Use of cannabis medicine for the treatment of spasticity-associated pain

O uso da medicina canábica para tratamento da dor associada à espasticidade

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ABSTRACT

BACKGROUND AND OBJECTIVES: Spasticity refers to the increase of resistance to joint passive movement according to its angular velocity. It is part of the triad of the pyramidal syndrome, along with the exacerbation of myotatic reflexes and muscle weakness, and is present in several lesions of the central nervous system, either in the spinal cord or brain. Pain associated with spasticity is caused by muscle spasms, activation of trigger points, joint deformities, interference with the position of body segments, and difficulty in movement control. For a more precise therapeutic intervention, the detailed physical examination of the locomotor system and spasticity can be completed by using specific spasticity evaluation scales. Multiple sclerosis (MS) is the clinical condition for which there are the greatest number of studies using cannabinoids to control spasticity. The objective of this study was to perform a literature review of the possible role of cannabinoid drugs in the control of spasticity and the pain associated with it.
CONTENTS: The literature shows moderate evidence that the combined use of 9-tetrahydrocannabinol and cannabidiol increases the number of people reporting improvement in spasticity.
CONCLUSION: It is possible to believe that the complaint of musculoskeletal pain associated with spasticity accompanies this improvement with the use of nabiximols, but there are still gaps in the literature for this specific topic.

Keywords: Cannabinoids, Muscle spasticity, Musculoskeletal pain, Rehabilitation, Treatment.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A espasticidade refere-se ao aumento da resistência ao movimento passivo articular conforme a sua velocidade angular. Ela faz parte da tríade da síndrome piramidal, junto com a exacerbação de reflexos miotáticos e fraqueza muscular, e está presente em diversas lesões do sistema nervoso central, de topografia medular ou encefálica. A dor associada à espasticidade é causada pelos espasmos musculares, ativação de pontos-gatilho, deformidades articulares, interferência na posição dos segmentos corporais e dificuldade para o controle do movimento. Para uma intervenção terapêutica mais precisa, o exame físico detalhado do aparelho locomotor e da espasticidade pode ser completado pelo uso de escalas de avaliação específicas. A esclerose múltipla é a condição clínica para a qual há maior número de estudos com uso de canabinoides para o controle da espasticidade. O objetivo deste estudo foi realizar uma revisão da literatura sobre o possível papel dos fármacos canabinoides no controle da espasticidade e da dor associada a ela.
CONTEÚDO: Há na literatura evidências moderadas de que o uso combinado de 9-tetrahidrocanabinol e canabidiol aumenta o número de pessoas que relatam melhora da espasticidade.
CONCLUSÃO: É possível acreditar que a queixa de dor musculoesquelética associada à espasticidade acompanhe essa melhora com uso de nabiximol, mas ainda há lacunas na literatura para esse tópico específico.

Descritores: Canabinoides, Dor musculoesquelética, Espasticidade, Reabilitação, Tratamento.

INTRODUCTION

Spasticity is a motor sign associated with a neurological injury, characterized by increased muscle stretch reflexes. Typically, it is characterized by increased muscle resistance triggered by passive manipulation of a limb segment with high angular velocity[1]. The muscle activation resulting from the motor stimulus may be intermittent or sustained involuntarily. Spasticity usually occurs after spinal cord and/or brain injuries such as stroke (approximately 25% of patients)[2], traumatic brain injury (TBI)[3], spinal cord injury (SCI) (65-78% of patients)[4,5], MS (80% of patients at some stage of the disease)[6,7] and cerebral palsy (CP) (more than 90% of patients)[8].
Spasticity is typically associated with pyramidal tract lesions and is part of the pyramidal syndrome, appearing together with paresis and exacerbation of myotatic reflexes[9]. After an upper motor neuron lesion, three fundamental phenomena occur in the gene-

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HIGHLIGHTS
- Spasticity is a frequent complication of pyramidal system lesions, whose association with neuropathic pain contributes to compromised functionality.
- Musculoskeletal pain related to spasticity can refer to muscle spasm, trigger point activation, joint deformities, poor positioning or change in motion.
- The effectiveness of cannabinoids for controlling spasticity is further proven in multiple sclerosis.

