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Chapter

Spasticity and Dystonia: A Brief Review

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Abstract

Spasticity and dystonia are two neurological conditions with a broad range of clinical manifestations that can emerge at any age. Although the spasticity and dystonia symptoms are caused by different pathophysiological mechanisms, both of them may cause functional impairment that contributes to a poor quality of life. Spasticity is characterised by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex. It mostly occurs in disorders of the central nervous system (CNS) affecting the upper motor neurons, such as multiple sclerosis, amyotrophic lateral sclerosis, cerebrovascular diseases, cerebral palsy, traumatic brain injury, stroke, and spinal cord injury. Therapeutic options may combine, in various proportions, physical therapy, occupational therapy, self-rehabilitation, the use of orthoses and assistive devices, drug treatment, orthopaedic surgery, and neurosurgery. Dystonia is defined as a syndrome of involuntary movement that manifests as excessive muscle contractions that frequently cause twisting and repetitive movements or abnormal postures. It is often intensified or exacerbated by physical activity, and symptoms may progress into adjacent muscles. Dystonia has many different manifestations and causes, and many different treatment options are available. These options include physical and occupational therapy, oral medications, intramuscular injection of botulinum toxins, and neurosurgical interventions.

Keywords: spasticity, dystonia, treatments, oral drugs, rehabilitation

1. Introduction

According to Lance and colleagues, spasticity is a "...motor disorder characterised by a velocity dependent increase in the tonic stretch reflex with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome..." [1]. Over time, the interest of clinicians on spasticity has increased more and more, topics ranging from pathophysiology to clinical relevance and treatment options [2–8].

However, in everyday management of patients' spasticity symptoms, much more complex situation would be there, full of clinical problems. In fact, other positive and/or negative signs may be observed together with increased muscle tone and deep tendon reflexes. Abnormal cutaneous reflexes, spasms, co-contraction, Babinski reflex, and also dystonia, are described as positive phenomena, and weakness, fatigability, and reduced dexterity are considered negative ones. In clinical practice each problem that we have to treat may have different pathophysiological explanations [9]. A central nervous system lesion determines the upper motor

neuron syndrome, induced by an interruption of descending pathways, which connect the highest centres to the spinal cord. Alternatively, reactivity of spinal cord circuits may be modified by a direct damage, through a different way to elaborate the input from peripheral afferents. It is important to differentiate immediate to delayed consequences of damage to the highest centres in the CNS. The delayed consequences lead to a rearrangement of reactivity in spinal cord circuits, in which it is considered a basis of spasticity. Moreover, spasticity may itself be modified by the consequences of paresis and immobilisation, i.e. development of contractures. Several pathophysiological mechanisms may explain the development of spasticity due to CNS lesions. These mainly include defective inhibition, such as postsynaptic inhibition of alpha motor neurons or presynaptic inhibition of 1a afferents. There is also a defective excitation of inhibitory interneurons underlying reciprocal inhibition, autogenetic inhibition, or recurrent inhibition [10].

Dystonia is defined as a neurological disorder characterised by sustained or intermittent muscle contractions, determining unusual movements and postures or both. Typically dystonic movements are patterned and twisting and may be tremulous. Often, dystonic movements may be started by voluntary action, worsening with typically an overflow muscle activation (Consensus 2013) [11]. Dystonia classification is based on clinical characteristics and aetiology. Indeed, except for hereditary forms, dystonic syndromes may be caused by birth-related or other physical trauma, infection, and poisoning or due to pharmacological treatments, particularly neuroleptics. The clinical characteristics include age at onset, temporal pattern, body distribution, and coexistence of other movement disorders. The etiologic characteristics are the presence or absence of nervous system pathology and the pattern of inheritance [11].

Focal dystonia is a neurologic movement disorder, due to an incorrect sensorimotor modulation, determining involuntary, excessive muscle contractions. Writer's cramp is a specific type of focal dystonia that affects the fingers, hand, or forearm. Writer's cramp is a task-specific dystonia, characterised by hands twisting into odd postures. A specific task induces this sign. Other skilled task-specific movements may induce focal hand dystonia, such as playing a musical instrument, typing, or sewing. Writer's cramp is known also as musician's cramp, focal hand dystonia, arm dystonia, finger dystonia, task-specific dystonia, and occupational cramp or dystonia.

Task-specific dystonia like writer's cramp may appear in anyone. It usually appears between 30 and 50 years of age. Task-specific dystonia, particularly musician's cramp, is more common in men.

Two types of writer's cramp could be described:

1. Simple writer's cramp, which appears only during writing. The abnormal postures spring up soon after you pick up a pen. So, it only affects the ability to write.

2. Dystonic writer's cramp appears not only during writing but also during other activities with your hands, like shaving, dressing, or applying makeup.

Probably, repetitive movements determine a remapping of the brain's sensorimotor areas. Bad posture of the hands while holding a pen or pencil associated with overuse seems to cause simple writer's cramp. Dystonic writer's cramp is less common than simple ones and may represent a symptom of generalised dystonia. In this case, the involuntary movements can appear also during other non-writing tasks, such as using a fork or handwashing. Rarely, writer's cramp could be the early onset of a generalised dystonia, which is associated with the DYT1 gene [12].

