







## Review Article

# Amyotrophic Lateral Sclerosis and Pain: A Narrative Review from Pain Assessment to Therapy

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Received 28 April 2023; Revised 11 February 2024; Accepted 6 March 2024; Published 16 March 2024

Academic Editor: Enzo Emanuele

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Amyotrophic lateral sclerosis (ALS) is the most frequent neurodegenerative disease of the motor system that affects upper and lower motor neurons, leading to progressive muscle weakness, spasticity, atrophy, and respiratory failure, with a life expectancy of 2–5 years after symptom onset. In addition to motor symptoms, patients with ALS have a multitude of nonmotor symptoms; in fact, it is currently considered a multisystem disease. The purpose of our narrative review is to evaluate the different types of pain, the correlation between pain and the disease's stages, the pain assessment tools in ALS patients, and the available therapies focusing above all on the benefits of cannabis use. Pain is an underestimated and undertreated symptom that, in the last few years, has received more attention from research because it has a strong impact on the quality of life of these patients. The prevalence of pain is between 15% and 85% of ALS patients, and the studies on the type and intensity of pain are controversial. The absence of pain assessment tools validated in the ALS population and the dissimilar study designs influence the knowledge of ALS pain and consequently the pharmacological therapy. Several studies suggest that ALS is associated with changes in the endocannabinoid system, and the use of cannabis could slow the disease progression due to its neuroprotective action and act on pain, spasticity, cramps, sialorrhea, and depression. Our research has shown high patients' satisfaction with the use of cannabis for the treatment of spasticity and related pain. However, especially due to the ethical problems and the lack of interest of pharmaceutical companies, further studies are needed to ensure the most appropriate care for ALS patients.

## 1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder of the motor system which causes a wide range of debilitating physical, but it has also been associated with extramotor impairments (i.e., mood disorders, cognitive and language impairment, sleep problems, sialorrhea, and pain). ALS is no longer considered a purely motor disease, but a multisystem disease with extramotor involvement [1–3]. Incidence of amyotrophic lateral sclerosis (ALS) may hover around 1.6 cases per 100,000 population, but it has been demonstrated that there is a global variation in prevalence and

incidence of ALS, with a higher incidence in some regions of the western Pacific [4]. The pathogenic mechanisms in ALS remain unknown, but several clinical phenotypes have been identified that underlie different molecular and genetic mechanisms. Dominant gene mutations are found in 10% of ALS patients. The mutated genes involved are genes encoding Cu/Zn superoxide dismutase (SOD1), TAR-DNA binding protein 43 (TDP-43), fused in sarcoma/translocated in liposarcoma (FUS/TLS), and C9ORF72. Instead, 90% of patients with unknown familial history are referred as sporadic ALS (sALS), and 5% of these patients are found the same gene mutations seen in familial ALS (fALS) [5].

Several studies have shown that neuronal death in the brain and spinal cord of ALS patients is caused by increased oxidative stress and glutamate excitotoxicity, neuroinflammation, and mitochondrial dysfunction [6–8].

Emerging evidence suggests that the damage not only affects neurons but also neighboring non-neuronal cells such as astrocytes, ependymocytes, and oligodendrocytes, resulting in the loss of these support structures and therefore faster progression of the disease [9, 10].

Another important distinction of patients with ALS is based on anatomical region of neuropathology, resulting in a different pattern of onset and a different prognosis.

Typical or “classical” form of ALS affects simultaneous upper motor neurons (UMNs) as Betz cells in layer V of Brodmann’s area 4 and lower motor neurons (LMNs) as alpha motor neurons in the motor nuclei of the brainstem and Rexed lamina IX of the anterior horns in the spinal columns [5].

In patients with the typical form, the first symptoms consist of progressive hypoesthesia and hypotrophy of the limbs, initially asymmetrical and more frequently of the upper limbs. Neurological examination will evaluate both signs of impairment of the peripheral motor neuron (atrophy, weakness, and fasciculations) and of the central motor neuron (hyperexcitable osteotendinous reflexes, hypertonia, and pyramidal signs). The most frequent cause of death in these patients is respiratory failure which occurs on average within 3–5 years of onset.

Atypical form of ALS includes all cases in which there is much longer survival, or pure UMN or LMN involvement [5].