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sis of spastic paresis. Initially, the corticospinal pathways lesion interrupts muscle commands, leading to immediate paresis, which can be defined as the lack of command to the agonist muscles when there is an attempt to generate force or movement. This insufficiency can result from a lack of adequate recruitment of motor units or a decrease in the frequency of discharges[9].

Second, in addition to the paresis itself, simultaneously to loss of movement and contraction, there is immobility of the affected region, which can facilitate the installation of muscle shortening in the body segment. The reduction in regional blood circulation due to paresis leads to relative hypoxia, which promotes fibroblast proliferation and accelerates the loss of muscle tissue. Consequently, there is a loss of performance and muscle shortening, in addition to reduced extensibility of connective tissues of musculoskeletal support (tendons, muscles, ligaments, joint capsule, fascia, vessels, and nerves). This process, which starts soon after the installation of immobility, is intensified over days or weeks if no preventive treatment is installed[9,10].

The third pathophysiological mechanism is related to adaptive changes in high brain centers and spinal cord, causing the recruitment of other descending pathways, such as rubroespinal, tectoespinal, reticuloespinal, and vestibuloespinal. These pathways may become uninhibited to compensate for corticospinal lesions, generating permanent muscle activity. In the spinal cord, there is a loss of inhibition of interneurons, creating mechanisms that lead to an abnormal or exaggerated increase in reflex pathways[11,12]. Associated with this phenomenon, clonus may occur, which is initiated by passive movements during activities, such as being dressed by the caregiver or being bathed by others, or by active movements, such as walking or grasping[3,12,13].

The dystonic spasticity can be defined as the chronic tonic muscle activity together with spasticity, that is, a muscle hyperactivity at rest, without triggering factors, which leads to postural and joint changes. Several of these postures can be recognized in hemiparetic patients after a stroke or TBI, such as the ankle in equinus and varus position, associated with hallux extension, internal rotation of the shoulder with flexion and pronation of the elbow and flexion of wrist and fingers. In the upper limb, these same patients commonly present an adducted shoulder, in internal rotation, with the elbow flexed and the forearm pronated[11-14].

Signs of spasticity are also observed with co-contraction, which is the exaggerated and unwanted contraction of the antagonist muscles during voluntary contractions, that is, two antagonist muscle groups contract simultaneously around a joint.

The co-contraction occurs in individuals with good voluntary motor control, but it decreases the precision of the movement, with consequent loss of functional capacity. Examples of this alteration are the contraction of the flexors that occurs during the attempt to extend the elbow, wrist, and fingers in the upper limb; the contraction of the hip extensors, which hinders its flexion during the swing phase, with reduced step amplitude; and, finally, the limitation of the ankle dorsiflexors, also during the swing phase of the gait, resulting in a tendency to plantar flexion and reaping pattern in hemiparesis. There are other types of muscle hyperactivity, such as dyskinesias, associated reactions and atetheses due to extrasecondary co-contractions, associated with excessive cutaneous or nociceptive response[15].

Muscle hyperactivity can vary during the day and by the position of the joints involved, including cervical positioning, and it is essential to dynamically evaluate the patient and listen carefully to him/her about in which positions or activities he/she has more functional difficulties. Other important factors involved in these changes are temperature, stress level, and nociceptive factors, such as urinary tract infections, wounds, onychomycosis, among others. The simple spasticity measurement at rest does not properly assess the individual's functional condition[16].

The purpose of this study was to conduct a review of the literature on the possible role of cannabinoid drugs in controlling spasticity and its associated pain.

CONTENTS

Pain associated with spasticity

When the central nervous system injury results in inability to perform functional voluntary movements, spasticity keeps the affected limbs in vicious positions. The imbalance of the forces that act on joints in the segment with spastic paresis implies in the formation of joint contractures that can contribute to the appearance of secondary lesions[15]. Patients who develop spasticity of the toes flexor muscle groups can, for example, develop flexion contractures of the interphalangeal joints which result in claw deformities. On dorsal region of the clawed toe, painful calluses appear due to the friction of interphalangeal joints with the shoes; on the other hand, on the extremities of these toes, painful points may appear, associated to difficulty in the growth of the nail, which is pressed against the sole of the shoe[15].