1.1 Pathophysiology of spasticity and dystonia syndromes

Typically, spasticity is considered as a specific "pyramidal" sign; nevertheless, selective lesions of the primary motor cortex or corticospinal tract often induce hypotonia, deficit, or weakness in distal movements, without inducing spasticity [4]. Only the involvement of non-primary motor areas (premotor and supplementary areas) and the corticoreticulospinal fibres together with cortical lesions may induce spasticity. Corticoreticulospinal fibres sends through the dorsolateral reticulospinal tract descending just anteriorly to the corticospinal tract, a massive bilateral inhibitory projection to spinal motor neurons, which are located in the lateral funiculus of the spinal cord. So the fact that a selective lesion of the anterior limb or the genu of the internal capsula predominantly induces spasticity without an evident motor deficit and vice versa can be explained by the different courses of corticoreticular and corticospinal fibres in the internal capsula. Hence, a lesion involving the corticoreticulospinal fibres will lead to a decreased inhibition (or to an increased facilitation) of the spinal cord and ultimately to spasticity [13, 14]. Three fundamental phenomena occur after a lesion to the central motor pathways assigned to motor command execution:

1. *Paresis:* the quantitative lack of command directed to agonist muscles when attempting to generate force or movement.

2. *Soft tissue contracture and contractile muscle property changes:* shortened position induced by immobilisation due to paresis, causing soft tissue and muscle alterations. [13].

3. *Muscle overactivity:* as a consequence of corticospinal pathway lesion, which causes loss of motor command, brainstem descending pathways are activated. Most of these brainstem descending pathways tend to be constantly active, as a consequence a constant muscle activity is maintained. Releasing of growth factors locally is induced in the spinal cord level by the lack of regular descending excitation to the lower motor neurons. So these phenomena induce local sprouting from neighbouring interneurons, creating perfect conditions in order to synthetise new abnormal synapse network, leading to the creation of new abnormal reflex pathways [8, 9].

1.2 Spasticity

Among these changes, which gradually develop, spasticity represents the principal sign detectable. A simple definition of spasticity is an *increase in velocity-dependent stretch reflexes* [9, 10] which can be evoked at rest by muscle stretch or tendon taps.

Principal key points:

- A tonic stretch reflex.

- Mediated by type 1a fibre nerve, predominantly in the muscle spindle. Passive muscle stretch induces exciting of muscle spindle, which sends sensory input back to the spinal cord through monosynaptic way principally but also oligo- and polysynaptic reflexes, which at the end induce an efferent impulse to the muscle, causing contraction.

- Velocity-dependent.
- Length-dependent.

1.3 Spastic dystonia

The term "spastic dystonia" was coined by Denny-Brown in 1966 to define tonic-chronic muscle activity that is present in a spasticity pattern, during rest [15]. Thus, spastic dystonia could be described as a spontaneous overactivity at rest, not induced by a primary triggering factor [14–16]. It is easy to recognise it in patients with spastic paresis, as spastic dystonia causes specific bad postures in joints and body. For example, in the upper limb, the shoulder can stay internally rotated and adducted with a flexed and pronated elbow and flexed wrist and fingers. Equinovarus deformity represents a specific spastic dystonia in the lower limb, and it is characterised by plantar flexors and/or toe flexors, which may be painful and disabling during walking.

1.4 Spastic co-contraction

Spastic co-contraction is defined as an "unwanted, excessive, level of antagonistic muscle activity during voluntary command on an agonist muscle, which is aggravated by tonic stretch in the co-contracting muscle" [13]. Spastic co-contraction in spasticity pattern is a descending phenomenon, most probably due to misdirection of the supraspinal drive. It may be caused by loss of reciprocal inhibition during voluntary command [9, 10]. So, voluntary command of an agonist muscle is the first step, which induces spastic co-contraction. In patients with good or fairly good motor control, spastic co-contraction is certainly the most disabling form of muscle overactivity, because it obstacles muscle physiological muscle voluntary recruitment.

1.5 Clinical evaluation

1.5.1 Passive range of motion

For each movement evaluated, the corresponding muscles and joints are stretched at a very slow speed, in order to keep below the threshold for eliciting a stretch reflex. The angle at which soft tissue offers a maximum resistance is defined as the passive range of motion for that joint [17].

1.5.2 Angle of catch or clonus and spasticity grade

For each movement evaluated, the clinician should stretch the corresponding muscles and joints as fast as possible for the examiner. The spasticity grade is determined by the joint angle at which catch or clonus appears, according to Tardieu scale [18].

1.5.3 Active range of motion

For each passive movement evaluated at first, the clinician asks the patient to carry out an active movement at maximal range, until the active movement produced by the agonist muscles is contrasted by the passive resistance together with the spastic co-contraction of antagonist ones. This angle measure is the effective active range of motion [18].

