction of the injection should be oriented towards the middle point of a virtual line connecting the ipsilateral ear's tragus and lobe [66]. A counter-resistance contralateral mandibular deviation can be performed once the needle electrode is placed to ensure EMG discharge (**Figure 7**).

The extraoral technique needs a more profound anatomical knowledge of the infratemporal fossa. The patient should be in a supine position, with the jaw opened at least 20–30 mm wide or sufficiently to create a window bounded by the zygomatic arch (above) and the mandibular notch (below), coronoid process limiting the anterior border, and the mandibular condyle to posterior. To perform the extraoral technique, the clinician should palpate the bony margins with the index and middle fingers. Once located the tentative puncture the needle electrode should be placed anteriorly to the temporomandibular joint and directed upward, forward, and deep under the zygomatic arch towards the sphenoid bones (which forms the sealing within the muscles lies) [67]. Some descriptions suggest that the point of entry to the technique is 35 mm from the external auditory canal (anterior to the condylar neck of the mandible) and 10 mm from the inferior margin of the zygomatic arch. Then, the needle is angled upward about 15° and directed towards the roots of the lasts upper molars to reach the inferior head of the lateral pterygoid [19]. The needle must penetrate (at least

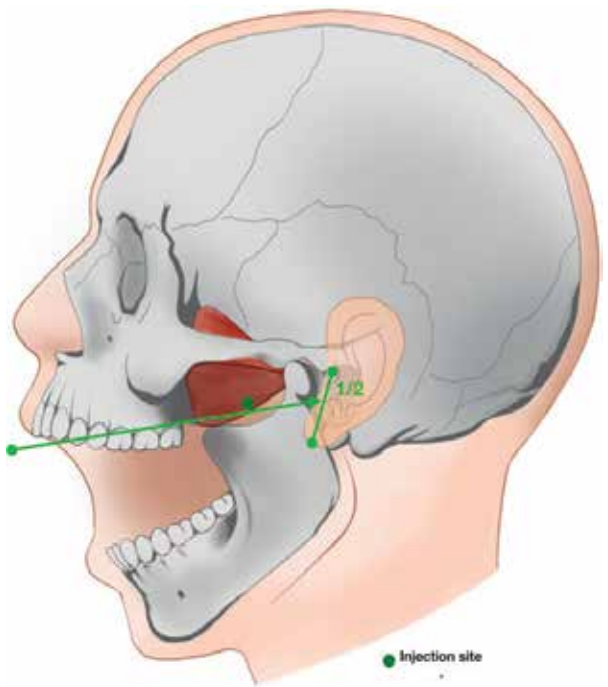

Figure 7. Intraoral injection technique to the inferior head of the lateral pterygoid muscle.

30–40 mm) through the masseter muscle and temporalis tendon before reaching the inferior lateral pterygoid head (**Figure 8a** and **b**).

2.5.2.2. Submental complex

The submental complex is primarily involved in jaw-opening oromandibular dystonia. This complex of muscles is constituted by three of muscles: the digastric muscle, the mylohyoid muscle, and geniohyoid muscle.

2.5.2.2.1. Digastric muscle

Similar to the lateral pterygoid muscle, the digastric muscle has two distinct components: the anterior belly and the posterior belly. The anterior belly has origin at the digastric fossa located in the submental area near the midline. Its fibers extend posteriorly and inferiorly. The posterior belly has its origin in the mastoid notch of the temporal bone and extends inferiorly and anteriorly to join with the anterior belly at the intermediate tendon attached to the hyoid bone. Both bellies participate in the mandible depression (opening). However, the anterior has more functional activity during jaw opening, while the posterior belly is also involved in elevating the hyoid bone during mastication and swallowing.

2.5.2.2.2. Mylohyoid muscle

The mylohyoid muscle is flat triangular muscle immediately situated superior to the anterior belly of the digastric muscle. It has his origin at the mandibular mylohyoid line, extending from the mandibular symphysis to the last inferior molar. The more medial fibers go inferior-medially and posterior towards the midline, where they meet with their contralateral

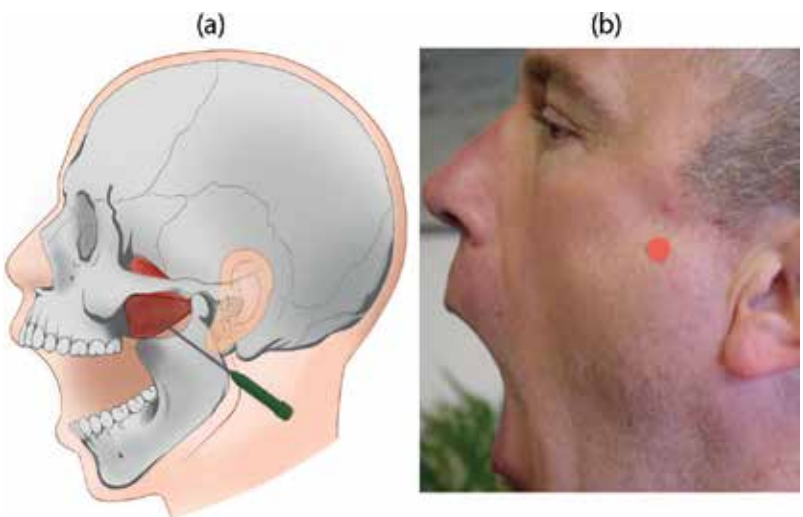

Figure 8. (a) Anatomical landmarks for extraoral injection technique to the inferior head of the lateral pterygoid muscle. (b) Extraoral puncture site for the inferior head of the lateral pterygoid muscle.

counterpart via mylohyoid raphe (where both muscles intermesh). The posterior fibers insert in the anterior surface of the hyoid bone. The mylohyoid assists mandibular opening and draws forward the hyoid bone during swallowing, thereby it also tends to push the tongue upwards (tongue protrusion). Likewise, the capacity to move the lingual floor from side to side helps mastication.

2.5.2.2.3. Geniohyoid muscle

The geniohyoid muscle is part of the oral cavity floor, primarily involved in drawing the hyoid bone forward during swallowing and assisting the opening of the mandible. It is a narrow muscle located superior to the medial border of the mylohyoid muscle. It originates from the mandibular inferior genial spine, extending backward and slightly downwards until it inserts on the anterior surface of the body of the hyoid bone.

In most occasions, the submental complex is almost fused together, making it difficult to separate one from another. These muscles can be palpated with the patient on an open mouth position. The recommended technique is performed by inserting the needle injection about 1 cm from the inferior border of the mandible, slightly lateral from the midline in both sides where the anterior digastric should be located. The anterior digastrics are easy to localize and are usually the initial muscles injected. If the clinical results are not satisfactory or the jaw-opening dystonia is severe, injections into the lateral pterygoids should be considered [19] (**Figure 9a** and **b**).

2.5.3. Jaw-deviating dystonia

The contralateral lateral pterygoid works in conjunction with the ipsilateral medial pterygoid to deviate the mouth to opposite side. The temporalis pulls the jaw to the same side. The injections follow the abovementioned techniques.

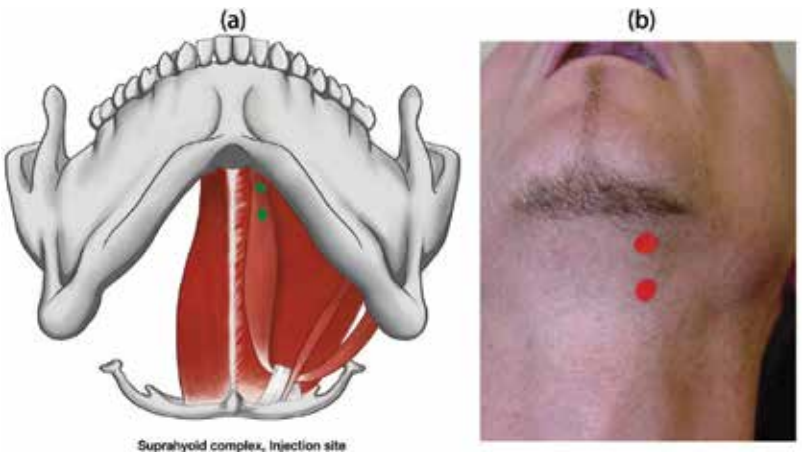

Figure 9. (a) Suprahyoid complex anatomy and injection sites. (b) Extraoral puncture site for the suprahyoid complex.

2.5.4. Perioral dystonia

The orbicularis oris is an intricated facial expression muscle that acts as an oral sphincter, consisting of numerous muscle fibers, partly from the orbicularis and partly from other facial muscles, that encircle the mouth. The angle and more lateral part of the muscle is formed by the buccinator, levator anguli oris, and the depressor anguli oris originating at the median plane of the lips (deep surface of the skin) in the maxilla and mandible. The fiber follows the trajectory of the upper and lower lips, inserting in the mucous membrane of the median lips. The orbicularis oris protrudes and purses the lips, producing grimacing of the mouth. Perioral BT application has been found beneficial in cases that produce severe social disability [68].

2.5.5. Lingual dystonia

Lingual dystonia is a rare but recognized form of OMDy, since the early descriptions made by Meige [11], only being present in about 7.6% of the OMDy cases [13]. Some authors have suggested that more severe forms may indicate the presence of heredodegenerative disease or secondary OMDy [69, 70]. However, there are also reports of severe forms of idiopathic tongue dystonia [70]. The most frequent form of lingual dystonia involves protrusive tongue movements that can be repetitive or sustained. Action-induced lingual dystonia can be triggered by regular physiologic activities such as chewing, swallowing, or speaking [11, 71–73]. Lingual dystonia can be substantially disabling and social embarrassing. Pronounced drooling is frequent in these patients. Also, patients may experience severe difficulties in feeding or wearing dental dentures if the dystonic movements tend to push food or objects out of the mouth [74]. Severe forms, only reported in secondary forms, may obstruct the upper airways and may even require intubation and respiratory support. If lingual dystonia coexists with jaw-closing dystonia, tongue biting may cause severe lingual mutilation [69]. BT injection seems to be an effective treatment approach in dystonic tongue protruding cases [74].

Since that most lingual dystonia cases are involved with tongue protrusive movements, the BT application often targets the genioglossus muscle.

Anatomically, the tongue is divided into two distinct sets of muscles: the extrinsic tongue muscles insert into the tongue from outside origins and the intrinsic tongue muscles insert into the tongue from origins within it. The extrinsic muscles move the whole tongue in different directions, whereas the intrinsic muscles allow the tongue to change its shape (such as curling the tongue in a loop or flattening it).

The genioglossus (genio = "chin") is an extrinsic tongue muscle that originates on the mandible and allows the tongue to move downward and forward. It is a fan-shaped muscle that occupies the majority of the volume tongue body. It originates from the superior genial spine to insert into the hyoid body (inferior fibers) and ventral surface of the tongue (superior fibers of the muscle were then mix with the intrinsic muscles of the tongue). When both genioglossus muscles act bilaterally, it promotes tongue protrusion and makes the lingual dorsum concave. Unilateral action produces deviation of the tongue to the contralateral side. BT application can be performed with a direct injection on the dorsal anterior surface of the tongue, starting at first 5–10 units per side to prevent dysphagia (**Figure 10**).

Figure 10. Genioglossus muscle injection sites.

2.6. Evaluation of treatment outcome

Response to BT application can be assessed by self-reported, observation, or a few available rating scales. The Movement Disorders Society Task Force on dystonia rating scales suggested that Oromandibular Dystonias Questionnaire (OMDQ-25) still needs further assessment to be validated and recommended [75]. However, the OMDQ-25 is clinimetrically valid, reliable, and sensitive to change in evaluating psychosocial and health-related change and improvement in OMDy [22]. Generalized dystonia rating scales, such as Burke-Fahn-Marsden Scale and the Unified Dystonia Ranking Scale, include orofacial subcomponents that can be useful in assessing the severity of the OMDy, guiding the treatment, and assessing the clinical response [29] (**Table 2**).

Type of Dystonia	Muscles Involved	Targeted Muscles	Botox®	Dysport®
			BT dose per side (Units)	
Jaw Closing Dystonia	Masseters	✔	25-50U	100-200U
	Temporalis	✔	20-40U	80-100U
	Medial Pterygoids	☑severe cases or not satisfactory results	15-50U	60-200U
Jaw Opening Dystonia				
	Submental Complex	✔	10-20U	40 - 80U
	Inf.Lateral Pterygoids	☑severe cases or not satisfactory results	15-25U	60 -100U
Jaw Deviating Dystonia	Contralateral Inf.Lateral Pterygoid	✔	15-25U	60-100U
	Ipsilateral Temporalis	✔	20-40U	80-100U
	Contralateral Medial Pterygoid	✔	15-50U	60-200U
Lingual Dystonia	Genioglossus	✔	10-50U	40-200U

Doses and muscle selection cited from [19], [29] and [76].
✔commonly injected in BT application opatative.

Table 2. Oromandibular dystonia subtypes, muscle identification and BT application.

3. Oromandibular dyskinesia and drug-induced extrapyramidal reactions

Orofacial dyskinesias are described as involuntary rhythmic, repetitive, and stereotypic movements of the face, lips, and tongue [77]. Clinical phenomenology varies in complexity and severity, ranging from almost being unnoticeable to complete social impairment (inability to eat, wear prosthetic dental devices, or perform social activities). As OMDy, oral dyskinesias can be spontaneous (primary) or secondary. Secondary dyskinesias are mostly part of drug-induced reactions or tardive syndromes but can also be secondary by subcortical infarcts, peripherally induced (related to edentulism and ill-fitting dentures), or be concomitant with neuropsychiatric conditions, dementia, or mental retardation [17, 78].

Milder forms of oral dyskinesias, featuring patterned and predictable stereotypies, are more common in spontaneous dyskinesia, dementia, neuropsychiatric conditions, and peripherally induced orofacial dyskinesias [2, 17]. Tardive orofacial dyskinesias are often more complex and severe, commonly labeled "Oro-Bucco-lingual" dyskinesias or "classic tardive dyskinesias" when the movements disorders manifest isolated [79].

3.1. Spontaneous orofacial dyskinesias

Spontaneous orofacial dyskinesia (SOD) is one of the less common forms of orofacial dyskinesias [17]. This subset is difficult to identify, mainly because of the inadvertent exposure to an offending drug is hard to discard. Hence, this term is usually coined when a detailed clinical description and characterization are lacking. SOD seems to be more prevalent in elderly, more commonly affecting females than men. Reports indicate that oral dyskinesias tend to fluctuate in time and their prevalence is highly variable [80].

Estimations on the prevalence rates vary from 1.5 to 38% among the population [81]. Reports on prevalence vary from 1.5 to 4% in healthy elderlies, 3.7% daycare centers elderlies, and 18–31.7% in elderly living at retirement homes [82–85]. The age-related factors involved in the onset of SOD are unknown and need further research.

Chronic schizophrenia patients have been reported to present more frequently SOD [86]. Descriptions of this coexistence between SOD and chronic schizophrenia patients have been made since before the introduction of antipsychotics drugs [87]. A study by Owens et al. showed that dyskinetic orofacial movements were present in chronic schizophrenia institutionalized patients with and without a history of chronic exposure to antipsychotic drugs, leading the author to suggest that the dyskinetic movements were probably related to the schizophrenia. However, some differences were observed between the two groups, showing more severe orofacial dyskinesias the group exposed to antipsychotic drugs [88]. The presence of SOD in chronic schizophrenia and other neurological disorders, such as autism, mental retardation, Alzheimer's disease, and Rett syndrome seems to be non-specific and needs further clarification [78].

3.2. Peripheral-induced dyskinesia

Peripherally oral factors have been suspected to play an important role in inducing orofacial dyskinesia. Edentulism, ill-fitting dentures, oral pain, and low perceived oral health seem to be strongly associated with oral dyskinesias [89].