The spastic contracture can be painful by itself, especially when the involved muscle group contains trigger points that can be triggered during the activation of movement. In this situation, the passive movement of a body segment in one direction can trigger the spasticity of the antagonist muscle group, causing pain. A good example is pain associated with the shoulder of spastic hemiplegic patients, which is triggered by the passive abduction movement during actions of washing the armpit or changing clothes, when this joint needs to be passively moved for arm elevation[17].

The improper positioning of the limb due to the movement incoordination caused by spasticity may cause musculoskeletal pain since it requires the body segment to discharge pressure at different points from those that are naturally prepared for this situation. For example, in the lower limbs, severe postures of hip and knee flexion and ankle plantar flexion deformity (equinus) may occur, hindering hygiene and positioning in bed and wheelchair, with increased risk of joint pain and formation of skin lesions by pressure[18].

In addition, the limb positioning inside ortheses can be compromised, with a pressure discharge in inappropriate places, causing pain and preventing the functional use of these instruments[3,19].

It is important to emphasize that the lack of spasticity control is associated with increased pain processes in the affected region, either by muscle spasm or by association with neuropathic changes and joint overloads. On the other hand, the increase in pain afference increases spasticity and forms a vicious cycle[10].

Assessment of the spastic patient with pain

A thorough clinical examination is essential for a better understanding of how muscle hyperactivity and spasticity act on functional activity. It is worth noting that neurological symptoms are present and must be evaluated in order to define the best strategies for the most effective treatment. This assessment is important because it makes it possible to check the rehabilitation treatment effectiveness[20,21].

A significant complication of spasticity treatment occurs because scales and tests are often subjective and of low sensitivity to reflect functional gains. To properly assess the patient with spasticity, regardless of etiology, the following measures obtained during the physical examination must be used[22]:

- passive joint amplitudes, seeking to quantify the totality of mobilization in all directions in which joint movement occurs. This test allows differentiating muscle retractions generated by immobility from the patterns associated with spasticity. This measure requires that the joint manipulation be done slowly and gradually to avoid increasing muscle hyperactivity[23];
- active joint amplitudes, when signs of muscle co-contraction and the presence of dystonic movements associated with functional loss can be better evaluated[23];
- the Modified Ashworth Scale (MAS) tries to quantify the resistance to passive mobilization with fast angular velocity, that is, with the triggering of spasticity. Despite being eminently subjective and influenced by muscle and joint conditions unrelated to spasticity, this measure is still the most clinically used and is the reference parameter in the literature on the subject. Table 1[24] describes the score levels used to describe the passive mobilization resistance in MAS;
- the presence of tonus, characterized by the repeated and involuntary contraction of a muscle group against a fast passive movement, is related to the severity of spasticity[23];
- the Tardieu scale compares the intensity of the muscle reaction to two modalities of muscle stretching: the slow stretching and the fastest possible stretching. This scale takes into consideration, besides the stretch velocity parameter (V) described above, the quality of the muscle reaction (X) and the angle of the muscle reaction (Y). For each muscle group, the response is measured at a specific speed in the two tested parameters, X and Y[25] (Table 2).

In addition, it is necessary to complete the functional assessment in order to better understand how muscle changes interfere with the performance of daily living and practice activities. The scales available in clinical practice are still not very sensitive to changes in muscle tone or, when they show quantitative changes, they are due to nonspecific modifications in functionality. More frequent use of the Functional Independence Measure (FIM)[26], Barthel's scale[20] or Spinal Cord Independence Measure (SCIM III)[27,28] may be recommended. In order to use more specific scales for the affected hemibody, the Fugl-Meyer scale and the block box test, among others, can be used, although they do not adequately measure the functional outcomes of spasticity treatment[20-22]. The quantitative or qualitative gait assessment or other parameters such as sensitivity and pain are also important for the best interpretation of the patients' functional difficulties[22].