1.5.4 Outcome measure

Tardieu score is a scale realised to measure spasticity that evaluates resistance to passive movement at both slow and fast speed. Individuals are evaluated both in in sit and supine position. There are two types of measures:

1. Quality of muscle reaction.

2. Angle of muscle reaction.

The quality of muscle reaction is scored as follows (range 0–4):

0. No resistance throughout the course of the passive movement.

1. Slight resistance throughout the course of the passive movement, followed by release.

2. Clear catch at precise angle, interrupting the passive movement, followed by release.

3. Fatigable clonus (<10 seconds when maintaining pressure) occurring at precise angle.

4. Infatigable clonus (>10 seconds when maintaining pressure) occurring at precise angle.

In order to consider joint angle, speed movement has to be defined:

- V1 is slow as possible.

- V2 speed of limb falling under gravity.

- V3 moving as fast as possible.

Regarding the joint angle, modified Tardieu describes:

- R1 as the angle of muscle reaction.

- R2 as the full PROM.

The angle of full ROM (R2) is defined at a very slow speed (V1). The angle of muscle reaction (R1) is detected when a catch or clonus appears during a quick stretch (V3) [19].

Ashworth scale, original version (1964), is a test which quantifies resistance to passive movement, with respect to a joint and with varying degrees of velocity. Scores range from 0 to 4:

0. No increase in tone.

1. Slight increase in tone giving a catch when the limb was moved in flexion or extension.

2. More marked increase in tone but limb easily flexed.

3. Considerable increase in tone, passive movement difficult.

4. Limb rigid, sometimes fixed in flexion or extension.

The modified Ashworth scale (Bohannon & Smith, 1987) is similar to the original one, except for a 1+ scoring category to indicate resistance through less than half of the movement [20].

2. Treatment options of spasticity

2.1 Indications for treatment

It's demonstrated that burden of care is higher in neurological patients who developed spasticity than that of those without it, in particular regarding treatment costs, quality of life, caregiver burden, and the effects of comorbidities [21]. The treatment of muscle overactivity may be considered when the condition is disabling. Muscle overactivity usually impairs motor command, so this itself justifies the treatment. Moreover, independently from the aetiological context, it contributes to impair patient's function [22]. Nevertheless, not all patients with muscle overactivity need a specific treatment. Treatment in spasticity should be carried out only after rigorous clinical analysis, in order to determine the severity of functional impairment. A multidisciplinary approach is necessary in order to obtain this specific assessment, being different according to patient's clinical condition; it may include variably physician, physical therapist, occupational therapist, nurse, and/or caregiver [22]. In order to obtain an individual, task-oriented therapeutic strategy, it is necessary to analyse a list of personal measurable objectives, which may be different for each patient. The clinical follow-up is required in order to show the benefits as well as adverse events. Muscle spasticity, which usually is responsive to drug treatment, is not the only motor impairment in spastic paresis. It is necessary also that physiotherapy is associated to drug treatment, in order to obtain maximum gain in paresis. For example, stretch programmes can be used to treat soft tissue shortening. Therefore, before treatment, the following three questions must be answered:

- Is muscle overactivity handicap an activity of daily living? Only after a detailed analysis of the functional impairment induced by spasticity, it is possible to carry out an appropriate treatment, which could be really effective to improve patient's quality of life.

- Is disability caused by muscle spasticity, or is it only a comorbidity? In the latter case, which components are involved? It is important to specify the quality of motor control and weakness. If motor impairment is induced or worsened by muscle overactivity, its treatment is to be considered mandatory, in order to be helpful to the patient [23].

- Does muscle overactivity involve one specific muscle group, or does it spread to other? The correct therapeutic approach depends on the answer.

Pharmacological interventions for spasticity can be divided into two groups: those that act systemically and those that act locally [24] with the locally acting treatments tending to be more invasive, systemically acting drugs used as a first step [24]. If a systematic approach, which includes baclofen, tizanidine,

or dantrolene, is not successful, local treatment is allowed [25], such as muscle botulinum toxin (BTX) injection or peripheral neurolytic blockade with alcohol or phenol [26]. Surgery is to be considered as the final treatment option; however, it is rarely used. If the principal aim is to inhibit neurotransmitter activity at one or more sites within the central nervous system, a systemic approach with specific drugs is to be evaluated. Targeted therapy could regard pre- or postsynaptic sites in spinal interneurons (at varying levels of the upper motor neuron pathway), alpha motor neurons, as well as primary sensory afferent neurons. So, the central nervous system is influenced by inhibitory effects of the neurotransmitters [27]. Oral administration needs high drug dose in order to cross the blood–brain barrier; therefore, side effects like dizziness could occur. In order to reduce the probability for these negative effects, it is possible to introduce some drugs directly into the cerebrospinal fluid, for example, by an intrathecal pump. For drugs used peripherally via injection directly to the nerve or muscle, systemic side effects are fewer.

2.2 Physical therapy

Physiotherapy is the basic treatment for all patients with spasticity [28, 29]. It may help limit muscle contractures and reduce overactivity for a short period. Physiotherapy together with drug treatment is fundamental to obtain the best functional gain, in order to help patients adapt to changes. In all cases, physiotherapy must be considered as complementary to drugs and surgery. In fact, stretching is considered an import goal in a physiotherapy session, as largely demonstrated [30]. Functional electrical stimulation allows spasticity reduction in antagonists of the stimulated muscles. An interesting use of electrical stimulation is the stimulation of hand and finger extensors during prehension training and mixing of overactive flexor inhibition with extensor activation [31]. Finally, it is important to educate patient in self-rehabilitation sessions comprehensive of stretching postures and active exercises, eventually assisted by caregivers and/or orthoses.