The symptomatology of patients with ALS varies mainly according to the somatic regions primarily affected, therefore depending on whether the onset is spinal or bulbar.

Patients with spinal onset complain of difficulty in making fine voluntary movements of the upper limbs, or they frequently stumble.

Clinical progression follows an anatomical contiguity; in fact, about 85% of patients with spinal onset also manifest bulbar symptoms over time [11].

A quarter of the patients, on the other hand, begin the symptoms with dysphagia or dysarthria, and in this case, it is defined as bulbar onset ALS, often associated with cognitive alterations and then followed by involvement of the limbs.

Patients with bulbar onset ALS have the worst prognosis, with the shortest survival (with a median survival of 2 years from the time of diagnosis). The disease has a rapid decline not only motor but also intellectual-cognitive [12].

Regardless of the different forms and onset, the management of patients with ALS is complex and often unsatisfactory. Some aspects of the disease are underestimated and undertreated, first the pain on which we focused in this review.

In the past, ALS was considered a painless condition, but research is assessing that pain is a common symptom in 15% to 85% of patients [13].

The aim of our study is to evaluate the different types of pain, the correlation between pain and disease’s stages, the pain assessment tools used for patients with ALS, and the available therapies focusing on the benefits of cannabis.

## 2. Methods

We systematically performed a literature search on databases such as PubMed, Cochrane, Google Scholar, and Embase using these keywords and all the possible combinations, “Nociceptive pain”, “Neuropathic pain”, “Central pain”, “Pain”, “Chronic pain”, “Cannabis”, “Cannabinoids”, “Cannabidiol”, “Amyotrophic Lateral Sclerosis”, “Spasticity”, “Treatments”, “Pharmacotherapeutics”, and “Pain assessment scales”, to identify the therapeutic actions of cannabis in ALS patients with pain. We included 304 articles published from 1964 to 2023 and only if they were clinical studies, clinical trials, RCT, preclinical studies, meta-analysis, systematic reviews, and narrative reviews. We excluded case studies, letters to the editor, grey literature, conference proceedings, case report, and case series. Searches were restricted to studies published in English language.

## 3. Results

**3.1. Pain in ALS.** The new guidelines from the International Association for the Study of Pain (IASP) define pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”

In the past, pain was dichotomously divided into nociceptive and neuropathic pain, the former caused by damage to a non-neuronal tissue with activation of nociceptors, and the latter due to an injury or disease of the peripheral somatosensory nervous system.

Recently, the IASP has introduced the term “nociplastic pain” to describe a pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain [14].

It is important to specify that these three types of pain can be present alone or together in the same pathological state of a patient, and diagnosing the predominant type of pain is important for setting the correct therapy [15].

Among the nonmotor symptoms of ALS, pain is one of the most impacting on the quality of life of these patients and their caregivers.

A positive correlation has been demonstrated between the severity of pain and the level of interference with the quality of life, highlighting an important causal link [16].

The interest of the scientific community has only begun to focus on studying the prevalence of ALS patients’ pain in the last two decades. Ganzini et al. have published the first report of the prevalence of pain, suffering, poor quality of life, depression, and hopelessness in people with ALS.

100 patients and 91 caregivers were interviewed, and it was deduced that suffering was rated as 4 or greater on a six-point scale by 20% of subjects with ALS, and 19% rated their pain as 4 or greater on a six-point scale [17].

Nowadays, research has continued in studying the pain of patients with ALS. The most recent analyses estimate a prevalence of pain between 15% [18–20] and 85% of ALS patients [16, 21–26].

Probably, this wide range is due to the different sample size, types of studies conducted, and assessment tools used.

Identifying the type of pain present in ALS patients is fundamental for correct clinical and pharmacological management. Our research has revealed controversial results.

One of the primary causes of pain in ALS is pain with neuropathic features that patients describe as intense and continuous burning, spontaneous tingling, allodynia, or hyperalgesia. These symptoms can affect the distal extremities such as the feet and hands or be widespread [13].

However, several studies have revealed that neuropathic pain is not a component of ALS pain because no patient reached the threshold required to diagnose neuropathic pain [16, 27]; others have demonstrated that neuropathic pain in ALS patients was present in a similar percentage to that found in the general population, from 6.9% to 10.0% [28–31].