Koller in a study, which compared 75 consecutive edentulous subjects to age-matched controls with teeth, found that 16% (12 individuals) of the edentulous subjects presented oral dyskinesia. Of them, nine presented mild oromandibular stereotypes and three subjects presented more marked dyskinesia, all of them displaying less complex dyskinesias compared to drug-induced dyskinesias [90].

A cross-sectional study in 1018 non-institutionalized patients found a 3.7% rate of prevalence of SOD. Interestingly, the subjects affected by oral dyskinesias reported more frequently edentulism with a high prevalence of ill-fitting dentures, oral pain, and poor buccal health perception. Furthermore, 52% of the edentulous subjects reported ill-fitting problems with their dentures in a higher proportion than the nondyskinetic controls and the tardive dyskinesia patients, leading the authors to suggest that in the absence of other putative factors, edentulism and orodental problems may trigger oral dyskinesia [89]. The nature of this association between orofacial dyskinesias and oral health factors requires further investigation and clarification and could be especially important to identify which dental factors may be amenable by good dental healthcare.

3.3. Drug-induced orofacial reactions and tardive orofacial dyskinesias

Shortly after the introduction of conventional neuroleptics, Frank Ayd in 1961, published a list of medications associated with various movement disorders, which he named drug-induced extrapyramidal reactions [91]. Since then, various reports associated with the use of medications and drugs were described and probably remain an important source of adult and pediatric movement disorders [92–95].

The terminology "Extrapyramidal Syndrome Reactions (ESR)" is commonly used in psychiatry to refer drug-induced dystonia, akathisia, and parkinsonism [96]. However, phenomenologically the term ERS lacks clarity, and clinically, the spectrum of persistent hyperkinetic and hypokinetic motor abnormalities is more precisely fitted into three distinct categories regarding their temporal profiles: acute and subacute drug-induced movement disorders and tardive syndromes. Acute drug-induced movement disorders often occurs within hours or days after the offending drug exposure; in subacute drug-induced movement disorders, the onset of the abnormal movements builds up slowly, after days or weeks of exposure [97]. Finally, tardive syndromes are due to the chronic exposure, almost never before than 3 months or 1 month in patients older than 60 years old, primarily after the exposure to dopamine receptor blocking agents (DRBA) [98].

3.3.1. Acute orofacial drug-induced movement disorders

Acute orofacial drug-induced movement disorders are primarily related to acute dystonic reactions, seen after the consumption of neuroleptics, emetics and gastrointestinal promotility agents, antidepressants, amphetamines, antiepileptics, and recreational drugs, among many others [99–101].

Typically, acute dystonic orofacial reactions start after a few days the offending drug is introduced, with 50% of the cases occurring during the first 24 hours and 90% of the cases within the first 5 days [99]. Motor symptoms are usually restricted to the head and neck, particularly as OMDy and complex cervical dystonias. Prevalence ranges from 2.3 to 60% and 2 to 3% in patients treated with typical DRBA and atypical DRBA, respectively [102].

Management consists in the suspension of the implicated drug, whenever is possible. Intramuscular or intravenous anticholinergic drugs are the most effective agents in treating acute dystonic reactions until the offending drug wears off. Benzodiazepines may be helpful but are not as effective as anticholinergics [99].

3.3.2. Tardive syndromes and tardive orofacial dyskinesias

The term "tardive syndromes" refer to a group of iatrogenic delayed onset of drug-induced persistent movement disorders [103]. Two essential aspects must be present to configure a tardive syndromes diagnosis. The first aspect is that continuous exposure to the offending drug must be present, more frequently seen in prolonged treatments with DRBA. If there is no medical history of prolonged exposure, another diagnostic should be considered. The second essential aspect is that regardless of the duration of the exposure, the abnormal movements will persist, continue, and often worsen after the offending drug is withdrawn [96].

In some patients, dyskinetic movements may appear immediately after the discontinuation, change, or reduction in dosage of neuroleptic medications, in which case the condition is called neuroleptic withdrawal-emergent dyskinesia. Because withdrawal emergent dyskinesia is usually time-limited, lasting less than 4–8 weeks, dyskinetic movements that persists beyond this window are considered as tardive dyskinesia [104].

Since the introduction of neuroleptics (DRBA), numerous reports emerged describing delayed orofacial involuntary stereotypies. Faurbye in 1964 initially coined the term "tardive dyskinesia" to describe late onset rhythmic, repetitive, persistent orofacial movements after long exposure to antipsychotic drugs [105, 106]. Other drugs distinct than DRBA have been related to tardive syndromes such as anti-emetics, tricyclic antidepressants, calcium channel blockers, norepinephrine selective reuptake inhibitors, and serotonin selective reuptake inhibitors can cause abnormal movements clinically indistinguishable from the DRBA-induced dyskinesias [107] (**Table 3**).

Typical antipsychotics
Chlorpromazine
Chlorprothixene
Droperidol
Flupentixol
Fluphenazine
Haloperidol
Levomepromazine
Loxapine
Mesoridazine
Molindone
Perazine
Perphenazine
Pimozide
Prochlorperazine
Thiothixene
Trifluprомazine
Zuclopenthixol
Atypical antipsychotics
Amisulpride
Aripiprazole
Asenapine
Clozapine
Iloperidone

Levosulpiride
Olanzapine
Paliperidone
Quetiapine
Remoxipride
Risperidone
Sulpiride
Ziprasidone
Antiemetics
Cisapride
Clebopride
Metoclopramide
Calcium channel blockers
Cinnarizine
Flunarizine
Serotonin/norepinephrine reuptake inhibitors
Duloxetine
Citalopram
Sertraline
Paroxetine
Fluoxetine
Tricyclic antidepressants
Amoxapine
Others
Lithium

Cited from: [78, 98, 107].

Table 3. Medications with the potential to cause orofacial tardive dyskinesia and drug-induced reactions (listed alphabetically).

In literature, this term is often used to define various types of hyperkinetic tardive manifestations. However, because many patients may present a combination of tardive abnormal movements, it is more appropriate to use the term "tardive syndromes" to classify all the different tardive phenomenologies including classic tardive dyskinesia, tardive stereotypy, tardive dystonia, tardive akathisia, tardive tremor, tardive parkinsonism, and tardive gait, among others [98].

Of the aforementioned tardive syndromes, the more prevalent presentations are classical tardive dyskinesia 30%, tardive akathisia 20%, and tardive dystonia 5–15% of the cases. Tics, myoclonus, tremors, pain, and other tardive syndromes are far less frequent [79].

A study by Orti-Pareja et al. described the frequencies of the different types of phenomenologies in a population of 100 patients diagnosed with tardive syndromes. The authors found that 72% of the patients presented oro-bucco-lingual dyskinesias, 30% tardive tremor, 22% tardive akathisia, and 16% tardive dystonia. In this study, 35% of the patients presented a combination of two or more tardive syndromes [108].

The presumed pathophysiology is thought to be related to chronic blockage of D2 and D3 dopamine receptors. Typical antipsychotics are more tightly bind and for more time to dopamine receptors than "atypical" antipsychotics, being more prone to produce tardive dyskinesia [109]. Other prominent mechanisms may be the facilitation of dopaminergic neurotransmission, postsynaptic supersensitivity, maladaptive neuroplasticity, increased neurodegeneration (neuronal loss, gliosis in the basal ganglia), and genetic susceptibility [110–112].

3.3.3. Tardive orofacial dyskinesias

Classical tardive dyskinesias or "tardive orofacial dyskinesias" are characterized by having an insidious onset of the symptoms, predominantly manifesting as relatively rhythmic, repetitive, and stereotypic movements of the face, mouth, tongue, and chewing movements (oro-bucco-lingual) [96].

Tardive dyskinesias tend to evolve into a full syndrome over days or weeks, persisting years or even decades after the offending drug is discontinued [107].

The clinical features often involve repetitive jaw movements, tongue protrusion, puffing of cheeks, lip smacking, lip puckering, or lip pursing affecting speech, swallowing, chewing, and occasionally producing tongue injuries. The onset of vertical, rhythmic perioral movements of the jaw with frequencies of 2.5–5.5 Hz (rabbit syndrome) or jaw tremor have also been described in chronic exposure to neuroleptics [77]. The abnormal oro-buccal-lingual movements can also extend to other body parts, including the trunk or the extremities [98].

With typical antipsychotics, the estimated prevalence is between 20 and 50% [113]. The estimated incidence is about 5% in younger individuals but tends to increase in middle age individuals and elderlies, particularly in women, probably due to the cumulative exposure to DRBA [107].

Tardive orofacial dyskinesia is potentially reversible in a subset of patients. However, remission rates after the discontinuation of the offending drug is relatively low, about 13% of the patients experienced complete resolution after 3 years and only 2% without having to include other pharmacological agents [114].

Treatment recommendations focus on patient selection (paramount for preventing tardive dyskinesias), use alternative medications whenever is possible, and making emphasis on avoiding long DRBA treatments. Slowly tapering of the offending drug is recommended mostly because sudden withdrawn can trigger withdrawn emergent dyskinesia [98, 107]. Evidence supports the idea that as sooner the causative drug is retrieved, the more likely is that tardive dyskinesia will

resolve [111]. Patients requiring antipsychotic drugs switching to atypical neuroleptics may still have risk of developing tardive dyskinesia [115]. About 60% of the patients will benefit with the reintroduction of the drug, but only for a low period of time [24].

Dopamine-depleting agents like tetrabenazine can be used in severe cases with moderate to good results. Other agents such as amantadine, clonazepam (only for short periods of time), vitamins, and antioxidants may help lessen tardive orofacial dyskinesia, but the evidence available is still inconclusive. Botulinum toxin injections have shown efficacy in reducing tardive dyskinesia in several clinical reports and small studies [98, 107].

4. Sleep and awake bruxism

4.1. Definition

Bruxism comes from the Greek term brukhein "to gnash the teeth" [116]. Research on sleep medicine, the pathophysiology of sleep and awake bruxism, and related comorbidities has changed old dental mechanistic beliefs based on dental occlusion to a more medical concept, hardly influenced by peripheral factors [117–119].

Bruxism is a trigeminal motor activity characterized by a repetitive and episodic muscle contractions producing grinding or clenching of the teeth, or bracing or thrusting of the mandible. By consensus, it can be categorized into two different circadian manifestations, occurring during sleep (Sleep Bruxism) or wakefulness (Awake Bruxism), being tooth grinding dominant during sleep and clenching activities more prevalent during wakefulness [120–122]. Evidence suggests that sleep bruxism and awake bruxism are probably not part of the same nosologic entity, each having some substantial similarities but probably having different etiologies and pathophysiology [123]. Sleep bruxism is considered a sleep-related movement disorder, and it is hardly controllable during sleep [124]; meanwhile, awake bruxism is an unaware stereotypic mandibular activity during wakefulness, when cognizant can be voluntarily controlled and terminated [116].

4.2. Diagnosis

During sleep, bruxism can be registered by quantifying the episodes of rhythmic activity of the masticatory muscles (also known as rhythmic masticatory muscle activity or RMMA) [125]. The RMMA corresponds to a rise in the electromyographic activity of the electrodes placed in the masticatory muscles and the chin, and it is produced by muscle contractions with a frequency of 1 Hz, helping distinguish it from other oromandibular movements or disorders during sleep (e.g., mandibular myoclonus, nocturnal vocalization, snoring, or swallowing) [126]. RMMA can take three forms of bursting patterns: (1) isolated muscle contraction lasting >2 s called "tonic"; (2) more than three bursts lasting 0.25–2.0 each, called "phasic"; and (3) the mixture between tonic and phasic bursts. It is important to note that RMMA may present with little or no tooth grinding at all [127].

A panel of international experts defined a diagnostic criterion, grading sleep bruxism into three diagnostic levels: The first criteria consists only in the anamnestic report, the second criteria adds to the anamnetic report a clinical assessment, and the third and definitive diagnostic level is based on a polysomnographic study [120, 124]. From the anamnestic standpoint, the presence of recent self-reported tooth grinding sounds during sleep is necessary, noted also or confirmed by a parent or a sleep partner. The second diagnostic level includes the anamnestic report plus clinical signs of abnormal tooth wear, the presence of jaw muscle fatigue or pain, temporal headache, or jaw locking upon wakefulness. Not better explained by other sleep disorders, medical or neurologic disease, medication use, or drug abuse [120].

Regardless that these two first diagnostic levels are widely accepted, evidence shows that report-based diagnosis in bruxism are subjective, possibly bias, lacks of acceptable specificity and sensitivity and needs further validation [125]. Then, some considerations should be taken into account before making an anamnesis-based or clinical diagnosis. First and foremost, studies have shown almost 50% discordance between PSG recording and self-reports, showing that self-report studies tend to overestimate bruxism [128, 129]. Also, it should be considered that tooth grinding tends to fluctuate with time and decline with age [130, 131]. Recent data shows that the assessment of sleep bruxism using subjective methods alone tends to overestimate the prevalence in 12.5% compared to PSG recordings [129, 132]. Moreover, a recent study aiming to assess the sensibility, specificity, and positive and negative predictive value among the different clinical diagnostics compared to PSG recordings found that the more sensitive clinical criteria corresponded to jaw fatigue upon awakening followed by a temporal headache. The most specific diagnostic criteria were jaw locking and muscle pain [133].

Awake bruxism is usually more difficult to diagnose, mostly because diagnosis relies on self-awareness of individual [134]. However, there is increasing evidence suggesting that once a person is made aware of their awake bruxism habits, he or she is more likely to give accurate feedback [135, 136].

4.3. Epidemiology

The prevalence of sleep bruxism is estimated mainly based on reports, being it highest during childhood approximately 14–20%, consolidating around 8–12% during adolescence and adulthood, and decreasing over 50 years to 3–5%. Several studies have found that when SB is present during childhood, it may persist into adulthood. However, as previously mentioned, most subjects show fluctuations and alternating periods of SB during the lifespan. Awake bruxism has been reported to have an estimated prevalence of 22.1–31% among the adult population [130, 131, 137].

4.4. Sleep and awake bruxism pathophysiology

Current understanding of the etiology and pathophysiology of SB is not based on a single factor explanatory model [138]. Instead, much of the pathological mechanisms are unknown or not well understand and are subject to interindividual variability [139].

Sleep bruxism starts with a cascade of physiological events that are temporally related to the onset of the RMMA episode [139]. Four to eight minutes before the onset, a cardiac sympathetic activity dominance can be observed [140, 141]. The cardiac autonomic activity is followed by an increase of electroencephalographic activity dominated by rapid frequency brain activity, i.e. arousal, in 50–80% of the episodes [142, 143]. Then, a rise in heart rate, fluctuations in respiratory breaths and oxygen saturation, a rise in the systolic and diastolic pressure, and an increase of suprahyoid muscles tone usually precede the onset of the RMMA [144–146]. This sequence of event is not always constant to all RMMA but highlights that sleep bruxism involves a complex interaction between the sympathetic system, cortical arousability, and respiratory functions. Posterior to the RMMA onset and the tooth grinding, most of the episodes are followed by swallowing (~60%) [147]. Sporadic RMMA is not infrequent in general population. However, individuals presenting sleep bruxism have more RMMA with more intense bursting patterns, manifesting primarily in pre-REM sleep during transitions between NREM1 and NREM2 stages [126, 138]. Sleep bruxism-induced muscle activity during REM sleep is less concurrent accounting for less than 10% of the RMMA episodes during sleep [125]. Individuals with sleep bruxism do not present alterations in their sleep architecture unless they present a comorbidities [129] (**Figure 11**).