2.3 Oral drugs

Pharmacologic approaches emphasise oral drugs, neuromuscular blocks, and intrathecal agents. Usually, antispastic therapy is initiated with oral drugs, even though adverse side effects are frequently reported as a systematic effect [32]. Treatment decisions on specific pharmacologic approach are influenced by chronicity, severity, and localisation of spasticity. It was demonstrated that pharmacologic treatments are most effective if used early, in order to avoid muscle shortening and contracture development [33]. However, the time to treat is the first problem to resolve, in particular for drugs. Correctly, spasticity treatment is recommended when it induces a significant functional impairment, in particular regarding daily living activities, or clinical disability such as bad posture, motor capacity, or nursing. When spasticity is diffusely distributed above all in lower limbs, often observed as a consequence of spinal lesions, its treatment is firstly indicated, than in cerebral lesions.

The general goal of medical treatment is to decrease spinal reflex excitability by reducing the release of excitatory neurotransmitters or by potentiating the activity of inhibitory circuits. In clinical practice it is important to differentiate objectives in giving spasticity drugs. The technical objectives are focused to induce tone reduction, in order to increase range of motion or ameliorating joint position and promote rehabilitative procedures. Nevertheless, we also have functional therapeutic objectives regarding gait improvement, daily living activity, self-care, and spasm and pain reduction. When we evaluate the real effectiveness of different drug

approaches, it is important to differentiate these therapeutic objectives. In order to achieve these therapeutic goals, most of the drugs currently used in spasticity influence the activity of the CNS neurotransmitters. Inhibitory neurotransmitters (GABA or glycine), as well as excitatory neurotransmitters (glutamate or the monoamines), are the main target. Diazepam, baclofen, tizanidine, and dantrolene represent the principal drugs more frequently used.

2.3.1 Diazepam

Diazepam, probably the first and oldest drug used in treating spasticity [34, 35], is a GABA-A receptor agonist. Its binding, to GABA-A receptors diffused in the brainstem and spinal cord, acts in increasing presynaptic inhibition. Consequently, reduction in the resistance to stretch is the principal clinical effect, showing an objectively increasing range of motion. Other clinical effects are also a reduction of deep tendon stretch reflexes and painful spasms [36]. Nevertheless, significant side effects are to be considered. The depressant effect of the drug on the CNS is the principal side effect, causing an influence on cognitive-level, consciousness status, leading to sedation, drowsiness, and attention or memory impairment. The same physiological mechanism explains weakness and motor discoordination caused by diazepam. Tolerance or dependency phenomena are often observed [37, 38]. Spasticity caused by spinal cord lesion, above all incomplete ones like in patients with multiple sclerosis (MS), is the principal indication to use diazepam, since the drug binding is mainly in the brainstem. Less literature are available for the use of diazepam in spasticity caused by cerebral accident, such as traumatic brain injuries, cerebral palsy, and stroke. In literature, a double-blind protocol is available showing the antispastic efficacy of diazepam, only in spinal cord lesions [39]. However, a possible strength and gait deterioration was also shown consistently in placebo-controlled studies.

2.3.2 Gabapentin

Gabapentin is approved as an antiepileptic drug. It is indicated also for postherpetic neuralgia treatment and as add-on therapy in partial seizures. GABA-B receptors are its target. Moreover, it is quietly safe. In a prospective, double-blind, placebo-controlled, crossover study, conducted on multiple sclerosis patients, a statistically significant reduction of spasticity was shown in gabapentin-treated patients compared to placebo [40]. The most efficient and safe dose range is still an open question. A dose range between 2700 and 3600 mg/day, as therapy for spasticity due to upper motor neuron syndrome, was found as efficient and safe. However, doses of 400 mg orally three times a day, in another double-blind, placebo-controlled crossover study, were shown to be effective in the treatment of spasticity and muscle painful cramps in patients with MS [41]. Nevertheless, considering the magnitude of the effect and the good tolerability of the drug, the evidence is on a weak recommendation for using gabapentin to reduce spasticity in MS [42].

2.3.3 Oral baclofen

Baclofen is another common drug diffusely used in spasticity. This drug is a GABA-B receptor agonist. Its physiological effect is a suppression of excitatory neurotransmitter release and, as a consequence, a potentiation of presynaptic inhibition. The main clinical effects are related mainly to the reduction in flexor-extensor spasms and mono- and polysynaptic reflexes. Obviously, related to its mechanism of action, this drug may induce dose-dependent side effects, quite

similar to those seen with diazepam [43], although less frequent and less severe. However, sedation, confusion, dizziness, drowsiness, fatigue, and ataxia have been described as the common side effects observed in baclofen studies. Spasticity due to spinal cord lesions is the main indication to treat with baclofen. Unfortunately, in literature, there are very little studies focused on functional changes, so as a consequence, there is no evidence for effectiveness on functional activities such as gait, ambulation, or daily living activities. Moreover, also for oral baclofen, a weak recommendation for treatment of spasticity in MS has been shown [42]. It's notable that there is no evidence of significant differences between diazepam, tizanidine, and oral baclofen, regarding therapeutic effects on spasticity [43, 44].