Perhaps these prevalence data on neuropathic pain could have undergone an evaluation bias due to the intake of riluzole by ALS patients, because riluzole blocks the presynaptic release of glutamate with possible attenuation of symptoms [28, 32–34].

Other primary causes of pain in ALS patients are cramps and spasticity, which are considered the most reported sources of pain, as evidenced by several studies [23, 35–40].

Caress et al. enrolled forty-one ALS patients in a prospective longitudinal study of the prevalence, frequency, distribution, and severity of muscle cramps. They interviewed patients by telephone from the early stages of the disease, every month, for up to 21 months. At the start of the study, 78% of the participants reported cramps, and of these patients, 34% described the cramp pain as moderate, while 24% as severe. During the study, the percentage of patients recruited with cramps increased to 95%. Moreover, patients with spinal onset had a higher frequency of cramps than patients with bulbar onset [37].

A cross-sectional survey on pain characteristics in amyotrophic lateral sclerosis had already reported very similar data on the incidence of cramps: 63% of 46 enrolled ALS patients [23].

The most involved body sites are the calf and thigh, followed by the hand and foot [23, 37].

It was found that cramps are more frequent during the night and less frequent during the day probably due to movement [23, 41].

The origin of the cramps is explained by the instability of the motor units at the level of the distal motor nerves and by muscle denervation, as shown with needle electromyography studies [42].

Fischer et al. confirmed that motor neuron's death is preceded by severe loss of motor axons, especially larger caliber ones, of the ventral root and significant denervation at the corresponding neuromuscular junctions [43].

Another accredited explanation for cramps and fasciculations was found in the hyperexcitability of motor units after axonal sprouting [23].

Park et al. have shown that anomalies of Na<sup>+</sup> and K<sup>+</sup> conductances contribute to the development of membrane hyperexcitability in patients with ALS and the consequent

muscle cramps and fasciculations, as well as triggering a neurodegenerative cascade through Ca<sup>2+</sup> mediated processes [44].

Another painful symptom is spasticity whose prevalence is between 11% [23] and 36% of patients with ALS [45]. 42.5% of spastic patients reported mild pain, while 16.7% of spastic patients had significant pain with NRS score > 4 [45].

Spasticity is caused by the reduction of suprasegmental control of spinal reflexes and by the alteration of the inhibitory mechanisms present in the spinal cord [46].

Spasticity increases the pathological decline of these patients, causing painful, violent, and paroxysmal contractions with rigidity of the involved muscles [47].

The secondary causes of pain in ALS patients are mainly nociceptive, resulting from non-neural tissue damage with activation of nociceptors due to mechanical or inflammatory stimuli [48].

This type of pain develops with the progression of the disease; in fact, the prolonged immobility associated with atrophy and muscle weakness causes degenerative changes in the musculoskeletal system and the joints, depleted of support [13, 49, 50].

The most frequent affected joints are those of the shoulder and of the hips [21, 49].

Musculoskeletal pain syndromes include adhesive capsulitis (or frozen shoulder) due to inflammation and atrophy of the periscapular muscles [49] and neck pain associated with "head dropping" and low back pain, due to muscle weakness and atrophy, joint degeneration, and unchanged decubitus [29].

Musculoskeletal pain occurs mainly in the later stages of the disease as a result of the stress, exerted on the bones and joints, due to atrophy and damages to the perimysium [39, 51].

Burke et al. evaluated the effectiveness of ultrasound-guided glenohumeral joint injections of local anesthetics and steroids for the management of shoulder pain due to adhesive capsulitis. The procedure offers the advantages of being a rapid outpatient treatment, requiring no ionizing radiation or sedation, and of reducing dependence on systemic pain medications with their potential gastrointestinal, renal, and neurological side effects. Injections into the glenohumeral joint have been shown to be safe and effective, but on their own, they may not completely resolve shoulder pain [52].

Several studies have shown the association between nociceptive pain in ALS patients with reduced mobility and skin pressure, affecting the back, shoulders, neck, and limbs more frequently [17, 18, 21–24, 39].

Patients complain of painful skin lesions such as decubitus ulcers caused by poor mobility [53], but they suffer more due to the ulcers on the face resulting of the mask in noninvasive ventilation (NIV). This is one of the main causes of poor compliance with the NIV [13]. It has recently been shown that neuronal damage and the consequent axonal sprouting with abnormal reorganization of the neuromuscular junction determine a mechanical and electrical dissociation in the muscle with microtrauma and inflammation of the tendons and ligaments as well [16, 54].