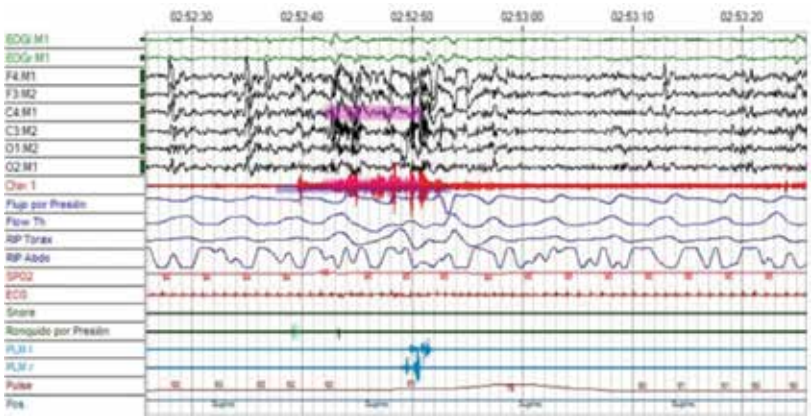

Figure 11. Sleep bruxism episode in a polysomnography study. Courtesy of Somno Clinic, Chile. www.somno.cl.

4.5. Sleep bruxism etiology

Multifactorial etiology of SB includes individual factors such as personality traits, environmental factors, genetics, circadian and ultradian rhythms, coping skills (anxiety/stress), neurotransmitters (more probably serotoninergic-related pathways), anatomic characteristics, sleep arousability, airway patency, and sleep disturbances among other factors.

Stress, anxiety, and maladaptive coping skills have been related to sleep and awake bruxism. Individuals with sleep bruxism usually are more stressed and exhibit more goal-oriented personalities and higher anxiety levels [148–151]. In children and adolescents, psychological factors have been found to be a putative risk for bruxism [152]. Personality traits and behaviors

like bullying, aggressiveness, neuroticism, increased sense of responsibility, tense personality traits, and antisocial conduct are associated with sleep bruxism [153–155].

Genetic predisposition is also postulated as an important etiologic factor, accounting for 48–52% of sleep bruxism phenotypic variance [156]. Heritability strongly correlates with sleep bruxism having a relative risk of 4.6 [157–159]. Single nucleotide polymorphisms of serotoninergic and dopaminergic neurotransmission have emerged as potential candidates showing strong association with an increased risk of sleep bruxism [160, 161]. These associations have not been found in awake bruxism which further support the idea that sleep and awake bruxism are two different nosologic manifestations [161].

Caffeine intake in high quantity is linked with an increased risk of sleep bruxisms in 1.5 times [162] through mechanisms currently unknown [163]. Heavy drinking and frequent alcohol intake during the day have also been associated with sleep bruxism. It is thought that fragmentation of sleep architecture and accumulation of neurotransmitters related to dopaminergic and serotoninergic pathways may be associated with the exacerbation of sleep bruxism [162, 163]. Similarly, tobacco consumption increases the risk of having sleep bruxism two times [162]. As well, several drugs and medications have shown activity in exacerbating sleep bruxism such as levodopa, selective serotonin reuptake inhibitors, tricyclic antidepressants, amphetamines, and MMDA, among others [127, 164, 165].

Airway patency studies have shown a positive association between sleep bruxism and sleep breathing disorders [166, 167]. In fact, about 50% of adults and children with obstructive sleep apnea present concomitant sleep bruxism [168–170]. Furthermore, self-reports studies in sleep apnea patients increase the risk of having bruxism, probably mediated by the occurrence of sleep arousals during respiratory events [171]. It has been hypothesized that the relation of sleep bruxism concomitant or posterior to hypopnea or apnea episodes may have a role in reinstating airway permeability during the events, suggesting a causative link [172]. However, there is not enough evidence to support this claim [173].

Nocturnal gastroesophageal reflux is another factor associated with sleep bruxism. Higher frequencies of SB episodes were associated with having more time of esophageal pH below 5.0 [174]. Miyawaki et al. showed a concomitance of RMMA events and gastroesophageal reflux episodes, more particularly when episodes had a pH lower than 3.0–4.0 [174]. Also finding the sleep position during sleep was influential in reducing RMMA and episodes of gastroesophageal reflux alike [175]. Moreover, clinical trials measuring the effect of proton pump inhibitors (PPI) in patients with comorbidity of sleep bruxism and gastroesophageal reflux have shown that the consumption of PPI reduces RMMA episodes of sand grinding noises significantly [176].

4.6. Management

In the absence of treatable comorbidities, treatment of sleep bruxism is not plausible. Instead, management should be focused on preventing tooth destruction and grinding and alleviating temporomandibular pain or concomitant headaches [125, 177]. Oral appliances tend to reduce

sleep bruxism episodes only in short-term, returning to the baseline activity within 7–10 days [178]. A recent systematic review showed the effectiveness of almost every type of oral appliances, providing a higher decrease of sleep bruxism episodes those that produce a certain extent of mandibular advancement (mandibular advancement devices) [178, 179].

In the presence of concomitant sleep breathing disorders, the first step should be taken towards managing sleep breathing disorders depending on the severity. In these cases, a mandibular advancement device or the use of CPAP should be preferred over upper maxillary appliances, mostly because evidence suggests that they may produce aggravation of hypopnea and apnea episodes [180, 181].

Pharmacotherapy for management sleep bruxism is mainly based on the use of off-label medication; only a few medications have shown some degree of effectiveness in reducing sleep bruxism. Clonazepam and clonidine have proven to reduce bruxism with respect to placebo [179]. A single-blinded, randomized controlled trial suggested that the use of gabapentin may be effective for the management of sleep bruxism especially in those patients with poor quality of sleep, but these preliminary results still need further corroboration with better designed clinical trials and more number of participants [182].

Botulinum toxin effects are in line with the expected pharmacologic effects; they are superior to placebo [183]. However, studies have shown that the use of botulinum toxin reduces the intensity of the RMMA bursts but not the frequency, which further confirms the central genesis of sleep bruxism episodes [184].

Regarding awake bruxism, EMG-based biofeedback programs seem to reduce tonic episodes of awake and sleep bruxism alike [185, 186].

A pilot study using mindfulness-based stress reduction programs has also shown efficacy in the management of awake bruxism (Unpublished data from Skarmeta et al.).

Author details

Nicolás Patricio Skármeta[1,2,3]*, Paula Espinoza-Mellado[1,4] and Pedro Chana[5,6]

*Address all correspondence to: nicolas.skarmeta@gmail.com

1 Faculty of Health Sciences, Occlusion and Orofacial Pain, School of Dental Medicine, Universidad San Sebastian, Santiago, Chile

2 Orofacial Pain and TMDs OPH Dental, Santiago, Chile

3 Orofacial Pain and TMDs Hospital del Salvador, SSMOr, Santiago, Chile

4 Orofacial Pain and TMDs at Hospital San Juan de Dios, SMMOc, Santiago, Chile

5 Departement of Neurology, Faculty of Medicine, Universidad de Santiago de Chile, Chile

6 Neurology at Centro de Trastornos de Movimiento (CETRAM), Santiago, Chile

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Section 3

Non-motor Syndrome of Primary Dystonia

Chapter 3

Non-Motor Symptoms in Patients with Primary Dystonia

Nikolina I. Semerdjieva and Ivan G. Milanov

Additional information is available at the end of the chapter

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Abstract

Isolated dystonia, previously referred to as primary, is the third most common movement disorder, characterized by involuntary muscle contractions causing abnormal movements and postures with or without the presence of tremor. No matter monogenic or sporadic, the form of dystonia is a growing evidence, suggesting the presence of non-motor components to the disorder. Dystonia patients suffer from reduced quality of life, which might be related not only to the dystonic movements itself but to different non-motor symptoms and signs, as well. Based on literature review, this chapter aims to focus on the association of different types of isolated/primary dystonia (forms of focal, segmental, and generalized dystonia) with some non-motor disorders, including sleep and psychiatric disorders, cognition, as though as pain and sensory symptoms, their pathophysiological and biochemical mechanisms, relations with the symptomatic treating strategies for the abnormal movements, and specific treatment for the non-motor signs.

Keywords: dystonia, non-motor, mechanism, quality of life, treatment

1. Introduction

The concept of dystonia has been changing much over time. Nowadays, dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation [1–3].

In 2013, an international panel of experts provided a consensus update on definition, phenomenology, and classification of dystonia [4–6]. Previously, dystonia syndromes were classified upon etiology, age at onset, and body distribution [4]. Dystonia was referred as primary where the dystonia with or without the presence of tremor was the only symptom present, frequently inherited as monogenic traits and usually lacks gross neuropathological changes [4, 5]. Dystonia-plus syndromes encompassed disorders where dystonia was a prominent feature, but combined with other neurological abnormalities (myoclonus, parkinsonism). In the heredo-degenerative form, dystonia was a symptom of an underlying neurodegenerative disorder, and secondary dystonia included a heterogeneous group of conditions, induced by structural lesions, infections, metabolic, or systemic disorders [6].

The present classification is based on two, more refined axes, namely clinical characteristics and etiology. The first encompasses age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and other neurological manifestations. The body distribution is described as focal, segmental, multifocal, generalized (with or without leg involvement), or hemidystonia. Associated features distinguish isolated dystonia in both genetic or idiopathic cases that are often resembled to as primary dystonia, and combined (dystonia plus, heredo-degenerative, secondary) dystonia. The second axis allows further division according to the presumed etiology [2–6].

Although dystonia is a rare condition in general population, the "pure," primary, isolated dystonia is the third most common movement disorder, after essential tremor and Parkinson's disease [7], and besides, the disorder influenced a major impact on the quality of life [1, 7].

Concepts on phenomenology has also renewed with decades, considering dystonia to be a solely motor disorder to an increasing recognition of associated neurological or psychiatric features which indicate that the disorder is not purely motor [2]. This resembles the growing knowledge on dystonia's pathophysiology where the recent insights from neurophysiologic studies identified functional abnormalities in the basal ganglia sensorimotor network and, more recently, the cerebello-thalamo-cortical pathway [7]. Besides the well-known lack of inhibition at different nervous system levels, dystonia is specifically characterized by abnormal sensory feedback, maladaptive plasticity in the sensorimotor cortex, and loss of cortical surround inhibition [4, 7].

Bearing in mind the new classification, where the term "primary" is no more recommended, and the circumstance that in majority of cases it resembles the new and more precise term "isolated", both terms are used in this chapter, in order to be correct when providing information from the studies cited, fully understanding that some time and efforts are needed to completely replace the old terminology with the new one.

Based on literature review, this chapter aims to focus on the association of different types of primary/isolated (forms of focal, segmental, and generalized) dystonia with some non-motor disorders, including sleep and psychiatric disorders, cognition, as though as pain and sensory symptoms, their pathophysiological and biochemical mechanisms, relations with the symptomatic treating strategies for the abnormal movements, and specific treatment for the non-motor signs.

2. Psychiatric disorders

Comorbid psychiatric disorders are defined as arising due to the effects of the movement disorder, but not merely present by coincidence. The existing epidemiological data demonstrate a 3–6 fold increased prevalence of psychopathology in dystonia patients compared with that in the general population [8]. Some studies reported more frequent psychiatric problems even in populations with different chronic disorders, suggesting that they may be a primary feature of the disorder [9, 10]; however, other did not confirm that observation.

The lifetime prevalence of psychiatric disorders can reach up from 70.9% in cervical dystonia (CD) and blepharospasm (BS) patients [10] to 91.4% in CD patients, compared to 35% in the general population [9–11]. Compared to CD and BS, data are limited on the prevalence of psychiatric disturbances with other forms of dystonia. Laryngeal dystonia is associated with an increased point prevalence but not lifetime risk of psychiatric comorbidity as compared to patients with vocal cord paralysis [12]. Another study failed to find differences in the point prevalence of psychiatric diagnosis in patients with laryngeal dystonia as compared to healthy age-matched controls [13]. Patients with focal hand dystonia did not show a difference in rates of primary psychiatric diagnoses, as compared to healthy controls [13], but in musician's dystonia, increased anxiety symptoms were reported compared to unaffected musician controls [14].

Behavioral and mood disorders have been studied most thoroughly in dystonia [15]. Depression and anxiety disorders were reported to be most frequent in isolated focal or segmental dystonia, with some studies reporting a higher prevalence of depression [13, 16, 17], and other of anxiety symptoms/panic disorders (29.5%), social phobia (41.3%) [9, 18], obsessive–compulsive symptoms (6.8–19.7%) [8, 9, 18–20], or alcohol abuse [9, 21, 22]. Psychiatric disorders, such as drug and substances abuse, psychotic episodes or schizophrenia, are occasionally reported in dystonia patients, with much less frequency [23, 24].

Studies of frequency and type of psychiatric disorders in patients with isolated focal dystonia have some limitations due to methodological differences in both the diagnostic criteria and the psychiatric interviews used, as some studies use the DSM criteria and others use questionnaires, which might lead to variations in the rate of psychiatric comorbidity [25]. The limited data and varied prevalence for psychiatric illnesses across different types of dystonia may confound interpretations of the etiology of psychiatric disorders as well [11, 26]. There may also be recall bias in studies of lifetime prevalence [11]. Notwithstanding these limitations, the majority of clinical investigations indicate psychiatric disorders to be frequently encountered in isolated/primary dystonia.

2.1. Depression

2.1.1. Epidemiological and etiological basis

Depression, along with the anxiety spectrum, is the most reported psychiatric disorder in the primary/isolated dystonia population. Depression is highly reported in CD patients, most

often in the diapason from 25 [26, 27] to 47% [28, 29], and that might be due to the fact that this is the most frequent form of isolated dystonia. Lifetime and point prevalence of major depression are increased. The lifetime risk for CD patients meeting diagnostic criteria for depression ranges from 15 to 53.4% [11]. A high prevalence of depression has also been observed in BS, ranging from 15 [26] to 37% [30]. Although increased, as compared to general population, some studies revealed that depression in BS did not statistically differ from those in patients with hemifacial spasm (HFS) [13, 31]. Some data suggested an increased depression level in laryngeal and focal hand dystonia, compared with healthy controls [8]. The lifetime prevalence of major depression in primary focal hand dystonia was reported to be 25.6%, and the recurrent major depression—17.95%. There is also more commonly a family history of depression in focal hand dystonia than in controls (41.02%). These rates contrasted with the lifetime prevalence of major depression in the general population of 17% [18]. Depression is reported at high level in axial dystonia (33%) [8], as well as in non-focal (e.g., segmental and generalized) and genetic forms of dystonia [32]. In manifesting and non-manifesting DYT1 mutation carriers, the risk of recurrent major depressive disorder is increased compared with non-carriers. Carriers had earlier age at the onset of a recurrent major depressive disorder than non-carriers, and the severity of motor signs was not associated with the likelihood of recurrent depression [33, 34]. By contrast, depression in isolated focal dystonias is estimated to be less frequent when compared to Parkinson's disease, which might be explained by the different underlying pathophysiological mechanisms [23].

There is conflicting epidemiological evidence as to whether depression is secondary to motor manifestations and subsequent psychosocial impairment, or a primary feature of the disease [25]. Factors in the etiology of depression are believed to be adverse life events and dysregulation of monoamine and dopaminergic neurotransmitter metabolism, with genetic predisposition playing a role [8]. It is proposed that cognitive and neurochemical abnormalities trigger aberrant activity within the basal ganglia which contributes to the clinical features of depression [8]. Adverse life events involving loss, identified as specific precipitants of depression, are prominent in dystonic patients. Depression in dystonia can be triggered by lack of satisfaction with social support, maladaptive coping strategies, self-depreciation, and altered body concept [8, 32, 35]. The disability and pain induced by the motor disorder may act as a nonspecific stressor and combine with other factors to induce depression [8]. It seemed that some proportion of depression may be secondary to motor disability and pain, as improvement in mood is reported in several studies with successful treatment of dystonia [15, 23].