Table 1. Modified Ashworth scale score[24]

Score	Status
0	No increase in muscle tone
1	Slight increase in muscle tone, with minimal resistance in the last degrees of joint amplitude
1+	Slight increase in muscle tone, in less than half of the joint amplitude
2	Increased muscle tone over the full range of motion, but no difficulty in achieving full passive range of motion
3	Considerable increase in tone, making passive movement difficult
4	Muscle stiffness

Treatment

The spasticity treatment must be interdisciplinary, since the therapeutic intervention of isolated health professionals tends to failure. The disabled person in the rehabilitation process has multiple needs, both physical and cognitive, emotional and social. Besides the medical team, representatives of physiotherapy, occupational therapy, nursing, social work, and speech therapy, as well as the patient's caregiver, should be part of the team[29].

Table 2. Tardieu Scale[25]

Stretching Speed		Action
V1	As slow as possible	Measure the range of passive motion (maximum range of motion)
V2	Speed at which the limb falls under the action of gravity	At these speeds it is possible to measure the interference of passive angular velocity on the range of motion and estimate spasticity
V3	As fast as possible	
Muscle reaction quality		
0	No resistance along the passive range	
1	Little resistance along the passive movement, without a clear lock at a specific angle	
2	Sure treatment of passive movement at a specific angle, stopping passive movement, but followed by relaxation	
3	Exhaustible bonus (< 10 seconds) at a specific angle	
4	Endless bonus (> 10 seconds) at a specific angle	

It is noteworthy that spasticity treatment is not always mandatory if there is no functional impairment. However, the pain associated with spasticity requires therapeutic intervention and muscle tone control. A thorough clinical evaluation makes it possible to determine which affected areas impair functionality and cause pain, guiding the therapeutic intervention[1].

Initially, it is possible to structure, in a didactic way, the spastic patient's treatment in identifying, treating and preventing conditions that exacerbate spasticity[30]. The specific situations that make spasticity more intense include other sources of pain, either musculoskeletal or neuropathic (considering that spasticity already presupposes a central nervous lesion, either encephalic or medullary). It is necessary to turn the focus to skin lesions such as pressure ulcers, which have an intense nociceptive component, but may not be perceived as painful when the nerve lesion also compromises ascending pathways. Another source of nociceptive afference are infections (urinary tract, erysipelas, onychomycosis), besides pain of visceral origin (constipation, urolithiasis) and venous thrombosis[31].

The adequate patient positioning must be done from the earliest stages, during activities such as sitting and lying down, observing the trunk support and the adequate articular positioning in the segments where there is strength reduction. Special attention must be given to shoulder, because, due to the loss of movement, in a few weeks there may be retraction of the joint capsule, favoring the appearance of subluxation and pain that is difficult to control. Other frequent changes occur in the upper limb (tendency to elbow and wrist flexion, associated with hand claw) and in the lower limb (hip and knee flexion and ankle equinus positioning)[14,18,32].

To avoid these patterns, intensive joint movement should be instituted, coupled with the use of preventive orthoses (thermomoldable material positioners) tailored to the patient's shoulder, as well as the ankle and feet. It is important to remember that orthoses should be used with caution, because in spastic patients, when poorly positioned they lead to increased local irritation, which worsens spasticity and favors the appearance of skin lesions[31].

The direct spasticity treatment should be considered in several ways, depending on its severity and the functional impairment that it causes. The physical therapy techniques should be the basis for spasticity treatment and should be instituted early, although there is no consensus in literature about which technique is the most effective. Physical therapy is important to control muscle tone through muscle inhibition, prevention of secondary joint injuries and specific functional training. To these measures, the use of electrotherapy is associated, in the functional electrical stimulation (FES) and transcutaneous electrical nerve stimulation (TENS) modalities, the first being used as motor training with control of co-contractions and the second as a sensory stimulus useful in pain control, because it exacerbates spasticity. Heat and cold modalities are also useful in controlling spasticity[24,29]. The correctly molded orthoses have an important role in controlling the tonus, especially after pharmacological treatment[31].