Hypotonus and muscle atrophy also contribute to the triggering of the inflammatory response [55].

The constant release of proinflammatory mediators contributes to maintaining a prolonged and intense stimulation of the neurons of the dorsal horn causing neurogenic inflammation and peripheral and central sensitization [56].

Several electrophysiological studies of peripheral nerves in people with ALS have confirmed such generalized sensory system abnormalities [2].

Furthermore, glial cell changes in the spinal cord and brain also underlie the development of chronic pain [57, 58].

Patients with nociceptive pain respond well to nonsteroidal anti-inflammatory drugs (NSAIDs) [59], which do not have effect on neuropathic pain [60].

Lopes et al. found that 46% of the 80 patients enrolled in their study suffered from chronic pain ( $VAS = 5.18 \pm 2.0$ ). Pain of musculoskeletal origin occurred in 40.5% and involved the head/neck area (51%) and the lumbar area (35%). 64.8% of patients took pain medication, and nearly 80% of these were analgesic or NSAIDs, with a relatively good response (70% reported pain relief) [28].

In some patients, pain assessment does not satisfy the diagnostic criteria for either nociceptive or neuropathic pain [47].

Several studies believe that central sensitization could be the explanation [13, 47].

Central sensitization has been found in various pathologies dominated by chronic pain in which there is an increase in the activity of the pathways to facilitate pain and the malfunctioning of the inhibitory pathways descending to pain [15, 61, 62].

Central sensitization is explained by the concept of heterosynaptic enhancement. Heterosynaptic enhancement represents a condition in which sensory inputs, even after being terminated, can amplify the subsequent responses of other unstimulated neurons, resulting in a greater reactivity of central nociceptive neurons to the afferent pathways [62–64].

Our research found that, to date, no studies have addressed the problem of widespread pain in ALS patients through central sensitization analysis, mainly due to the lack of standardized assessment methods. However, neuroimaging studies have shown that anatomical and functional lesions spread beyond the precentral cortices and corticospinal tracts to include the corpus callosum, prefrontal cortex, anterior cingulate cortex, thalamus, insula, amygdala, and midbrain. These functional impairments in ALS patients could explain chronic pain and the cognitive-emotional and affective component of painful sensations [65–67].

Several studies have evaluated the localization of pain in patients with ALS.

Rivera et al. analyzed in a cross-sectional study the characteristics of pain in sixty-four ALS patients (40 males, 24 females: median age 57 years). The most frequent location of pain was in the lower extremities (26%), upper extremities (25%), neck (12%), back (9%), shoulder (7%), hips (6%), abdominal muscles (4%), thorax/ribs (4%), jaw (2%), trapezius (2%), and headache (2%). In most patients, pain was present at more than one location [39].

The majority of the studies in ALS patients have shown similar results on pain localization. The body sites mainly

described by patients were lower and upper extremities and the back, but also widespread pain involving multiple body sites [13, 16, 21–24, 28, 68].

Pain intensity has been studied in several studies, with conflicting results.

Chiò et al. conducted a review highlighting that most patients with ALS describe the intensity of pain as mild ( $NRS < 3$ ) [13, 16, 21–23], but in other studies, pain intensity is mainly recorded as moderate ( $NRS$  between 4 and 6) [25] or severe ( $NRS > 7$ ) [24].

Recently, Hurwitz et al. have published a systematic review and meta-analysis: pain intensity is reported in seven of the included studies by a total of 1426 participants. 78.8% of patients reported moderate pain, 17.5% described severe pain, 1.7% very severe pain, and only 2% indicated mild pain [36].

In 2019, Edge et al. published a study about pain in ALS patients. They recruited 636 patients with ALS. The  $NRS$  was completed by 98.3% of patients, and 68.6% of them reported pain; of these, most had mild pain (median score was 2). Precisely, about half reported values of 1–4, and less than 5% reported values of 8–10 [69].

These differences between the results obtained could derive from the different study methods adopted and especially from the transversal nature of the studies analyzed.

**3.2. Correlation between Pain and Stages of Disease.** In literature, we have found several discordant studies about the correlation between pain and disease phases.

Some studies have supposed a prediagnostic role for pain in ALS patients [13].