The theory of deranging monoamine metabolism in dystonic patients may play a role. For example, a decreased synthesis of monoamine neurotransmitters in patients with DYT 5 dystonia may also have higher rates of depression than in the general population, perhaps due to a reduced conversion of tryptophan to serotonin [15]. Although there is no evidence from human studies, researches of a hamster model of primary dystonia have demonstrated altered levels of 5-hydroxytryptamine and noradrenaline in the basal ganglia, suggesting that monoamine metabolism may be abnormal in human primary dystonia, potentially predisposing to depression [8].

Often, depression manifests before the onset of the movement disorder, thus not representing a mere reaction to its burden [23]. A number of studies reported a higher pre-morbid incidence of depression and anxiety [9, 10, 16, 17, 20, 21, 23, 36] as well. The manifestation of depressive

symptoms preceding the onset of dystonia symptoms may lead to the hypothesis that depression forms part of the phenotype of isolated, especially focal, dystonia [21]. Although some effect on botulinum toxin (BoNT) treatment upon depression severity in CD patients was reported [30, 37], suggesting secondary depression, no similar association was observed in BS patients [30]. Moreover, an independent course of depression and dystonia was presented [26] in CD patients followed up for a period of 5 years. CD patients were BoNT treated, and the severity of dystonia was milder at the end of the follow-up, whereas no differences were observed in the severity of psychiatric symptoms. Psychiatric disorders remaining stable in spite of an improvement in the severity of CD suggested an independent origin of motor disturbances [28]. Furthermore, in another study, depression severity does not correlate with the dystonia severity nor does depression improve when dystonia is treated [15]. Thus, depression appears to be a feature of the clinical spectrum of focal dystonia and not just a reaction to motor symptoms. The pathophysiology underlying both motor and non-motor symptoms, however, remains poorly understood [38].

In addition, Heiman et al. revealed that the risk for early-onset, before 30 years, recurrent major depression was increased in both manifesting and non-manifesting DYT 1 mutation carriers compared to that in non-carriers. The severity of dystonia in manifesting carriers was not associated with the likelihood of major depression, and mutation carriers did not have an increased risk for other affective disorders. This lead to the conclusion that early-onset recurrent major depression is a clinical expression of the DYT 1 gene mutation that is independent of the motor disturbance. DYT 1 gene is likely involved in dopamine release or turnover, thus suggesting a link between basal ganglia disease and depression [34]. Functional imaging confirmed that striatofrontal circuits playing a role in the mood and behavior regulation might be affected in dystonia patients. They have shown that these non-manifesting carriers have a decreased D2 receptor binding in the basal ganglia [39] and hypermetabolism in the putamen, anterior cingulate, and cerebellar hemispheres [40].

Deep-brain stimulation (DBS) of the internal globus pallidus deserves special attention for its effect on mood. While most studies suggest that DBS for dystonia results in mildly improved or unchanged measures of depression [41], worsened mood and suicide have also been reported [42, 43]. Most of the patients who committed suicide, however, had an excellent motoric response from stimulation, providing further evidence that the severity of dystonia may not correlate with symptoms of low mood [15].

2.1.2. Treatment options

For treating comorbid depression, tricyclic antidepressants (TCAs), monoamine oxidase inhibitor (MAOI), and selective serotonin reuptake inhibitor (SSRI) could be administered. However, an important factor is the association between these agents and reversible drug-induced dystonia which occurs more commonly with SSRIs [8]. If antidepressant therapy worsens dystonia, changing to a different class of drug, or adding in an anticholinergic may, minimize, or prevent exacerbation of dystonia [8]. Cognitive-behavioral therapy (CBT) might ameliorate depression in dystonia patients by altering maladaptive coping strategies that contribute to the mood disorder [35].

2.2. Anxiety disorders

2.2.1. Epidemiological and etiological basis

In contrast to some studies that did not show a difference in anxiety scores between patients with isolated focal dystonia and controls [12, 13, 20, 21, 44], an increased frequency of anxiety disorders especially obsessive–compulsive disorder (OCD), social phobia, and panic disorder in patients with isolated focal dystonia, and predominantly CD, has been highly reported, though studies have some limitations [10, 14, 16, 17, 30, 31, 36, 45–50]. A matter of interest is the study conducted by Lencer et al. who described the personality profiles of isolated focal dystonia patients, affected of psychopathology as well, using a 5-Factor Personality Inventory —NEO-FFI [10]. A high lifetime risk for psychiatric or personality disorder (70.9%) in CD and BS was observed. An increased lifetime risk for the development of social phobia (OR 21.6; 23.3%), agoraphobia (OR 16.7; 10.5%), and panic disorder (OR 11.5; −0.8%) was found, as well as an increased prevalence rate of 32.6% for anxious personality disorders comprising OCD (22.1%) and avoidant personality disorders—specific phobia (16.3%), alcohol abuse (15.1%), and drug dependence (2.3%) compared to general population [10]. Anxiety disorders (except for social phobia), manifested prior to the occurrence of dystonia symptoms [10], were broadly reported [10, 17, 47]. When investigating the personality traits, focal dystonia patients demonstrated pronounced agreeableness, conscientiousness, and reduced openness. For conscientiousness, increased scores were observed without gender difference, indicating obsessive orderliness and perfectionism [10]. Similar personality profile with increased perfectionism and obsessiveness was found in dystonia-affected musicians, compared with non-dystonic musicians [14]. Trait anxiety was also increased in patients with focal hand dystonia as compared to a healthy case–control group [51]. These findings lead to a discussion that dystonia patients might share similar personality traits, which is more likely to reflect a common neurophysiological pathway. Besides, these personality traits are seen as long-term predispositions and are therefore likely to be present prior to the onset of dystonia. The repeated [11] observation that anxiety disorders preceded the motor dysfunctions in a majority of cases gives another argument to the presumption that primary focal dystonia might be viewed as a neuropsychiatric disorder rather than a pure movement disorder [10, 11, 51]. Furthermore, the 1:1 ratio of men to women affected may indicate that psychopathology is likely related to the pathophysiology of isolated focal dystonia, as in the general population, women usually show twice the rate of anxiety and major depression disorder diagnoses when compared to men [10, 11]. It might be presumed that the typical for dystonia disturbance of neural activity in motor loops, linking the basal ganglia via the thalamus to the frontal cortex, may also have an influence on the limbic loops which mediate attentional, cognitive, and limbic functions resulting in both altered motor and affective processing [52]. The link between networks subserving mental and motor functions may be provided by a direct affective input to the caudate nucleus and the thalamus originating from the amygdale and the orbitofrontal cortex. Dysfunction of the basal ganglia-thalamo-cortical circuits has been assumed to underlie both motor and psychiatric symptoms [53]. Similar hypothesis was supported by a recent study, comparing the prevalence rate of psychiatric disorders among different movement disorders, namely isolated focal dystonia, monogenic, and idiopathic Parkinson's disease [23]. Each

movement disorder appeared to present with different psychiatric comorbidity profile, with isolated focal dystonia expressing the highest rates of anxiety disorders (OR = 3.3). These findings suggested that psychiatric disorders be a part of the phenotypic spectrum of movement disorders with each associated with specific psychiatric disorders indicating disturbances in a different neural circuitry for sensorimotor control [23]. Affective or stress-related factors might modulate cerebral sensorimotor representations through interactions between limbic and sensorimotor networks, which could explain the observation that dystonic symptoms can be triggered by emotional stress [23, 54]. These considerations suggest that anxiety disorders, OCD, and other stress-related disorders share common alterations in sensorimotor systems with isolated focal dystonia [23].

A recent study in the Chinese population reported a higher prevalence for anxiety in CD (28.3%) and in BS (20.0%) patients, with no differences in the anxiety scores between the two dystonia subtypes, and no significant correlations between motor symptoms and anxiety scores, thus pointing toward an independent course of both conditions [26]. By contrast, Berman et al. investigated 478 adult-onset focal dystonia, where anxiety and social anxiety severity vary by onset site of focal dystonia, with higher anxiety in cervical and laryngeal, lower anxiety in upper cranial, and higher social anxiety in laryngeal, suggesting distinct psychopathology depending on the initial body region affected by dystonia [38]. However, the commonly observed social anxiety (31.7–72.7%, depending on the site of dystonia onset) might be associated with altered body image and attitudes toward illness, but not dystonia severity [38]. Further, a rapidly increasing positive relationship between the severity of dystonia and social anxiety in the laryngeal onset group was found, suggesting that speech difficulties in particular may lead to secondary stigma and social anxiety [38]. Another factor for developing a secondary social anxiety (social phobia) may be the pronounced personality traits of patients with focal dystonia, facilitating difficulties in coping with dystonia symptoms and thus avoid social situations and being evaluated by others [10]. In a study of 116 CD patients, a 71% lifetime prevalence of social phobia was found and it correlated with body image, and a "maladaptive attitude" toward their illness, and not the objective severity of the dystonia [36]. Much like depression and other forms of anxiety, one can hypothesize that self-esteem and body concept play an important role in the development of social phobia [36]. On the other hand, several studies suggest that social phobia occurs at increased rates in primary focal dystonia [10, 16, 36], even more common than in other possibly stigmatizing disorders such as alopecia areata and thus is unlikely to be a mere consequence of disfigurement [36].

The reported increased chances for alcohol abuse and drug dependence in men may be a consequence of the fact that motor symptoms in dystonia may be relieved by alcohol, benzodiazepines, or anticholinergic drugs [36, 38]. Interestingly, results from genetic studies suggest that there may be an additional neurobiological factor predisposing to substance-related disorders in primary focal dystonia [55, 56]. Genetic factors may be another shared neurobiological basis. Although beyond the scope of isolated dystonia, an interesting example is the finding that patients with myoclonus dystonia suffered more frequently from OCD and alcohol abuse, which might be partly caused by the mutation of epsilon-sarcoglycan (*SGCE)* gene [55, 56]. A confounding factor, however, might be that myoclonus dystonia improves with

alcohol, and this could be the reason for the higher alcohol dependence [15]. By contrast, no evidence suggesting a higher risk of anxiety disorders in DYT1 carriers was found [57].

Particularly interesting is the connection between OCD and isolated focal dystonia. A large recent study revealed that clinically significant obsessive–compulsive symptoms are over-represented in isolated focal dystonia as compared with both HFS and healthy controls [50]. Besides, OCD caused great disability and significant impact on quality of life [50]. Another study also confirmed obsessive–compulsive symptom scores above cutoff for clinical significance in patients with primary focal dystonia (CD, BS, and writer's cramp) when compared to healthy and chronic illness controls, with predominantly developed hygiene-related symptoms [20]. It remains unclear why obsessive–compulsive symptoms are not universally present in primary focal dystonia, but reported results might suggest a common neurobiological basis related to cortical-basal dysfunction [46]. On the other hand, a study, although small-sampled, found OCD to be increased both in focal dystonia and in HFS, compared to healthy controls, but with significant between groups thematic content, and usually with mild severity [58]. No significant differences in obsessive–compulsive symptoms emerged in a study comparing DYT1 carriers to a control population [57].

In summary, depression appears to be more likely to represent a primary feature of isolated dystonia, whereas other psychiatric abnormalities have a less certain relationship and require additional evaluation [15].

2.2.2. Treatment options

There are no specific guidelines or published pharmacological treatment trials of psychiatric illness in the context of isolated dystonia, and treatment is based upon regimens used in non-dystonic patients [11]. However, when treating comorbid psychopathology, certain modifications to standard regimens must be made to take account of issues of treatment safety and efficacy in patients with dystonia [8]. The core treatment for social phobia and panic disorder may rely on CBT with or without an SSRI, bearing in mind the potential of SSRIs to exacerbate dystonia [8]. CBT has an uncertain effect for social phobia in dystonia patients as they may genuinely experience excessive scrutiny and criticism in social circumstances because of their appearance [59]. A case report describes the efficacy of CBT in alleviating symptoms of CD [60], and another recent study reported satisfactory results in treating non-motor symptoms in dystonia patients with combined CBT and mindfulness program. An interesting fact is that benzodiazepines, often used in treating the motor symptoms, because of their muscle relaxation properties, have not been described with their known anxiolytic effect in primary dystonia [11]. For the treatment of OCD in dystonia patients, Exposure and Response Prevention (ERP), a technique in which the patient is repeatedly exposed to situations that provoke the ritualistic behavior and instructed to resist performing them, may be tried. Although evidence is insufficient, a single case report showed ERP effective in treating OCD associated with dystonia secondary to basal ganglia infarction [61]. Minding the disabling nature of OCD and safety of ERP, this treatment should be trialed in the cases of comorbid OCD [8]. There is an emerging need to examine the effects of psychiatric treatment on both motor symptoms and mental and physical aspects of quality of life. Such multidimensional approaches are necessary to improve the objective and subjective well-being of patients with dystonia [11].

2.3. Other psychiatric disorders

Beyond the spectrum of mood and anxiety disorders, but in line with the hypothesis of shared neuroanatomical pathways, psychotic features, not related to therapy, in patients with idiopathic dystonia were observed [20, 24], suggesting a probable common dysfunction of the cortico-cerebello-thalamo-cortical projections [24], although other studies did not find psychotic symptoms in dystonic patients [23]. Patients with CD may have difficulty identifying angry faces when compared to age-matched controls [62] or to identify auditory expressions of disgust [63]. These separate lines of evidence suggest an interesting association between dystonia and longstanding emotional processing deficits; however, the exact interplay between these symptoms is not clear [11].

2.4. Psychiatric disorders and quality in life in dystonia patients

Emerging data highlight psychiatric comorbidity, namely depression and anxiety, as the most important predictor of poorer health-related quality of life (HRQoL) in patients with focal and especially cervical dystonia [9, 64–66]. A recent study revealed that the first eight domains of HRQoL were significantly lower in dystonia patients compared to that in controls, and this strongly related to the presence of depressive and anxiety symptoms, pain, and disability, while there was no significant correlation with the objective severity of motor symptoms. The degree of disability was only predicted by the degree of pain and depressive symptoms, and pain was mostly associated with disability and anxiety symptoms [9]. These findings suggested psychiatric comorbidity as the most important predictor of a decreased HRQoL and argues against a decreased HRQoL as a sole consequence of living with a chronic, visible, and disabling movement disorder [9]. Similar data were reported in a number of previous QoL-related surveys [64–66]. In another recent large study on QoL of 96 CD patients, five components (disability, psychiatric features, pain, physical function, and severity of dystonia) explained 74.4% of the variance in disability. Psychiatric features had the largest contribution to disability, followed by pain, physical functioning, and severity of dystonia which had no significant contribution [29].

All these findings lead to the need for a systematic screening for psychiatric disorders in dystonia patients, as well as novel treatment strategies to be implicated for copying psychiatric problems in dystonia patients in order to improve disability levels and health-related quality of life.

3. Cognition

Etiology and pathophysiology of isolated dystonia remain incompletely understood, yet dystonia is associated with basal ganglia dysfunction, and there is growing evidence that the basal ganglia plays a role in both cognitive and motor functions, supported by neuroimaging studies, revealing changes in non-motor areas and the cortico-striatal-thalamo-cortical circuits in dystonic patients [67]. However, evidence supporting cognitive impairment in primary dystonia is limited and contradictory [68].