2.3.4 Tizanidine

Tizanidine, an imidazole derivative approved for the treatment of patients with spasticity [45], acts as an alpha-2 agonist, both in the spinal and supraspinal level. Presynaptic activity reduction of the excitatory interneurons represents the main physiological effect of this treatment. The coeruleo-spinal pathway, because of its involvement in the control of spinal cord activities, was shown as the main target in order to induce clinical effect during tizanidine treatment [46]. Consequently, reduction in tonic and stretch polysynaptic reflexes can be observed. Because of co-contraction reduction, which is observed, a possible effect on reciprocal inhibition is questionable. Possible side effects include sedation, dizziness, and dry mouth. Nevertheless, with respect to diazepam or baclofen, weakness is not reported as a great problem [47]. From the literature, the indications for its use are mainly in spasticity due to spinal cord lesions [48]. It has been particularly used in multiple sclerosis patients [49]. In spasticity caused by cerebral lesions, its efficacy is less well documented in literature. However, there are a certain number of reports regarding its antispastic efficacy, also in controlled studies vs. placebo. In the treatment of spasticity due to cerebral lesions, there are some evidences of its greater efficacy than diazepam [47]. However, there is very little information about the possible functional changes resulting from this treatment, i.e. quality of life and self-care. In fact, although it has been shown to have an antispastic effect, we do not know whether this will translate into long-term functional benefit for the patients. In clinical practice, tizanidine is usually well-tolerated. Drowsiness and dry mouth are the most common although are rare side effects. A range of 24–36 mg is normally the therapeutic dose (20% mean reduction in muscle tone), usually divided in three daily doses [50]. Like oral baclofen and diazepam, there is a consensus for a weak recommendation for the use of tizanidine [42].

2.3.5 Dantrolene

Among the oral dugs, dantrolene is the only one which acts outside the central nervous system [51]. It acts on the inhibition of calcium release from the sarcoplasmic reticulum, so, as a final effect, it reduces in muscle the excitation-coupling reaction between actin and myosin fibres. The documented clinical effects are a reduction of muscle tone and phasic reflexes, reduction of spasm, and an increased range of passive motion. Unfortunately, a frequent occurrence of side effects is described with this drug, such as gastrointestinal symptoms, weakness, and sedation although this is less than that seen with other treatments. Over all, a serious side effect with the use of dantrolene is hepatotoxicity, which occurs frequently [51]. In patients with spasticity due to cerebral lesions, dantrolene is the only drug with evidence of efficacy, so from a pure clinical point of view, this is very disappointing. In fact, dantrolene in approved in patients with stroke, cerebral palsy,

traumatic brain injuries, and spinal cord lesions. As shown for baclofen, also for dantrolene, there are many evidences of efficacy and safety of its antispastic effect proven vs. placebo, but no studies focused on functional changes in activities of daily living. It's notable that dantrolene is also used to prevent muscle stiffness and spasms caused by malignant hyperthermia (a rapid rise in body temperature and severe muscle contractions) that can occur during surgery with certain types of anaesthesia [52].

2.3.6 Cannabinoids

It is known, from many evidences, that the psychoactive ingredient in cannabis, delta-9-tetrahydrocannabinol (delta-9-THC), is able to treat muscle spasticity and pain. Two types of cannabinoid receptors can be described: CB1 and CB2. CB1s are located both in the central and peripheral neurons. CB1 and CB2 receptors are equally activated by delta-9-THC, a cannabinoid receptor agonist [53, 54]. On the contrary, cannabidiol, a natural cannabinoid, is inactive on the CB1 receptor. Some studies reported that cannabis extracts, containing approximately equal concentrations of delta-9-THC and cannabidiol administered through sublingual way, can significantly reduce spasticity. During the last years, several studies investigated and argued on the efficacy and safety of oral cannabinoid administration in MS patients as an add-on treatment for spasticity. A multicentre, double-blind, placebo-controlled trial showed that in MS spasticity treatment, cannabinoid may help to treat MS-related spasticity and pain [53]. However, according to the results from clinical trials, it is not allowed to use cannabinoids in MS as a general use. In a recent study, 630 MS patients affected by muscle spasticity were randomised to be treated with oral delta-9-THC, cannabis extract, or placebo for up to 12 months. The results showed a controversial effect; in fact, there was a small treatment effect on muscle spasticity and disability as functional independence measure, but patients' sensation was that these drugs were helpful in treating their disease [54]. Adverse side effects are generally mild, in particular dry mouth, somnolence, dizziness, nausea, and rarely intoxication. However, there is a need of longer-term studies to evaluate other, well-known, adverse side effects of cannabinoid such as risks of lung cancer and other respiratory dysfunctions. A recent multicentre observational study confirmed the efficacy and safety of delta-9-THC in clinical practice, as an effective and safe option for patients with MS with moderate to severe spasticity resistant to common antispastic drugs [55]. In a recent consensus, a significant recommendation for the use of cannabinoids in spasticity emerged, particularly for oromucosal spray nabiximols, as treatment of spasticity in MS; the strength of the recommendation is strong [42].