The pharmacological therapy for spasticity should be instituted after the answer to the following three questions[32,33]: "is the muscle hyperactivity actively or passively problematic?", "Is spasticity the main cause of the patient's disability or is it one more cause?" and "Is spasticity limited to one or a few muscle groups or is it global?". The treatment through oral drugs, systemically, can currently be performed successfully using the following: baclofen, tizanidine, gabapentin, dantrolene, clonidine and benzodiazepines, but they all have systemic adverse effects that decrease muscle tone globally and cause drowsiness, which interfere with the rehabilitation process, besides being associated with toxicity and tolerance development[29,33,34] (Table 3).

For a more accurate and balanced control of focal spasticity, chemical blocks are used, with phenol or alcohol[35], or with botulinum toxin[1]. A useful way to assess the real action of spasticity on the limbs and their function is the use of transient nerve blocks, with trunk injection, or of the muscle motor points, with local anesthetics such as lidocaine or bupivacaine. These blocks cause transient paralysis for about 2 to 4 hours, depending on the agent used, which allows assessing the joint contractures and how the patient's function is with spasticity control, although there is not enough time to modify the motor patterns[35]. The blockades allow spasticity control

Table 3. Treatments for spasticity and adverse effects.

Drugs	Mechanism	Dosage	Adverse Effects
Benzodiazepines	GABA-A Agonist	Variable	Sleepiness
Baclofen	GABA-B Agonist	15 – 18 mg	Dizziness, weakness, possibility of withdrawal syndrome
Dantrolene	Derivative of hydantoin, which inhibits the release of calcium (acts directly on the skeletal muscle)	25 – 300 mg	Dizziness, nausea, hepatotoxicity
Tizanidine	Alpha-2 presynaptic receptor agonist	8 – 36 mg	Orthostatic hypotension, constipation, dry mouth, hepatotoxicity
Clonidine	Alpha-2 presynaptic receptor agonist	0,1 – 2,4 mg	Dry mouth, hypotension and syncope
Gabapentin	Selective inhibitor of voltage-dependent calcium channels	100 – 2400 mg	Dizziness, drowsiness
Lamotrigine	Calcium channel inhibition	25 – 500 mg	Dizziness, exanthema
Cyproheptadine	Alters the activity of serotonin, histamine, and acetylcholine	4 – 32 mg	Sedation
Tetrahidrocanabidiol	Acts on CB-1 and CB-2 receptors	Variable	Potential cognitive deficit and anxiety

in more focal areas, with limited effect in extensive areas, as is the case of patients with spastic hemiparesis or very severe spastic tetraparesis, in which the quantity of regional procedures becomes very large, as well as the blocking agents dosage, which would exceed the recommended safety levels[24,36,37].

The treatment of spasticity with the use of cannabinoids began after reports of symptom relief in patients with MS who used inhaled cannabis, which led to studies with synthetic cannabinoids or their extracts[38]. It is important to emphasize that the presence of pain in spastic patients is frequent, but multifactorial, being linked to immobilism, increased muscle contracture and local neuropathic changes.

It is important to highlight that the spasticity symptoms accompany other neurological symptoms, such as altered sensitivity, altered consciousness, and the presence of pain, including chronic pain of central origin, and local neuropathic changes[1,11].

Neuropathic pain and pain associated with muscle spasms are common symptoms in MS. Animal models have suggested that activation of the cannabinoid-1 receptor (CB1) can reduce both types of pain. Systemic administration of cannabinoids produces analgesia in experimental models of acute and chronic pain. In animal models, the endocannabinoid system has shown a role in reducing spasticity[38].

Cannabinoids may act presynaptically in reducing glutamate release by activating CB1[33] receptors, and by reducing glutaminergic effects after exposure to 9-tetrahydrocannabinol (THC)[33-37]. There are also studies showing alteration of endocannabinoids and their receptors in animal models of MS. Furthermore, the use of cannabinoid antagonists worsens spasticity[37]. These studies showed that the use of CB-1 agonists and Delta-9-THC showed greater effectiveness in reducing and controlling spasticity[33-37], but the endocannabinoid system is complex and has not been fully elucidated.