Allam et al. assessed nine patients with primary cranial dystonia and found a sustained attention deficit in patients, compared with health-matched controls, despite well-preserved intellectual skills. BoNT treatment improved concentration endurance (sustained attention) to control values, suggesting that executive dysfunction in CD could be a secondary phenomenon, due to the disrupting effects of dystonia [69]. A constellation of attentional-executive cognitive deficits was confirmed by another study, assessing patients with young-onset generalized (both DYT 1 positive and negative) and adult-onset focal and segmental dystonia and healthy controls with the Cambridge Neuropsychological Test Automated Battery, although interpretations might by confound by the heterogeneity of the group and concomitant therapy with dopaminergic and anti-cholinergic medication [70]. The speed of information processing, language, spatial, memory, and general intellectual skills were well preserved [70]. Aleman et al. reported disturbed attention skills and a decreased capacity of performing complex motor tasks involving coordination of both hands in BS patients, compared to matched controls, revealing a cognitive impairment, independent from depression, anxiety, and premorbid intelligence. These findings were not dependent on symptom severity or disease duration, strongly suggestive of broad cortical involvement, including prefrontal and parieto-occipital dysfunction in focal dystonia [71]. In addition, the authors observed that BS patients made, although not statistically significant, more errors and more perseverative answers on The Wisconsin Card Sorting Test (WCST) than expected according to population means [71]. Several other studies support the evidence that when compared to healthy controls, patients with primary dystonia performed worse on the WCST [69, 72]. Assuming that the impairment of executive functions in dystonia patients might be partially due to some confounding factors such as depression or symptom-related distraction, Lange et al. compared the BS patients results achieved on the WCST, with the results of HFS patients. Furthermore, the authors compared global cognitive functioning, psychiatric symptoms, health status, and impulsiveness in both groups, thus trying to eliminate confounding factors. BS patients committed significantly more errors on the WCST, suggesting that cognitive inflexibility in idiopathic BS patients results from the specific pathophysiological processes underlying primary dystonia, which may arise from changes in cortico-basal ganglia circuits [73]. By contrast, when assessed with the Frontal Assessment Battery, executive function was not altered in BS compared with HFS [74]. Another study of 10 patients with primary dystonia, who differed in terms of body distribution, did not reveal any deficits in executive function or working memory either, but observed significantly lower word fluency than the healthy controls [75]. A set of neuropsychological tests was administered to non-depressed, non-demented patients with cranial-cervical dystonia and healthy control subjects. Patients with cranial-cervical dystonia showed deficit on working memory, processing speed, visual motor ability, and short-term memory, suggesting cortical and subcortical changes in the basal ganglia-thalamo-cortical circuits and their functional subdivisions of the oculomotor, prefrontal, and cingulated circuits that play an important role in executive functions, visual reproduction and visual–spatial coordination, working memory, attention, learning, and potentiating behavioral-guiding rules [76]. Such findings were confirmed in a recent large study of 68 primary BS patients and matched controls. The prevalence of cognitive deficits varied between 22.0% measured by the Mini-Mental State Examination (MMSE) and 32.3% measured by Addenbrooke's Cognitive Examination-Revised (ACE-R). The most frequently affected domains were visuospatial

function (30.9%) and language (30.9%), followed by memory (27.9%), orientation/attention (26.4%), and verbal fluency (22.0%). Patients with cognitive deficits showed lower QoL, especially in the subdomains of physical and social functioning, as the poor performance on the ACE-R was related to poorer QoL [68]. Another recent study investigating 60 CD patients, 60 BS patients, matched with 60 controls, found poor cognitive performance in 25% of CD and in 35% of BS patients assessed by ACE-R, with a lack of correlation between cognitive performance and severity of motor symptoms, suggesting that cognitive decline may be a clinical expression of dystonia [26]. By contrast, in non-DYT 1 primary generalized dystonia, no cognitive deficit compared with healthy controls has been detected in two studies [77, 78], and no cognitive abnormalities have been found in either manifesting or non-manifesting DYT 1 gene carriers [79].

In summary, the available data are contradictory ranging from subtle or no alteration of cognitive functions in primary dystonia [79], to cognitive impairment, influencing patients' QoL [68]. However, the most reported cognitive deficits are in the area of attention [68–71], executive functions [70, 76], word fluency [68, 73, 75], and visuospatial domains [68, 76]. The second contradictory is related to the etiology of the available cognitive impairments—whether they represent a part of the disease or a secondary alteration. Indeed, some may be related to the distracting effects of abnormal movements and pain, which may impair attentional processes, tending to improve with dystonia treatment [69]. Comorbid depression and anxiety (OCD), the use of some medications (e.g., anticholinergic) may also affect the cognition [80]. On the other hand, recent studies consider these factors and tried to avoid them in their study design and consecutive analyses [68, 71, 73, 76]. The limitation with most studies is the small sample size, and in some of them combining dystonia subtypes [69]. The different sensitivities of the neuropsychological batteries adopted in these studies with different research focuses and the use of different control groups may have also contributed to the inconsistent findings and hindered the cross-study comparisons [68].

4. Sleep disturbances

4.1. Impaired sleep quality (self-reported)

Most of the available studies reported an increased rate in impaired quality of sleep (QoS) in isolated/primary focal [26, 81–84], segmental, and generalized dystonia when compared to healthy controls [81]. The prevalence rate, dependent on the different studies for focal dystonia ranges, between 36 [26] and 45%, as most studies focused on CD and BS patients [82]. Although differences in QoS scores in CD patients might be partly confounded by depression, the differences QoS scores in BSP were not influenced by Beck Depression Inventory [83]. An impaired QoS was observed more frequently in CD compared with controls, even when controlling for the effects of depression, anxiety, and benzodiazepine use [84]. CD patients suffered worse QoS than BS patients, which might be partially due to pain, common in CD but absent in BS [26, 83]. The predictors for worsened QoS were mostly associated with depression (26%), restless legs syndrome (19%), and bruxism (in CD), but not severity of dystonic

symptoms [82]. Lack of correlation between QoS and severity of dystonia in both CD and BS patients suggested that insomnia might be a comorbidity disorder in patients with BS or CD [26, 83], pointing to an intrinsic mechanism of sleep disturbances rather than a direct effect of dystonic muscle activity [82]. Furthermore, QoS did not improve following BoNT treatment, despite a robust improvement in CD severity. This dichotomy suggests that sleep aberrations in CD require separate focus for effective treatment and cannot be viewed as secondary complications of the motor elements of this condition [84]. Although insomnia showed a tight connection with depression, the causal relationship between QoS and depression remains unknown. Overall, insomnia might be a feature of primary cranial and cervical dystonia [26, 83]. Nocturnal sleep disturbances correlated significantly with the HRQoL. They negatively impacted the QoL even when controlled for comorbid depression [81], suggesting that the assessment and treatment of insomnia-related complaints should be considered in global management plans of patients with dystonia [83].

4.2. Excessive daytime sleepiness

Excessive daytime sleepiness was not as common as QoS impairment, with a frequency varying from 6 [82] to 27% [81], depending on the study sample and design. Some studies failed to find a significant difference in daytime somnolence compared to the healthy population [82, 84], although a higher percentage of daytime sleepiness, measured by Epworth Sleepiness Scale (ESS), was found in CD patients, compared with both healthy controls and patients with other focal movement disorders [85]. A critical evaluation assesses the use of anticholinergic medications that may account for some but not all of this increase in sleepiness in the CD group. Disease severity and other common medication use (benzodiazepines, antidepressants) were not associated with increased ESS scores [85]. No improvement in daytime somnolence was observed with BoNT treatment, despite improvement in CD severity [84]. The excessive daytime somnolence correlated significantly with the HRQoL; however, these effects were not observed when controlled for depression [81]. These preliminary findings on daytime sleepiness suggested that further investigation into disordered sleep is warranted [85].

4.3. Polysomnography

In several studies of severely involved patients with dystonia musculorum deformans, the polysomnographic findings were characterized with increased latency to sleep, with a specific pattern of spindle activity, characterized by pronounced, high-amplitude spindles that were continuous for all stage 2 and portions of stage 3 sleep, and reduced sleep efficiency, suggesting a clinical significance [86, 87]. These findings, however, were not confirmed in further polysomnographic investigation [88]. Abnormal movements in patients with Meige's syndrome and BS appeared to be present during sleep but decreased in frequency and amplitude in all sleep stages. [89], whereas in CD patients, though sleep architecture was significantly affected (with a decreased sleep efficiency and an increased sleep latency), activity over cervical muscles disappeared during all the sleep stages, reaching significantly decreased values when compared to healthy controls. Thus, the reported poor QoS and impaired sleep architecture in CD cannot be related to the persistence of muscle activity over the cervical muscles [90]. These findings elicit

the need of further studies on sleep, including polysomnographic investigations in patients with different types of dystonia [91].

4.4. Fatigue

Besides sleep disorders, a large study on focal, segmental, and generalized dystonia observed moderate to severe fatigue in 43% that significantly correlated with HRQoL even when controlled for depression and sleep disturbances. The symptoms of fatigue persisted despite improvement of motor symptoms after BoNT treatment [81]. Subjective ratings of both energy and tiredness associated with HRQoL even when controlling for depression were reported in another study [92]. In dystonia, the frontal and subcortical circuits are known to be dysfunctional as seen in fatigue. Thus, a hypothesis of possible overlap in pathophysiology at a central level was proposed [81]. Notably, pain was correlated with fatigue but not sleep or sleepiness, supporting the dissociation of these constructs and suggesting a potential contributory role [81].

In summary, it seems that sleep impairment may be a feature of primary dystonia that is independent of the severity of the motor symptoms of the disorder. It is, however, correlated with depression, and therefore it is not clear at present if there is a primary sleep abnormality in dystonia [15]. Secondary effects of pain and medications also may play a role in the etiology of sleep disturbances [80]. Further studies on sleep including polysomnographic recordings are warranted to address this issue. And finally, sleep needs to be targeted in therapy. Preliminary evidence suggests that sleep is not sufficiently improved after BoNT treatment, thus QoS should be included as an outcome in treatment studies. If the finding that sleep is not improved after state-of-the-art treatment is replicated, standard sleep treatments such as CBT and the newer forms of behavioral therapy for insomnia need to be evaluated and, if necessary, adapted for patients with dystonia [91].

5. Sensory disturbances

One characteristic feature of idiopathic focal dystonia is the role of sensory feedback that manifests as the phenomenon of geste antagoniste or "sensory tricks," which refers to various maneuvers used by patients with focal dystonia to temporarily relieve their dystonic spasms, offering a strong evidence that dystonia is also a sensory disorder [93]. On the other hand, sensory stimulation might trigger dystonia, for example, a loud noise producing spasmodic torticollis. Sensory symptoms may also precede the onset of dystonia or develop concomitantly [25, 93]. Abnormal sensory input might be as well a trigger for dystonia. Trauma to a body part is often a precedent to dystonia of that part, grittiness or dryness of the eyes is common in blepharospasm [25, 93].

Sensory function, particularly in the somatosensory domain, has been shown to be compromised in patients with primary dystonia, both in adult-onset focal forms and in genetically characterized DYT 1 dystonia [94, 95]. Studies have revealed evidence of abnormal somatosensory spatial and temporal discrimination, higher in dystonic patients than in healthy subjects [94–98].

Temporal discrimination is the shortest time interval for which two successive stimuli are perceived as separate. This is essential for somatosensory functions such as kinesthesia, graphesthesia, vibratory sense, and stereognosis [93]. Temporal discrimination is impaired in patients with dystonia, and the deficit is more pronounced in focal dystonia compared with the generalized form [93]. Bradley et al. found abnormal temporal discrimination threshold (visual, tactile, and mixed) in 97.3% of CD, 85.7% of writer's cramp, 88.8% of BS, 90.1% of spasmodic dysphonia patients, and in 62.5% of musician's patients. The sensory abnormalities were also present in unaffected relatives, possibly indicating a non-manifesting gene carriage [96, 97]. Given that nonaffected DYT 1 gene carriers may show similar abnormalities to clinically affected individuals, sensory deficits could constitute a subclinical endophenotypic trait of disease that precedes overt clinical manifestations [95]. Proprioceptive afferent-related functions, and particularly kinesthesia and vibration-induced illusion of movement, are abnormal in patients with focal dystonia. This abnormality occurs in both affected and unaffected body regions with similar results being reported in asymptomatic first-degree relatives [25]. The degree of temporal discrimination impairment is positively correlated with the degree of severity of dystonia. This discrimination deficit was identified in both the affected and unaffected hand, implying that the deficit is a result of a central process of dystonia itself, rather than a byproduct of the abnormal muscle contractions [99, 100].

Spatial discrimination differentiates two spatially separated stimuli and is measured as the shortest distance between the stimuli that are perceived as separate [93]. Altered spatial discrimination thresholds are found in familial and sporadic adult-onset focal dystonia patients and in some unaffected relatives who may be non-manifesting gene carriers [101]. Molloy et al. also find spatial discrimination to be impaired in affected, as well as in clinically normal body regions for a wide range of focal dystonia, but not affected in generalized dystonia, suggesting either partially separate pathophysiologic processes in both subtypes of dystonia, or early adaptive changes or compensatory mechanisms in generalized dystonia [94].

Further evidence of the involvement of the sensory system in dystonia comes from a number of studies that have investigated mechanisms of synaptic plasticity in cortical sensorimotor areas by means of transcranial magnetic stimulation. These neurophysiological studies have revealed impaired cortical somatosensory processing, which may be due to an abnormal inhibitory interneuron activity and abnormal sensory motor integration in patients with dystonia [25].

In summary, sensory symptoms and sensory system abnormalities are present in dystonia patients. Sensory symptoms may also precede the onset of dystonia [25]. Neurophysiological studies revealed defects of temporal and spatial discrimination, of integration of sensory stimuli, and of proprioceptive afferent processing as well as movement representation which have been observed not only in affected body parts but also in those remote from dystonic symptoms. This finding reflects diffuse neurophysiological and neuroimaging sensorimotor abnormalities reported in dystonia regardless of the clinically affected body part [25, 95].

On the basis that there may be abnormalities in processing somatosensory inputs, several neurorehabilitative approaches have been developed including upper limb or finger immobilization, sensorimotor training, and transcutaneous electrical nerve stimulation. Although the

real efficacy of these treatments has yet to be confirmed in randomized, blinded, and controlled studies, it may be that rehabilitation of the somatosensory processing improves motor symptoms. This could provide efficient strategies to aid functional recovery, mainly in focal hand dystonia, in which the available medical treatments offer little benefit [95].

6. Pain

Pain is one of the most common complains in dystonic patients, reaching approximately 84% of CD patients and a major source of disability [102]. Although commonly associated with CD, significant pain may be reported by patients with BS, masticatory dystonia, and limb dystonia. In some patients with cervical dystonia, pain is much more debilitating than abnormal head postures [103].

One potential reason for pain to be so prevalent in dystonia may be a reduced stimuli threshold [104]. Patients with dystonia may also have alterations in pain processing even in body parts without dystonic involvement [104]. Another potential mechanism for excessive pain includes alterations in the somatosensory system. Ongoing depression, common in this population, correlates with symptoms of pain [80], but pain intensity often correlates poorly with the severity of dystonic contractions or amplitude of involuntary movements [6]. Lastly, sleep itself may mitigate against pain [80].

No recent studies have evaluated any other pharmacologic agents to specifically treat either primary or secondary dystonic pain symptoms. Double-blind, randomized controlled trials assessing whether analgesic agents could lead to objective measures of additional decreased pain in dystonia patients are needed, particularly in patients refractory to BoNT [80].

7. Autonomic dysfunction

In dystonia patients, most of the autonomic dysfunction is related mainly to treatment with anticholinergic medications or BoNT, and especially with BoNT B, although Tiple et al. found that CD patients have mild, subclinical abnormalities in autonomic cardiovascular regulation, heart rate and systolic blood pressure variability, and cardiopulmonary baroreflex sensitivity prior to therapy, which do not worsen after BoNT-A injection [105]. Tinter et al. reported patients treated with BoNT-B to have less saliva production and greater severity of constipation, than those treated with BoNT-A [106]. Another study of CD patients reported that BoNT side effects consisted of dryness of mouth, accommodation difficulties, conjunctival irritation, reduced sweating, swallowing difficulties, heartburn, constipation, bladder voiding difficulties, head instability, dryness of nasal mucosa, and thrush, again, occurring far more often after BoNT-B than after BoNT-A, suggesting a systemic spread of BoNT-B [107].