2.4 Botulinum toxin

BTX type A is considered as the first-line treatment of multifocal muscle overactivity, thanks to its better efficacy and safety profile with respect to systemic approach with drugs. Different from baclofen or tizanidine, the efficacy of BTX type A has been demonstrated in self-care improvement (in particular for washing and dressing) and in active movements for the leg, with gait improvement if possible. Except for using kinematic analysis, no improvement was possibly shown in active movement or function in the upper limb. Pain was also reduced by BTX treatment as demonstrated in literature. Four forms of BTX are currently available in Europe: three type As (BOTOX®, Allergan; Dysport®, Ipsen-Pharma; Xeomin®, Merz) and one type B (Neurobloc®, Elan-Pharma). It is absolutely recommended to keep in mind that the units of these four toxins are different, being

specific for each one. Injection sites are better detected, using electrical stimulation, as anatomical markers alone may induce to an inaccurate target. The use of ultrasound guidance, particularly in children, in identifying muscle site injection, is an interesting study object; however, this technique has not been evaluated with respect to electrical stimulation guidance for its efficiency. Generally, there are no immediate postinjection complications (except for a little pain as a side effect related to injection itself). Above all, during the first 3 weeks after each injection treatment, there would be a low risk of adverse events (swallowing disorders and botulism-like syndrome), so patients and caregivers must be warned as well as encouraged to eventually consult if necessary. The effects of treatment could be assessed 1–6 weeks after the injection, based on personalised goals decided before treatment. The effect of the toxin is not permanent, so repeated injections are often needed; nevertheless, a long-lasting effect is also observed. No repeated treatment is recommended without a specific assessment. When and if needed according to functional evaluation, a minimum delay of 2–3 months between injections must be respected, in order to reduce the risk of an immunologic reaction that may induce a permanent inefficacy of subsequent treatments. Each subsequent treatment should be planned after an accurate functional evaluation according to the pre-therapeutic identified goals and task, as well as tolerance. So, a review of the dose and treated muscles could be scheduled. If therapeutic effects continue to be evident, repeated injections can be planned [33, 56–60]. Physical therapy has to be considered after BOTOX injections. Regarding maximum doses, according to European Consensus, it should be considered:

- Per session: 1500 MU Dysport® 600 U BOTOX®.

- Per site: 125 MU Dysport® 50 U BOTOX®.

It is notable that these dosages are identified relatively to acceptable side effects, in order to be safe. Moreover, each product could be effective with different doses for each patient, in terms of both efficacy and safety [61]. As well as the cannabinoid, there is a strong recommendation of the use of BTX to reduce muscle tone in spasticity do to multiple sclerosis [42].

2.5 Alcohol and phenol

Localised and loco-regional spasticity may effectively be treated by selective neurolysis. Coagulation and denaturing of proteins induced by phenol perineurally injected lead to cellular and axonal damage. Unfortunately, this chemical denervation is irreversible; moreover, the effects of phenol are not selective because also vascular and sensory structures can be destroyed [62]. In fact, the main recommendation choosing this approach is to identify preferably the nerves to be treated with a low sensory activity and a high motor predominance (i.e. obturator or musculocutaneous nerves, etc.). However, this focal treatment is usually not used as a first-line therapy, except in the case of particularly problematic overactivity affecting a big area under a single motor nerve control, for example, musculocutaneous nerve for biceps brachii muscle or obturator nerve for thigh adductor muscles. This may allow to use in the same patient BTX to treat other muscles, without the risk of an overdose. Electrical stimulation is used to identify a nerve, in order to perform injection on it. Firstly, a transient motor block may be a plan, in order to evaluate if chemical neurolysis might be significantly effective and safe. In fact, the efficacy and/or advantages eventually deriving from alcohol or phenol treatment could be evaluated before, in particular with respect

to surgery (above all, tissue fibrosis induced by alcohol or phenol, which may hamper surgery approach). Advantages are the low cost and the long duration of effect. In clinical practice, 5–7% concentrations of phenol in aqueous solution are administered.