CANNABINOIDS IN THE TREATMENT OF SPASTICITY

Recently published reviews show the effect of cannabinoid use in controlling spasticity. One study covered 11 reviews on the treatment of spasticity in patients with MS (21 articles)[39]. The use of inhaled cannabis, THC, CBD, THC+CBD, dronabinol or nabilone, or oral cannabis extracts were evaluated. This review of the studies suggested that there is moderate evidence that cannabinoids, especially nabilone and nabiximol, reduce spasticity. The following year, the same group produced a new systematic review in which most articles used the Ashworth scale as the final outcome measure, associated with individual perception. The findings from smaller studies did not have their results reproduced in other studies with larger samples, which were mostly negative for changes in the Ashworth scale[38].

A problem reported by the cited studies is that this scale is not recommended for the assessment of patients with MS, in view of the variability of this group's disabilities. For pain control, the results of these two reviews were inconclusive[38,39]. These results were confirmed by a more recent review that included 25 randomized clinical trials that compared the use of placebo and synthetic cannabinoids by oral spray, adding up to 2290 patients between 18 and 60 years of age[40].

For spasticity control, the conclusion is that the formulation increases the amount of people who perceive a reduction in severity - odds ratio (OR) 2.51; 95% CI 1.25 to 4.04 - with moderate degree of certainty. Based on the previous argument about the interference of spasticity in the genesis of musculoskeletal pain, it is expected that these cannabinoids act similarly in controlling this pain modality. For the control of neuropathic pain, this review only identified one small study with a substantial relief effect in this group of patients compared to placebo (OR 4.23; 95% CI 1.11 to 16.17)[40,41].

In the pediatric population, there is only one randomized study, in which the administration of cannabinoids (CBD+-THC) did not imply spasticity reduction in children with cerebral palsy[42].

Adverse effects resulted in permanent discontinuation of treatment with nabiximol in 30% to 40% of patients. After prolonged use of the drug, a reduction in adverse events was seen, which were mainly fall-related injury (approximately 6%), dizziness (up to 4%), fatigue (up to 2.5%), nausea, and drowsiness (around 2% each). Psychotic events and suicidal thoughts were reported by 2.5 - 6.0% of patients. Abuse of the drug (doses greater than 12 sprays a day) triggered events such as anxiety, nausea, fatigue, and paranoia in 8% of patients[43-47].

Although the use of cannabinoids in chronic pain shows some benefit, its participation in patients with pain associated with spasticity is still unclear[45]. It is not yet known which cannabinoid could promote better effect, or what would be the best dose and period of use, and its adverse effects of long-term use are not fully comprehended. In a recent cost-benefit analysis, the use of nabiximol was recommended for controlling spasticity in patients with MS, some infantile convulsive syndromes and chronic pain, but these conclusions may be significantly modified according to clinical practice and health system characteristics, such as cost and frequency of multidisciplinary therapeutic care or surgical indications[48].

It is interesting to consider that the pain associated with spasticity does not depend on the spasticity intensity, which is clinically observed in the pain relief before the spasticity control after the introduction of the drugs[6,13]. This observation is also valid when the spasticity treatment is performed by procedures such as neuromuscular blockades with botulinum toxin. In this case, it is suggested that the pain reduction may have occurred prior to the spasticity reduction by the mechanical effect of muscle needling, similar to the acupuncture effect, since the motor points on which the botulinum toxin infiltrations are performed coincide 70% of the time with the acupuncture points of Traditional Chinese Medicine[38,47].

CONCLUSION

Cannabinoid therapy has been shown to be an adjuvant in controlling spasticity and pain. Despite the greater pathophysiolo-

gical knowledge of the use of cannabinoids and the endocannabinoid system, there is still a need for further clinical studies to determine the best doses, blends and the therapy start timing.

AUTHORS' CONTRIBUTIONS

Eduardo de Melo Carvalho Rocha
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