A special interest is that reported by Hentschel et al. where cardiovascular autonomic imbalance with sympathetic predominance occurs as a non-motor manifestation of CD, associated

to comorbid depression. A decreased heart rate variability and orthostatic hypotension were observed at a significantly higher rate when CD was combined with a mood disturbance, without other significant differences in autonomic function [108]. These results draw attention to the need to identify and treat depression in dystonia.

8. Conclusion

Isolated, previously defined as primary dystonia, appeared to be no longer accepted as a solely motor manifestation, but a number of evidences pointing toward a disturbance in many non-motor domains emerged through decades. Most of the studies available focused on the examination of the coexisting mood and anxiety spectrum disorders and disturbance in the sensory system, but sleep and cognition disruptions have also been reported at a higher rate. There are still controversies as to whether non-motor symptoms reflect a secondary dysfunction to the motor impairment or share common etiological and pathogenetical mechanisms with the dystonic disorder. The exploration of future therapeutic approaches should be focused not only on treating the movement symptoms but non-motor presentations as well. Future investigations in the field of epidemiology, etiology, and treatment of non-motor symptoms in isolated dystonia are warranted in order to enlighten the bizarre nature of this movement disorder.

Author details

Nikolina I. Semerdjieva* and Ivan G. Milanov

*Address all correspondence to: nikolina.semerdjieva@gmail.com

University Hospital “St. Naum”, Sofia, Bulgaria

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Tardive Dyskinesia

Chapter 4

Tardive Dystonia due to D2 Antagonists and Other Agents

Maria Skokou, Evangelia-Eirini Tsermpini, Adamantia Giamarelou, Athanasios Gogos and Philippos Gourzis

Additional information is available at the end of the chapter

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Abstract

Tardive dystonia due to D2 antagonists or other agents is a potentially severe extrapyramidal side effect emerging after long-term drug treatment, prevalent but not limited to psychiatric populations. Its course is often deteriorating, and available treatments are frequently far from satisfying. It presents with sustained muscle contractions, abnormal postures, and repetitive twisting movements and leads to increased psychiatric morbidity, mortality, and decline of quality of life. Inadequate clinical skill and awareness of tardive dystonia can lead to neglect or misdiagnoses, considered as conversion symptoms or of psychogenic origin. Since the syndrome is persistent and often treatment resistant, prevention should be a mainstay of clinical care. Emerging evidence supports positive effects of atypical antipsychotics, particularly quetiapine and clozapine. Therapies such as tetrabenazine, valbenazine, deutetrabenazine, anticholinergics, baclofen, benzodiazepines, vitamin E, or non-pharmacologic interventions, namely botulinum toxin A, deep-brain stimulation, have been found to be helpful in some cases of tardive dystonia. This chapter comprehensively illustrates multiple aspects of this entity, including recent advances on etiology, pathophysiology, clinical presentation, epidemiology, pharmacogenomics, and treatment, aiming to enhance and deepen clinicians' and researchers' awareness of tardive dystonia, with the final goal of ameliorating patients' prognosis and quality of life.

Keywords: tardive syndromes, tardive dyskinesia, tardive dystonia, antipsychotics, clozapine, quetiapine, diagnosis, extrapyramidal side effects, D2 antagonism, pharmacogenomics, treatment

1. Introduction

With the advent of antipsychotic drugs in the 1950s, a new era in the treatment of schizophrenia began, one that substantially altered the course of the illness and offered many benefits to patients and the society. Along with therapeutic advance, new troubles emerged, as it was soon realized that neuroleptics caused important side effects, among which drug-induced movement disorders could be seriously problematic. Tardive syndromes, largely represented by tardive dyskinesia and tardive dystonia, still remain challenging in many respects.

"Dystonia Tarda" was a term firstly used in 1973 to define a dystonia which appeared as a delayed undesirable effect in patients exposed to neuroleptic drugs [1]. Case descriptions appear in the literature even earlier, but a definition of the term "Tardive Dystonia" came from Burke et al. [2] who also implemented diagnostic criteria. The syndrome consists of involuntary, sustained muscle contraction(s), usually slow, often painful, affecting the face, neck, limbs, or trunk [3]. The involuntary muscle contractions can cause abnormal postures and twisting movements, which are often disfiguring and socially awkward.

Tardive dystonia (TDt) belongs to a constellation of persistent motor and sensory syndromes, collectively called tardive syndromes (TS), manifesting as a result of dopamine receptor blocking agents (DRBAs) or, less often, by other types of drugs (**Figure 1**). Tardive dyskinesia (TDk) was the first to be observed, in the 1950s, typically comprising rhythmic, repetitive oro-buccal-lingual involuntary movements, which, however, can also appear in trunk, limbs, and pelvis [4]. Later, TDt was also described as a distinct, frequently co-occurring or independently manifesting condition. Although the term "tardive" implicates a long exposure and

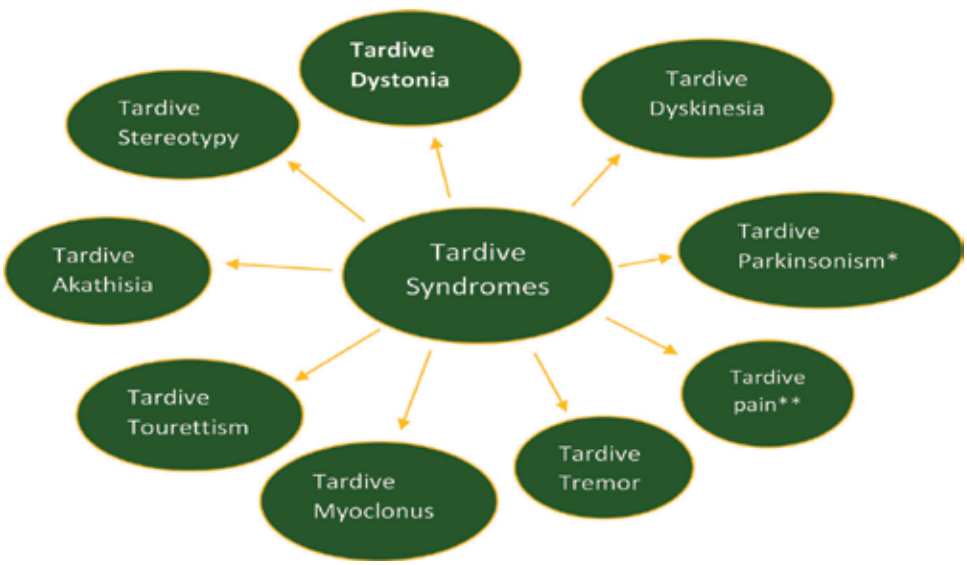

Figure 1. Tardive syndromes occurring in neuroleptic-treated patients. *Tardive parkinsonism is not solidly established, but probably signals the presence or unmasking of idiopathic parkinsonism. **Tardive pain refers to chronic oral or genital pain and is considered by some authors as a type of tardive akathisia, with a severe focal sensory discomfort.

delayed onset, tardive syndromes can actually show up even days after the administration of the offending agent, notwithstanding that risk increases with longer exposure durations. Another important feature is their persistent nature, meaning that they persist or even worsen following discontinuation of the offending drug [5].

Progress in the field has demanded much effort, regarding the clinical recognition of the syndrome, pathophysiology, prevention, and treatment. One reason for this is that TDt often occurs simultaneously or as a component of TDk, or other tardive syndromes, and researchers have difficulties to deal with it separately. Moreover, there is often some confusion in the study, as authors may sometimes use the term tardive dyskinesia in order to refer to a variety of tardive syndromes. Much work examines tardive syndromes in general, and it is difficult to extract data referring specifically to TDt. Still, the distinction and separate examination of TDt is important, because it differs from TDk in respects of presentation, course, prognosis, and treatment; it is frequently more debilitating and treatment resistant; it is associated with a poorer quality of life, a reduced treatment compliance, and psychiatric morbidity [6–8]. Another task is to differentiate tardive dystonia from acute dystonia, emerging acutely and within days after the initial administration of anti-D2 agents, predominantly in young males, as well as from other types of dystonia. Tardive syndromes due to anti D2 agents are schematically depicted in **Figure 1**.

In their pioneering work, Adityanjee et al. had hoped that tardive dystonia together with tardive dyskinesia would in the future be a matter of historical interest, thanks to the advent of new, better antipsychotics [6]. Almost 20 years later, these movement disorders are not at all lost, not yet forgotten. Continuing to be a serious burden, they call for better understanding, prompt recognition, prevention, and optimized treatment.

2. Epidemiology

The prevalence of TDt has been estimated between 0.4 and 21.6% of neuroleptic-treated patients, in earlier studies [6], which distinguished tardive dystonia from tardive dyskinesia (**Table 1**). Most of them have included chronically ill patients. The study by Sethi et al. [13] was conducted on a veteran sample and also included mild manifestations of TDt, which is possibly the reason for the relatively high reported prevalence. Moreover, in a sample of 194 mainly Afro-Caribbean chronic psychotic patients, TDt was overall found in 13.4%, together with TDk in 9.8%, together with parkinsonism in 4.6%, and together with akathisia in 1% of patients [17]. To compare, the prevalence of TDk, which is the most frequently observed tardive syndrome, has been reported to be 20–40% by a recent review [3].

More recently, the CATIE trial examined the efficacy, tolerability, and cost-effectiveness of the first- and second-generation antipsychotics and has provided some epidemiological data for extrapyramidal side effects, including TDk and/or TDt. The proportion of patients who met modified Schooler-Kane tardive dyskinesia criteria ranged from 8.3 to 9.6% with Second Generation Antipsychotics (SGAs) and 11.8% for perphenazine. There were no statistically significant differences between treatment groups on any TD indicator [18], but TDk was not discriminated from TDt by the researchers.

Study	Number of neuroleptic exposed patients	Tardive dystonia prevalence (%)
Yassa et al. [9]	351	2
Yassa et al. [10]	558	1.6
Friedman et al. [11]	331	1.5
Chiu et al. [12]	917	0.04
Sethi et al. [13]	125	21.6
Inada et al. [14]	716	2.1
Sachdev et al. [15]	100	1
Raja [16]	200	4

Table 1. Early studies examining the prevalence of tardive dystonia.

A difficult question to answer is the differential risk of getting TDt after the administration of first- (typical) and second-generation (atypical) neuroleptics, when studies are conducted on subjects who have lifetime histories of exposure to both. A recent Korean study has attempted to deal with this issue [19]. The authors retrospectively and cross-sectionally examined the incidence and prevalence of TDt, apart from TDk, in 80 non-elderly (mean age ± SD: 33.1 ± 8.2) psychotic patients receiving SGAs, who were never treated with typical neuroleptics. The median time of exposure to antipsychotics was 66.8 months, 73.0, 58.8, and 88.0 months for patients without TDt or TDk, patients with only TDk, both, and only TDt, respectively. The sample was exposed at the onset of dystonia or previously to risperidone, amisulpride, olanzapine, aripiprazole, clozapine, ziprasidone, and quetiapine, with the most frequently prescribed antipsychotic being risperidone (72.5% of the subjects). Other received agents were benzodiazepines, antidepressants, and mood stabilizers. TDt was determined by applying the Burke criteria, at two separate examinations, and was observed in 13 patients, 8 of whom also had TDk. Prevalence was calculated to be 14.1% (11 out of 78 patients, since 2 were referred to the center for TDt). Tardive oculogyric crises occurred in another six. When only moderately and severely affected patients were included, prevalence dropped at 5.1%, which is similar to the prevalence estimated earlier, in the context of typical neuroleptics exposure (mean 5.3%) [20]. TDt and TDk were significantly associated ($p = 0.021$). A history of acute dystonia significantly increased the risk for TDt ($p < 0.001$). Having comorbid obsessive compulsive symptoms was also significantly associated ($p = 0.024$), but when corrected for clozapine use, which could provoke obsessive compulsive symptoms and be used for the treatment of TDt, significance weakened ($p = 0.074$).

In a similar line, Lee et al. estimated the incidence and prevalence of tardive syndromes in a sample of psychotic patients (n = 123, mean age ± SD: 45.6 ± 13.8) exposed to antipsychotics for a period of at least 6 months, excluding those receiving a long list of other agents implicated in tardive syndrome occurrence, which is antidepressants, reserpine, tetrabenazine, methyl-dopa, lithium, calcium-channel blockers, anticholinergics, and others [21]. The prevalence of TDt was 12.2%, with TDk being 21.1% and overall tardive syndrome prevalence 28.5%. The prevalence of nonremitting TDt was 7.3% and tardive syndrome 15.5%. A longer duration of

symptoms and more severe extrapyramidal symptoms (EPS) predicted nonremission of tardive syndromes in general. Risk factors for the emergence of tardive syndromes were EPS and physical illness (stroke, diabetes mellitus, hepatitis, chronic pain, cancer, and other chronic illnesses, e.g., hypertension, hyperthyroidism, renal stone, gastric ulcer, hyperlipidemia, benign tumor such as ovarian tumor and uterine myoma, and heart disease), but odd ratios were not calculated specifically for TDt. No difference in risk was found comparing first- generation antipsychotics (FGAs) to SGAs.

Moreover, in another retrospective study, Lee et al. set out to calculate the prevalence of tardive movement disorders in patients receiving antidepressants [22]. Out of 158 subjects, exposed to antidepressants for at least 6 months, but not to other agents causing tardive syndromes, 14% had at least one tardive syndrome and 10.4% manifested TDt. Non-remitted TDt was 5.1%. Notably, TDk was found at a lower rate (3.2%). Other tardive syndromes were tardive tremor (1.3%), tardive parkinsonism (1.3%), tardive tics (1.3%), tardive sensory syndrome (1.3%), and tardive myoclonus (0.6%). Patients exhibiting tardive syndromes had received SSRIs (fluoxetine, paroxetine, and escitalopram), SNRIs (venlafaxine and duloxetine), TCAs (amitriptyline and trazodone), NaSSA (mirtazapine), and NDRI (bupropion). The use of SNRIs and previous marriage significantly increased the risk of tardive syndrome occurrence, but the authors again do not differentiate between syndromes. Apart from this study, there are only few case reports linking antidepressant use with TDt [22–24], and, therefore, solid conclusions must await further studies.

The Genetic Risk and Outcome of Psychosis (GROUP) study is a prospective, naturalistic study on a large, relatively young (age: 27 ± 7 years; illness duration: 4 ± 4 years) cohort during 3 years of antipsychotic treatment. Drug-related movement disorders (DRMDs) as well as a variety of clinical outcomes were studied. The aim of the authors was to study the incidence, prevalence, and persistence rates of DRMDs at an early stage of the psychotic illness (schizophrenia and other non-affective psychoses), without prior treatment confounding [25]. Eligible patients for inclusion in the prevalence, incidence, and persistence analyses were 828 at baseline (age: 27 ± 7, illness duration, mean: 4 ± 4 years) and 447 at follow-up. The prevalence of the DRMDs other than parkinsonism and akathisia did not differ significantly between patients treated with FGAs and SGAs, neither between olanzapine and risperidone, the two most frequently prescribed SGAs. Prevalence at baseline, 3-year follow-up, and 3-year incidence of TDt were 1.5, 1.8, and 1.6%, respectively. The incidence of TDt was low, probably due to a modest cumulative antipsychotic exposure in this population and in line with some previous reports (0–0.7%).

The rising prevalence of TDt in later retrospective and cross-sectional studies, compared to earlier ones, might reflect better recognition, the use of standardized tools and criteria, and lower symptom severity thresholds for the diagnosis. Indeed, in a study by Lee et al., when prevalence is calculated based only on moderately and severely ill patients, the estimation diminishes to 5.3%, similar to older studies reporting 0.4–4% [21]. Commenting data on FGAs and SGAs, it seems that the initial expectations in the beginning of the atypical antipsychotics era of banishing TDt and other tardive syndromes once and for all are far from being fulfilled. Still, TDt due to SGAs, albeit of similar prevalence, is possibly milder and more likely to remit (50 vs. 33% for SGAs and FGAs, respectively) [21].