2.6 Intrathecal baclofen

Intrathecal baclofen (ITB) is a long-term treatment with continuous, intraspinal administration via an implanted pump that reduces spasticity, especially in spinal injury patients and in multiple sclerosis [63, 64]. For this reason, ITB has become the first choice in intractable generalised spasticity, especially when oral administration fails to be effective. ITB efficacy in reducing spasticity was demonstrated by several studies [65]. Through direct infusion into the cerebrospinal fluid, the baclofen can be concentrated regionally, avoiding liver metabolism, so it is totally available for its therapeutic effects. In fact, with respect to oral baclofen administration, the ITB, bypassing the blood–brain barrier entirely, needs much lower dose in order to obtain the same CSF concentrations; it has been determined that the ITB dose is 100–1000 times smaller than the oral daily dose. Depending on the pump model, it is possible to modify infusion rate, according to the patient's needs. In several studies ITB was shown as safe and effective in reducing spasticity. The complication rate was found to be low, and the efficacy was maintained over time [64]. A reduction in the Ashworth scale from 3 to 4 to 1 after ITB implantation was reported in several studies. Also spasm frequency significantly decreased. Some activities of daily living, in particular the ability to sit in a wheelchair and nursing care, improved after ITB implant. In some cases, authors showed that patients with less severe disability experienced an improvement in the ability to transfer, thanks to ITB effect [66]. Side effects, such as vertigo, nausea, nystagmus, dysmetria, mouth dryness, headache, amnesia, bladder, and sexual dysfunction, have been described in about 4% of patients and mainly are not life-threatening. As a red flag, it is notable that concerning gastrointestinal function, ITB could affect peristalsis, which could be severely slowed down to paralytic ileus. Nevertheless, constipation has previously been reported as an infrequent ITB-induced adverse effect, ranging from 3 to 10% of treated patients [67], rarely leading to death [68]. Therefore, recognition of constipation in patients treated with ITB is very important, not only because constipation is a possible side effect, being reported in some study, but also because it may be also a life-threatening complication. ITB has been used in patients with leg diffuse muscle overactivity. This type of treatment should be used above all in patients, in which muscle overactivity impaired posture, nursing, and personal independence or causes pain [63]. Several assessments are required before planning a definite pump implantation, performing drug test injection via lumbar puncture or via a temporary access device. Efficacy may be evaluated during the following 3–4 h. The first test dose is usually recommended up to 50 μg in adults, picking up gradually to a maximum dose of 150 μg, eventually reached after 3 days. A risk of overdose should be always evaluated, in particular regarding the effects on consciousness level and respiratory disorders. So, a specialised medical team is needed in order to monitor patient after and during the 4 h following the test. Only after the end of this test, if the treatment has been well-tolerated and effective, the team may make the decision to implant the pump. It is important to monitor the patient during the entire follow-up period, in order to prevent and/or detect collateral effects related to the procedure (displacement and/or obstruction of the catheter, infection, etc.), which may induce a serious withdrawal syndrome. ITB is often recommended for the treatment of spasticity, with a strong evidence of efficacy [42].

2.7 Surgery

Surgery may play an important role in the treatment of chronic muscle overactivity or for the after-effects induced by spasticity that become functional impairments (e.g. irreducible equinovarus foot), but it is not the first-line treatment. Because of its potential adverse events and its definite effects, surgical techniques should be reserved only in selected patients in order to reach different goals: hygiene, standing, transferring, walking, and the use of assistive devices. It involves neurosurgery and orthopaedic surgery. Surgical procedures may include one or more of the techniques described below. Peripheral neurotomy may include partial or segmental resection of a motor nerve, involving spastic muscles. In order to balance agonists and antagonists overlapping the muscle activity, a selective peripheral neurotomy is recommended to maintain a "functional" muscle tone. Collateral branches of the posterior tibial nerves and obturator nerves are commonly the main targets for the legs (e.g. ankle clonus, equinus, inversion of the foot). For the arms, neurotomy of the musculocutaneous, median, and ulnar nerves showed good results regarding efficacy and safety [69]. Other surgery techniques, such as rhizotomies, although used, have potential collateral effects and complications [70]. Musculoskeletal surgery, performed on the muscle or the tendon itself, aims to treat spasticity consequences, such as contracture and joint deformities. Tendon transfers (e.g. *tibialis* anterior) and lengthening are conservative treatments commonly proposed [69]. Tenotomy may be considered in the case of muscle contracture without active functional objectives [69]. Hip displacements and foot deformities induced by severe spasticity may be sometimes treated with osteotomies [69]. Arthrodesis may be the only solution to stabilise joints, notably ankle and foot joints in case of severe paresis associated with strong muscle overactivity and hypoesthesia [69].

3. Treatment options of dystonia

3.1 Indications of treatment

Treatment options of the management of dystonia include pharmacological therapies, injections, and surgical interventions. The main pharmacological therapies are anticholinergics (particularly trihexyphenidyl), baclofen, benzodiazepines (particularly clonazepam), and dopamine-related medications. However, medical therapy in dystonia is largely empiric and at times may seem anecdotal. Three main neurotransmitter systems are involved: cholinergic generally acting as antagonist at postsynaptic M1 receptor, GABAergic-like baclofen, and dopaminergic systems. Dopaminergic treatments can be divided into two: levodopa and dopamine reducing medications like presynaptic dopamine depleters such as tetrabenazine and postsynaptic dopamine-blocking agents, such as clozapine or neuroleptics. The therapeutic strategy, carried out by Fahn [71], is to "start low and go slow": medications should be started at a low dose and upped slowly to the lowest effective dose, in order to reduce symptoms without side effects. The rate of titration may depend on age: every 3–4 days in children, compared to every 1 week in adults. A combination approach is used when monotherapy achieves a "good" dose, but symptom control is incomplete. The question is which medications should be started first?