Summing up risk factors for TDt, mostly established ones are younger age, male sex [20], longer duration and higher doses of antipsychotic exposure, mood disorders, brain injury, mental retardation, dental procedures, diabetes mellitus, alcohol and substance abuse, and a previous acute dystonic reaction [3, 6, 8]. It has been reported that the presence of TDk increases the risk of TDt by 8.7 times [17]. Males tend to have a younger age at onset of TDt than females [5].

3. Offending drugs

Offending drug is considered to be an agent to which a patient is exposed currently or in the past and is believed to have contributed to the provocation of TDt. Many studies deal with offending drugs associated with tardive syndromes in general, or TDk, and information for TDt has to be extracted or is confused with information for other tardive syndromes. A list of drugs that have been associated with the emergence of TDt is provided in **Table 2**. The syndrome may appear while the patient is on the drug, or after the drug's reduction or discontinuation, without being any "safe" period of exposure [7]. It is presumed that any drug exerting direct or indirect anti-D2 properties can be incriminated. Regarding antipsychotics, the emergence of the syndrome seems to be extremely rare following clozapine or quetiapine exposure, probably due to their very low D2 affinity and fast dissociation from the dopamine receptor; in fact, they represent a therapeutic option [26, 27]. Numerous case reports are found in the study for several antipsychotic drugs [28–31]. A matter of serious concern is the administration of extended release preparations, for example, paliperidone palmitate [32, 33],

Antipsychotics
Typical
Atypical
Antidepressants
Buspirone
Antiepileptics
Lithium
Antiemetics
Calcium-channel blockers
Psychostimulants
Cocaine
Pseudoephedrine
Chemotherapeutic agents
Memantine

Table 2. Offending drugs implicated in TDt.

as in this case, the responsible drug cannot be easily removed or substituted. Classes of antidepressants (SSRIs, SNRIs, NASSA, NDRI, and TCAs) probably act by overstimulating of the basal ganglia serotonin 5-HT2 receptors, leading to dopamine antagonism, while noradrenergic hyperactivity might also play a role [22, 24]. Antiemetic and prokinetic agents centrally blocking D2 receptors on the chemoreceptor-trigger zone are also implicated, such as substituted benzamides (metoclopramide, clebopride, and cisapride) and prochlorperazine, which is a phenothiazine [34]. Calcium-channel blockers (nifedipine, cinnarizine, and flunarizine) may alter central dopamine production through N-type calcium channels and produce tardive dystonic reactions [35, 36]. On rare occasions, antiepileptics (e.g., carbamazepine [37] and lamotrigine [38]), lithium [39, 40], psychostimulants, by altering dopamine neurotransmission (e.g., cocaine and norpseudoephedrine [41–43]), chemotherapeutic agents, possibly through a delayed toxic effect on basal ganglia (e.g., 5-fluorouracil and doxorubicin [44]), buspirone [45], and memantine administered accidentally at a double than recommended daily dose [46] have been reported. Dopamine agonists can cause dystonia in the presence of parkinsonian pathology [39]. Anticholinergics have been found to worsen symptoms of TDk [47], but, on the contrary, they seem to improve TDt [6].

4. Diagnosis, clinical presentation, and course

The criteria of TDt have been set by Burke et al. and these are the following: (1) the presence of dystonia (sustained, involuntary, usually slow-twisting movements), (2) the onset of dystonia was during ongoing treatment or within 2 months of discontinuation of antipsychotic drug treatment, (3) in the presence of other tardive syndromes such as akathisia or dyskinesia, dystonia should be the main feature, (4) clinical and laboratory evaluation should be provided to exclude other causes of dystonia, and (5) negative family history of dystonia [2]. All five are required for a definite diagnosis [2, 48]. The authors had studied a sample of 42 patients with TDt, and the onset of the symptoms began after 3 days to 11 years of antipsychotic treatment [2]. Kang et al. have used the Burke criteria with minor revisions [49]. Tardive dystonia is classified in DSM-5 under the chapter "medication induced movement disorders and other adverse effects of medication" as a diagnostic entity separate from tardive dyskinesia [50]. This represents a progress from DSM-IV-TR, where it was classified under the collective term "movement disorder not otherwise specified." It is most probable that such a departure will aid better recognition and also enhance research. In ICD-10, it is classified as "G24.0, drug-induced dystonia."

TDt typically presents with sustained involuntary muscle contractions, which cause abnormal postures and twisting movements especially on the upper limbs, neck, trunk, or face [5]. It is classified according to the affected body parts as focal (one body part affected), segmental (two or more body parts which are contiguous), multifocal (two or more distant body parts affected), and generalized (affects the trunk and at least two other body parts) [6]. The involvement of cranial-cervical area is described in 87% of patients [7], which is the most common in TDt, and presents with retrocollis (dystonic cervical movement where the head is drawn back), anterocollis (the head is drawn forward), and torticollis (the head is turned to the side). Opisthotonous is also a frequent manifestation, with trunk involvement, most

evident during walking. The trunk is arched backwards, with the arms at adduction and extension and the wrists flexed [6]. Other cases manifest clinically with focal or segmental dystonia such as tardive oculogyric crises (involuntary ocular deviations), or involve the jaw (jaw deviation), oromandibular area (trismus), and blepharospasm [51]. Pisa syndrome refers to a tonic flexion of the trunk to one side of the body, leading to a slight lean, whereas Meige syndrome is described as oromandibular dystonia (involuntary and often forceful contraction of the muscles of the jaw and tongue) and blepharospasm (involuntary muscle spasms and contractions of the muscles around the eyes) [52].

Pain and strange somatic symptoms were described by few patients in the early stages of TDt [7]. The involuntary movements of TDt seem to get better or vanish during sleep and worsen under stress, leading to a fluctuating picture. They can be partially controlled by simple maneuvers such as a sensory trick response, where a gentle touch on the chin or neck or a forcible one with certain amount of pressure can alleviate dystonic movements [49, 53].

All forms of dystonia, which include lower limbs only, are more common in idiopathic dystonia and not in TDt [6]. None of patients with TDt had a lower limb involvement without face or neck involvement, too [2]. As already mentioned, TDt is frequently co-occurring with other tardive syndromes, such as TDk, Tardive akathisia (TDa), Tardive myoclonous (TDm), and Tardive tourettism (TDr) (**Table 3**). Patients with TDt are more aware of their movement disorders than patients with TDk [54].

The onset of TDt is insidious, mostly at first with focal dystonia (83%), affecting most frequently the face and neck; it may be heralded by increased eye-blinking or tick-like movements, and over time, it can evolve to segmental and generalized [7]. The course is progressive for months and then persists and remains static for years [2]. Unfortunately, remission rates are low, with a mean of 10%, in a mean follow-up period of 6.6 years [2, 5, 7, 49]. Tapering and withdrawal of the offending drug is important for remission and increases this possibility fourfold [7].

Studies	N	Number of patients with more than one tardive syndrome	Tardive syndromes
Sachdev et al. [54]	15	9	TDt, TDk
		6	TDt, TDa
Burke et al. [2]	42	16	TDt, TDk
Wojcik et al. [55]	32	27	TDt, TDk
		2	TDt, TDm
Kang et al. [48]	67	28	TDt, TDk
		21	TDt, TDa
Kiriakakis et al. [7]	107	32	TDt, TDk
		24	TDt, TDa
		1	TDt, TDr

Table 3. Clinical overlap of TDt and other tardive syndromes.

Prognosis of TDt is poor and disability in patient's everyday activities frequent. Movement disorders and their symptoms affect social life and emotional condition too. Deterioration in speech, vision, eating habits, sitting, gait, and sexual ability have been reported [9, 56, 57]. Oculogyric crises and blepharospasm, and cranial-cervical dystonia, can gravely inhibit daily living activities, such as driving and personal grooming, for example, shaving, combing, or dressing. Muscle contraction and activity may lead to abnormal positions of the body. Sometimes, fractures occur, resulting from the way of walking or standing. A potentially painful situation can be present [52, 56]. Even though rare, the involvement of laryngeal or respiratory muscles can occur in TDk [58] and TDt [59] and can be very distressing or even life-threatening.

Social avoidance, isolation, and stigmatization concerns are common in patients with TDt, as abnormal postures and contractions impose a strange appearance. Furthermore, work productivity, finding an employment, and coping with family roles become compromised. Quality of life accordingly deteriorates, to a greater extent in patients with generalized dystonia than in those with focal [60], and is associated with anxiety and depression [61].

5. Differential diagnosis

For the unfamiliar clinician, the diagnosis of TDt can be difficult. Clinical overlap with other tardive syndromes could possibly lead to a missed diagnosis, or a misdiagnosis. Strange postures can be considered as mannerisms in a psychotic patient, and deterioration with anxiety together with amelioration with relaxation or sleep can lead to a mistaken diagnosis of conversion disorder, other psychogenic condition, or hypocrisis.

Differential diagnosis begins with differentiation from other types of movement disorder or tardive syndromes, by deciding on the dystonic kind of the symptoms. Then, it must be distinguished from other primary and secondary dystonias (**Table 4**) [2, 3, 5, 39, 54, 62].

Acute dystonia
Idiopathic torsion dystonia
Focal dystonia
Secondary dystonias due to focal brain lesions
Brain injury, tumor, vascular damage, infectious, post-infectious, paraneoplastic
Secondary dystonias due to diffuse brain damage
Ischemic, hypoxic, metabolic, toxic
Dystonia-plus syndromes
Heredodegenerative dystonia (Wilson ´s disease, Huntington ´s disease, and others)

Table 4. Differential diagnosis of TDt.

Acute dystonia appears for 48–72 h after the use of neuroleptic drugs. After discontinuation or reduction of the responsible drug, it completely resolves within 48 h [2]. Acute dystonic reactions impressively respond to the administration of anticholinergics, such as biperiden 5 mg or procyclidine 5 mg, antihistamines like promethazine 50 mg [20], and benzodiazepines like clonazepam 0.5–4 mg.

Idiopathic torsion dystonia may be clinically indistinguishable from TDt. A leg involvement would be more suggestive of idiopathic dystonia. Cervical position such as head bent toward the shoulder (laterocollis) and torticollis may be seen more frequently in idiopathic dystonia, whereas retrocollis (hyperextension of head and neck backwards) is more usually encountered in TDt [51, 62]. In a recent work, Godeiro-Junior et al. [63] compared a series of 20 patients with neuroleptic-induced tardive cervical dystonia with a group of patients suffering from idiopathic cervical dystonia and found no differences that would be able to differentiate them on phenomenological grounds. The authors concluded that previous or current neuroleptic exposure remained the critical diagnostic clue, pointing to a diagnosis of TDt. Apart from this, the presence of another tardive syndrome, for example, dyskinesia or akathisia, also supports this diagnosis. Correct assessment is crucial, not only for management but also for legal reasons, in case of a lawsuit for antipsychotic adverse event [64].

6. Pathophysiology

The pathophysiology of TDt has not yet been elucidated and remains speculative to a large extent. It has been suggested that it may share some pathophysiologic mechanisms with idiopathic dystonia. Basal ganglia seem to represent a central key player in the etiology of primary and secondary dystonias, including TDt. Cerebellar abnormalities are probably also implicated, and it has been recently demonstrated that these two structures are directly interconnected, with disynaptic loops [65]. On a receptor and neurotransmitter level, the development of tardive syndromes is thought to correlate with dopamine receptor upregulation and hypersensitivity, following their chronic excessive blockade [66, 67]. D2 blockade together with D1 lower occupancy may lead to sensitization of D1 neurotransmission and a D1/D2 imbalance output, resulting in pathological movement [68]. The production of free radicals and oxidative stress, abnormalities of GABA input to striatal neurons and altered synaptic plasticity, altered serotonin receptor signaling, upregulation of D3 receptors and degeneration of striatal cholinergic neurons are also suggested as the possible contributing mechanisms, but most relevant work again does not discriminate between TDt and TDk [69, 70].

A possible insight to the neurobiological processes underlying the dystonic phenomenon may be provided by the different potential of typical and atypical antipsychotics to produce more severe dystonic symptoms, and in particular by the fact that switching to very low potency agents, such as clozapine and quetiapine, seems to ameliorate or even reverse dystonic movements [26]. The concept of atypicality has been introduced early and was initially defined as (1) a drug with antipsychotic efficacy at a dose that has a low risk of producing EPS, prolactin elevation, and tardive dystonia/dyskinesia, (2) a drug that has a greater affinity for the 5HT-2A receptor than for the D2 receptor, and (3) a drug that has a greater efficacy in treating positive,

negative, and cognitive symptoms of schizophrenia. Notably, among SGAs, considered to be atypical, only clozapine has demonstrated some superior efficacy in symptoms as in (3) [71]. It is supposed that 5HT-2A antagonism permits the release of dopamine in the nigrostriatal pathway, thus preventing the emergence of motor symptoms, whereas antipsychotic efficacy by D2 blocking in the mesolimbic pathway is preserved [72]. Another aspect of atypicality refers to the rapid dissociation hypothesis, where atypicality is attributed to the property of blocking D2 receptors long enough for antipsychotic efficacy and shortly enough for avoiding EPS. Clozapine and quetiapine uniquely dissociate from D2 receptor fastest. It takes less than 60 s to dissociate from 50% of D2-cloned receptors, a tremendously faster process than haloperidol, which does so in more than 25 min [73]. In this case, endogenous dopamine can bind in D2 receptors, between antipsychotic doses, and it is hypothesized that the system is thus allowed to exert the phasic nature of normal dopamine transmission, considered to be crucial for normal physiologic actions [74]. On the contrary, typical antipsychotics bind much longer on receptors, and the normal phasic dopamine neurotransmission is distorted to a much greater extent. It has been demonstrated by PET studies that haloperidol and typical antipsychotics produce an increased D2 receptor density in the striatum of humans and animals [75, 76]. Future research is hoped to elucidate and expand our knowledge on mechanism of TDt, with the aim of finding better treatments.

7. Pharmacogenomics of drug-induced dystonia

The term "pharmacogenetics" was first introduced by Friedrich Vogel, in 1959, and refers to the association between an individual's genes and response to a drug or else, the individualizing of treatment [77, 78]. Later, in 1997, Marshall introduced the term "Pharmacogenomics" which, due to the advances of technology and whole genome-sequencing techniques, refers to the impact of multiple genes and specific genetic variations on drug response, including maximum efficacy, but also the minimization of adverse drug reactions. This developing field is expected to contribute to optimal drug choice, in terms of efficacy and safety [78].

To select an antipsychotic drug or dose, psychiatrists take into account many factors, such as the age of the patient, the gender, exercise attitudes, smoking status, liver and renal function, other comorbidities, and co-medications, [77, 79]. Further, different genetic profiles of patients and specifically genetic variations that are associated and affect the pharmacokinetic and pharmacodynamics properties of a drug will lead to different response, including efficacy and toxicity. These genetic variations may cause decreased plasma levels, which will result in a decreased efficacy, or increased plasma levels, which may lead to the appearance of an adverse drug reaction [77]. A variety of publications aim to associate genetic variations of genes involved in pharmacokinetics and pharmacodynamics and drug-induced TDt or TDk, without discriminating between the two. Research is mainly directed toward the genes that metabolize drugs or drug transporters and receptors [79, 80].

One of the most studied and well-defined genes is *CYP2D6*. One-fourth of all drugs are primarily or secondarily metabolized through *CYP2D6*, including many antipsychotics and antidepressants. *CYP2D6* in humans is found on chromosome 22q13.1, and until today, more

than 100 allelic variants have been identified. The phenotype, depending on the alleles, can be Ultra rapid Metabolizer (UM), Extensive Metabolizer (EM), Intermediate Metabolizer (IM), and Poor Metabolizer (PM) [77, 80]. Importantly, different ethnicities have different allelic distributions and therefore their drug metabolism differs [80].

Although researchers have focused on many genetic variations located on *CYP2D6* and their association with the development of TD, results are conflicting. There are studies that failed to indicate an association between TD and *CYP2D6*1, CYP2D6*2, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*15a, CYP2D6*17* (Ohmori et al. [81]; Ohmori et al. [82]; Arthur et al. [83]; Armstrong et al. [84]; Brockmöller et al. [85]; Lohmann et al. [86]), but also studies that indicated an association or at least a trend of association between the studied alleles of *CYP2D6* and TD. A study in 1998, in 100 Japanese patients with schizophrenia, indicated a statistically significant association in allelic level between *CYP2D6*10* and TD, which remained significant even after adjustment for variables by regression analysis [82]. The same year, another group focused on 45 Caucasian schizophrenic patients of Austrian origin, and the potential association between *CYP2D6*3, CYP2D6*4,* and *CYP2D6*5* mutations and TD. There was a trend of correlation between *CYP2D6* genotype and TD development, and, in particular, heterozygotes for one mutation presented a higher risk of TD [87]. Similarly, patients with at least one mutation, *CYP2D6*1, CYP2D6*3* or *CYP2D6*4*, indicated a higher incidence of TD [88]. A trend of association between PM and TD severity was also detected in the study by Andreassen et al. who conducted an investigation of *CYP2D6*1, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6,* and *CYP2D6*7* in 100 schizophrenic patients from South-East Scotland [89]. Two other studies, which also performed a gender analysis, indicated that female schizophrenic patients with TD had a higher frequency of *CYP2D6*10* allele than men [90] and that males with a non-functional or a partially functional allele of *CYP2D6*1* to *CYP2D6*1, CYP2D6*10B, CYP2D6*14, CYP2D6*18, CYP2D6*19, CYP2D6*25, CYP2D6*26, CYP2D6*31, CYP2D6*36,* and *CYP2D6*41* had a higher risk of TD than those of wild type [91]. A significant association was also found between increased metabolism of FGAs and TD [92]. Finally, in the study by Ellingrod et al., in a cohort of 37 Americans with schizophrenia, the larger part of smokers with *CYP2D6*1/*3, *4* suffered from TD [93].

Researchers have also studied *CYP1A2* gene. Studies concerning TD and 734C/A [94–96] as well as *2964G/A* [94] of *CYP1A2* in patients with schizophrenia fail to detect any association. However, C homozygotes were found to be associated with higher AIMS scores in two independent studies performed in 200 and 2015 [97, 98].

Regarding dopamine receptor genes, *DRD1, DRD2, DRD3,* and *DRD4* receptors have been investigated by a variety of laboratories.

In a study of 2011, in which *DRD1* and specifically *rs5326, rs4532,* and *rs265975* polymorphisms were investigated, only *rs4532* was found to be significant, with CC genotype being associated with TD [99].

As for *DRD2*, rs1801028, rs1800497, rs1799732 (Hori et al. [100]; Kaiser et al. [101]; Koning et al. [102]; Park et al. [103]), rs1801028 [101, 104], rs1799978, rs1079597, Val96Ala, Leu141Leu, Pro310Ser [101], rs1800498 [102, 103], rs6275 [103], and rs6277 [102] did not present any statistically

significant association either in allelic or in genotypic level. However, concerning rs1800497 on *DRD2*, there is an older study which was performed in a group of patients with schizophrenia, indicating that this polymorphism may affect the development of TD differently [105].

Many scientific groups focused on rs6280, located on *DRD3* gene. The majority of the studies indicated no association between alleles and genotypes with TD development (Utsunomiya et al. [106]; Løvlie et al. [107]; Chong et al. [104]; Gaitonde et al. [108]; Rietschel et al. [109]; Garcia-Barceló et al. [110]; Basile et al. [111]; Koning et al. [102]; Segman et al. [112]). However, there are four studies which succeed in correlating TD with either the Gly-allele [113], the Gly homozygotes [114, 115], and the heterozygotes [116]. Still, a study that studied seven candidate genes, including *DRD3* and rs9817063, rs2134655, rs963468, rs324035, rs3773678, rs167771, rs11721264, rs167770, rs7633291, rs1800828 polymorphisms, as well as *DRD4* gene and specifically, rs3758653, failed to prove any association with antipsychotic-induced movement disorders [117].

Concerning serotonergic receptors, *HTR2A*, *HTR2C,* and *HTR6* genes have been investigated. *HTR2A* gene and especially rs6313, rs6311, and rs6314 were the subject of research in many groups. According to some studies, there was no association between TD development and rs6313, rs6311, and rs6314 [102, 111, 118]. Nevertheless, a study of 2011 regarding *rs6313* showed a relation between T allele and TD development [119], whereas a study of 2001 found higher frequencies of T homozygotes in patients without TD and also allelic differences between patients with and without TD [120]. Segman and his group indicated that patients with TD had higher frequencies of 102C (rs6313) and 1438G (rs6311) alleles and also that CC (rs6313) and GG (rs6311) were associated with higher AIMS scores [121].

Proceeding to *HTR2C*, ser-allele of polymorphism *rs6318*, located in this gene, was found to be more common in patients with TD [112], but also rs6318 indicated no statistical significance in two other studies [102, 119]. Further, rs3813929 indicated no association, and rs518147 was more frequent in patient with TD than those without [102, 122]. The study of Bakker studied rs569959, rs17326429, rs12858300, rs4911871, rs5946189, and rs1801412 polymorphisms of *HTR2C* and found no association between them and TD, either in genotype or in allele level [117]. *HTR6* and rs1805054 were studied in a group of 173 Japanese schizophrenia patients, and no association was observed with TD development [123].

Summing up, there are significant genetic associations between patients with schizophrenia that suffer from drug-induced TD, implicating that dopamine and serotonin systems, as well as CYP genes, participate in TD development. All included studies performed genotyping analysis with well-established and accurate laboratory techniques, like PCR-RFLP, sequencing, and TaqMan assay, whereas studied cohorts included patients of different ethnicities and races, including Caucasians, Chinese, and Japanese patients, diagnosed according to the diagnostic criteria of the Diagnostic Statistical Manual or the International Classification of Diseases. Assessment of TD was mainly performed using the Abnormal Involuntary Movement Scale (AIMS). In many studies, the study population was not large enough to achieve a statistically significant association. For this reason, studies in larger sample sizes need to be done in order to shed more light in the contribution of genetic background in patients who face drug-induced TD.

Furthermore, the majority of studies do not distinguish the terms “dystonia” and “dyskinesia.” Most of these studies concern dyskinesia, which also includes cases of dystonia, and it is difficult to separate them. Future research with better defined studies differentiating between the two conditions is necessary for the better definition of outcomes. Also, factors such as advanced age, gender, ethnicity, dose and drug duration, symptoms, smoking status, alcohol use, co-medication, comorbidities, and family history of psychiatric disorders or TD are risk factors associated with the development of TD [124] and should be taken into consideration when investigating the correlation between TD and genetic factors.

8. Treatment

The best pathway to care is prevention, and for a difficult to treat condition such as TDt, prevention is of paramount importance. Keeping this in mind, increased guardedness must distinguish clinical care for the selection of antipsychotic treatment. Rational use of antipsychotics, that is, using as indicated and not for doubtful reasons, caution to use in mood disorders, not using without a clear indication, not using for longer than needed, should guide clinical decisions. High dosages and polypharmacy should be avoided. Atypical antipsychotics should be preferred over typical ones, even though there is some debate concerning an increased risk for metabolic syndrome, with certain SGAs [125]. Therapeutic levels of lithium and antiepileptics should be monitored and kept within the recommended range; the use of an antiemetic that passes the blood-brain barrier at a lower extent, for example, domperidone instead of metoclopramide, would be wise [35].

When TDt has already been established, a first option would be to lower the dose or stop the offending agent, if the condition of the patient allows it, or substitute the responsible drug with another agent with better side-effect profile. Correct assessment of the patient must take into account the fluctuating course and diurnal variation of dystonia. In bipolar patients, it gets worse during depressive phases [16]. There are reports of SGAs, including clozapine (as monotherapy or administered with clonazepam), olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, amilsulpiride, and perospirone, being effective as a treatment of TDt [52]. However, switching from FGAs to SGAs as a class has not been consistently proven to benefit [27]. Switching from the offending drug to quetiapine or clozapine seems to make more sense, as both drugs have very low affinity for D2 receptors and are not expected to induce dystonic reactions themselves, but only extremely rarely. Recent studies (one open label and one case series, for quetiapine and clozapine, respectively) [26, 126] have demonstrated efficacy, but evidence remains insufficient to make a strong recommendation. Choosing between the two favors quetiapine, because of the serious side effects associated with clozapine (e.g., agranulocytosis) [26].

If the above strategies are insufficient, or not possible, other options can be employed [16]. Several medications have been used to treat dystonia, and the therapeutic approaches include pharmacologic treatment and other types of interventions such as chemodenervation with botulinum toxin, surgery, deep-brain stimulation (DBS), physical, and supportive methods. There are lacking guidelines concerning the selection of dystonia treatment, so the clinical practitioner may choose between recommended therapeutic methods, often guided by personal experience and the patients’ needs [127].

Botulinum toxin can be a therapeutic option, since it has been shown to be helpful in the treatment of several dystonic manifestations like blepharospasm [128], oromandibular dystonia [129], laryngeal dystonia [130], cervical dystonia [131], and writer's cramp and other limb dystonias [132].

Tetrabenazine, a dopamine-depleting agent, can also be an effective treatment for some patients with dystonia, with a starting dose of 25 mg daily, and titrated up to a target dose up to 100 mg daily. It seems that tetrabenazine is more effective in patients with TDt than those with idiopathic dystonia [133]. Adverse reactions include drowsiness, parkinsonism, depression, insomnia, agitation, anxiety, and akathisia [134]. More recent studies have examined deutetrabenazine and valbenazine, which, like tetrabenazine, are also selective vesicular monoamine transporter 2 (VMAT2) inhibitors, but better tolerated than tetrabenazine. The two substances have been very recently approved for the treatment of TDk (which is considered to include TDt) by the US Food and Drug Administration [27].

Acetylcholine-related drug use is one of the most common treatment strategies in dystonia, and they are frequently prescribed for dystonic reactions (including drug-induced dystonia). Anticholinergics such as trihexyphenidyl, starting from low doses such as 2 mg daily and a final dose ranging from 6 to 40 mg daily [134], benzatropine, biperiden, procyclidine, orphenadrine, and ethopropazine [135], have been broadly used in many types of dystonia, and the effectiveness seems to be quite satisfying. However, there are limitations for their use, regarding less tolerability of anticholinergic use in older adults and because high doses are demanded [136]. Their typical side effects include cognitive dysfunction, memory impairment, depression, confusion, dry mouth, constipation, urinary retention, blurred vision, and deterioration of narrow-angled glaucoma.

Baclofen has been reported to be effective in patients with TDt [137], especially in patients with blepharospasm, compared to other types of dystonic reactions. Drowsiness, dizziness, nausea, and fatigue are considered to be the drug's main adverse reactions [138].

Benzodiazepines such as alprazolam, clonazepam, chlordiazepoxide, and diazepam have been used in the treatment of dystonia, according to multiple small or retrospective studies [134]. They act as GABA receptor agonists, as they enhance GABA receptor function and GABA neurotransmission. Most common side effects include sedation, cognitive impairment, abuse, tolerance, depression, ataxia, and motor disturbances. Vitamin E has also been proposed as a potential treatment in TDt, and dystonic symptoms improvement has been reported after its administration [139].

Deep-brain stimulation (DBS) has been proposed as a safe and promising treatment for patients suffering from disabling and refractory tardive dystonia, resulting in rapid and long-term improvement in those patients [140].

9. Conclusions

Tardive dystonia is a motor tardive adverse event, resulting from exposure to anti-D2 agents, mostly antipsychotics. It is frequently debilitating and treatment resistant, and although

progress has been made regarding clinical diagnosis and recognition, the neurobiological basis of the condition remains elusive and offered treatment far from satisfactory. Pioneering work must be guided toward a better understanding of normal movement control and pathophysiological processes of abnormal and dystonic movements. Pharmacogenomic studies will be further contributing to identify genetic variations associated with the appearance of drug-induced TDt in the future and are expected to lead to more individualized selection of treatment for each patient, aiming to provide a better outcome. In total, several lines of research are ultimately hoped to usher in better care for people in need of antipsychotic treatment.

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Conflicts of interest

The authors declare no conflicts of interest.

Author details

Maria Skokou[1], Evangelia-Eirini Tsermpini[2], Adamantia Giamarelou[3], Athanasios Gogos[3,4] and Philippos Gourzis[1,3,5]*

*Address all correspondence to: pgourzis@upatras.gr

1 Department of Psychiatry, General University Hospital of Patras, Patras, Greece

2 School of Medical Sciences, Department of Pharmacy, University of Patras, Patras, Greece

3 School of Medical Sciences, Department of Medicine, University of Patras, Patras, Greece

4 Department of Psychiatry, General Hospital "Evangelismos", Athens, Greece

5 Department of Psychiatry, General University Hospital of Patras, School of Medicine, University of Patras, Patras, Greece

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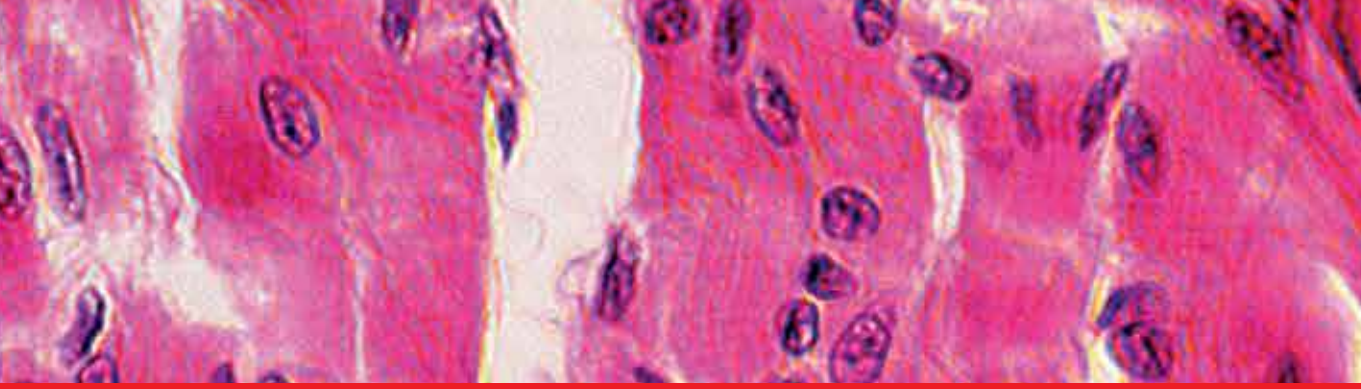

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The book contains four chapters discussing dystonia from a new perspective. Dystonia may result from either diffuse or localized pathology of the cerebral cortex, brain stem, or spinal cord. Management of dystonia is challenging, and specific goals should be identified. Dystonia is considered one of the most disabling conditions in the pediatric age group, which may remain until adulthood; treatment is usually unsatisfactory.

Meige's syndrome, or "oromandibular dystonia," may be misdiagnosed as temporomandibular joint or psychogenic disorder, which will alter management and delay proper treatment. Dystonia with non-motor disorders includes sleep, cognitive, pain, sensory, and psychiatric disorders, and their pathophysiological and biochemical mechanisms and specific treatment are discussed.

This book will be of interest to GPs, neurologists, family physicians, and internal medicine specialists.

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