3.2 Cholinergic system agents

In 1952, beneficial effects of trihexyphenidyl in writer's cramp and "dystonia musculorum deformans" were first reported [72, 73]. The first open-label study of

high-dose anticholinergics in dystonia using trihexyphenidyl and ethopropazine was conducted by Fahn [71]. Various forms of dystonia, both "primary and secondary," can be treated with anticholinergics, except for tardive dystonia and Meige syndrome. Studies showed a good effect in 61% of the children and 38% of the adults, with mean trihexyphenidyl doses of 41 and 24 mg, respectively. More benefit was demonstrated in children, possibly due to better tolerability, and in patients who received treatment earlier, within 5 years of disease onset [74]. Several studies have demonstrated that anticholinergic drugs may be useful to treat various forms of dystonia including focal [75], cranial [76], and secondary dystonia including dystonia in cerebral palsy [74], after ischemic stroke [77], and in tardive dystonia [78]. Side effects can be divided into central ones, which include sedation, cognitive slowing, confusion, memory impairment, psychosis and chorea, and autonomic side effects, which include blurred vision, due to mydriasis, dry mouth, urinary retention, and constipation.

3.3 GABAergic system agents

Baclofen was reported to be useful in tardive dystonia [79]. Just in 1988, Greene published a retrospective open-label study, showing that 20% of 108 patients had benefits from baclofen at a mean daily dose of 82 mg [80]. Later, Greene and Fahn also reported beneficial effects of baclofen in 7 of 16 patients with idiopathic childhood dystonia [81]. ITB was tried initially for spasticity and later in dystonia [82]. In 1991 Narayan and colleagues showed the efficacy of ITB in axial dystonia not responding to other drugs [83] and subsequently in dystonic cerebral palsy with lower extremity involvement [84]. Albright reported the use of intraventricular baclofen in two patients with dystonic cerebral palsy, one of whom previously failed ITB therapy and the other has a complex spinal anatomy precluding the intrathecal procedure [85]. Nevertheless, baclofen is generally considered as a second-line agent, due to its significant side effects like drowsiness, dizziness, fatigue, and nausea. Regarding benzodiazepines, diazepam therapy was described in "dystonia musculorum deformans progressiva" and spasmodic torticollis [86]. In 1988, the benefit of clonazepam was shown by Greene in 16% of 115 patients with dystonia, also including secondary dystonia [80]. Also in acquired hemidystonia, as shown in a report of 33 patients, clonazepam and diazepam were found to be the most effective drugs. Clonazepam and diazepam are the two most commonly used drugs, partly due to their relatively long half-lives. The side effects of benzodiazepines include sedation, depression, nocturnal drooling, and behavioural disinhibition. Benzodiazepines are considered a second- or third-line agent.

3.4 Dopaminergic system agents

In 1976 Segawa firstly used levodopa as a treatment in dystonia, showing a dramatic response to low-dose levodopa in two patients affected by "hereditary progressive dystonia with marked diurnal fluctuations" [87], later named Segawa syndrome. In dystonia therapy, levodopa is used (1) as an aetiology-specific treatment in dopa responder dystonia and (2) as a symptomatic therapy in other forms of dystonia where the dramatic response to levodopa is unfortunately not replicated. Levodopa may also be used to treat dystonia symptoms which may complicate a parkinsonian syndrome [88]. In clinical practice, levodopa or dopamine agonists are rarely used to treat dystonia symptomatically. The side effects of levodopa include nausea, orthostatic hypotension, and psychosis. In 1972, Swash reported only a slight benefit of tetrabenazine in spasmodic torticollis [89]. In 1982, a double-blind crossover trial by Jankovic demonstrated an improvement in 11 of 12 patients [90].

Tetrabenazine has been used in various forms of dystonia; however, benefits are greater in tardive dystonia than that of the other forms [91]. Tetrabenazine is rarely used as a first-line agent, except in tardive dystonia [92].

4. Conclusions

Spasticity and dystonia syndromes and their consequences negatively impact the quality of life of patients, so management of symptoms represents an important care issue. The best choice of antispastic treatments depends not only on the level of spasticity but also on the outcome achievable, according to a task-oriented rehabilitation programme. In this respect, it is important to underline the importance of the individualised rehabilitative project, which can be carried out only through a multidisciplinary approach, in which all available options must be targeted to the real needs of the patients, keeping into account that the final goal is the reduction of disability and improvement of the quality of life. With advances in diagnosis and treatment, therapeutic strategies for the management of spasticity and dystonia symptoms, including pharmacological treatments, have evolved. Progresses in other areas such as BTX, neuromodulation, and disease-specific treatment have changed the way patients are treated. Nevertheless, dystonia remains a challenging field in both diagnostic and therapeutic aspects. Further understanding of its pathophysiology may shed light on more specific therapies. In conclusion, the management of spasticity and dystonia may include a proper diagnosis and classification with an evaluation of the aetiology underlying the pathological features and a clinical assessment of the functional impairment. For both conditions, therapeutic approaches, usually limited to symptomatic therapy, must then be tailored to the individual needs of the patient.

Conflict of interest

Vincenzo Cimino has received grants for congress participation from Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA.

Clara Grazia Chisari has received grants for congress participation from Almirall, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA.

Francesco Patti has received honoraria for speaking activities by Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA; he also served as an advisory board member of the following companies: Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA; he was also funded by Pfizer and FISM for epidemiological studies; he received grants for congress participation from Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA.

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