Patients with ALS described pain as an initial symptom, occurred up to two years before motor impairment [18, 70].

An Italian study showed indirectly similar results, analyzing the intake of analgesic drugs prior to the ALS onset. ALS patients used drugs for pain more frequently than the general population, and this occurred up to 2 years before disease onset [71].

The types of pain most frequently reported at the onset of disease were painful cramps in the hands and legs, muscle spasms [13, 18, 40, 72, 73], and shoulder pain in about 10% of patients [49].

In a cross-sectional study of 108 ALS patients, 55 men and 53 women, the presence of pain at disease onset was retrospectively assessed: 20.4% of patients reported pain at the onset of the disease [40].

Comparable results were found in a cross-sectional study focusing on pain and sensory changes: 80 patients were included, and 21.6% of them described having chronic pain before the development of ALS [28].

Stephens et al. provided a higher percentage in a larger cohort. They recruited ALS patients to complete an online survey on pain. 424 participants responded to the survey, and 75% of the sample reported pain.

Fifty percent of the 318 pain patients reported that the pain preceded the motor symptoms of ALS and was still present at the time of the interview.

Similar to what has been described in other studies [3–10], no correlation was demonstrated between the severity of pain



and the disease duration. Pain can be occurred in every stage of the disease, without differences in frequency between the early and late stages [16, 21–24, 30, 39, 74].

In addition to the discordant studies on the presence of pain in the early stages, there is also conflicting evidence on the correlation among the pain intensity and the disease duration and the functional deterioration.

Some studies have suggested no correlation between the pain intensity and disease duration but have shown that pain intensity (PSI) tended to be higher when the ALSFRS-R score was lower [23, 29, 39].

Others have indicated that the pain intensity has strong relationships with loss of function (as measured by ALSFRS-r) and with disease duration [21, 75, 76].

The results of a longitudinal study on the evaluation of the physical and psychological state of 69 patients with ALS found that using the VAS, the intensity of pain increased by 1 point from the first to the last visit. The median number of days between the first and last assessment was 104 (range 35 to 846 days). Between the first and last assessment, increases were evident for pain (2.3 to 3.3;  $p$  0.003) and suffering (4.1 to 5.0;  $p$  0.03) [77].

Simone et al. evaluated laser-evoked potentials (LEPs) in relation to the clinical characteristics of 24 patients with ALS. This study showed that pain intensity (measured with the VAS) was significantly higher in patients with longer disease duration. Furthermore, the negative correlation between pain intensity and muscle strength suggests that pain may be an indirect symptom of the disease, resulting from motor deficits and posture [78].

Numerous previous studies have showed that pain intensity increases with ongoing disease, evaluating that 20% of examined patients described a change in pain intensity from moderate to severe [17, 79–81].

Furthermore, they reported that pain is more frequent in the final stages of the disease [17, 79].

The literature in favor of the higher frequency of pain in the later stages of ALS is copious [59, 82–86].

These different conclusions that we have found in the literature are mainly due to the dissimilar study designs and different confounding factors. We have noted some limitations in these studies: there are often small patient cohorts and few longitudinal studies and heterogeneity in the assessment techniques used. All this can have repercussions for prompt pharmacological or nonpharmacological intervention.

The need for a standardized approach in assessing all aspects of pain in ALS is becoming increasingly clear.

**3.3. Pain Assessment Tools.** Pain assessment is of fundamental importance to implement the necessary care to obtain the best possible quality of life for the patient.

There are several tools for assessing pain and its characteristics such as intensity, type, location, and interference with QoL. (Supplementary Table 1).

In clinical practice, both one-dimensional (NRS, VAS, VRS, FPS, and WBFPRS) and multidimensional (BPI, MPQ, and PAINAID) scales are used.

One-dimensional scales only measure pain intensity and no other factors, while multidimensional scales also evaluate other aspects of painful sensation.

The numerical evaluation scale (NRS) has the advantage of not requiring any paper support for its use and evaluates the intensity of pain from 0 (no pain) to 10 (the most terrible pain imaginable).

The NRS consists of a numerical scale from 0 to 10 where a value of 0 indicates no pain, while a value of 10 indicates maximum pain.

Values between 1 and 3 indicate the presence of mild pain, and values between 4 and 6 revealed moderate pain, while values between 7 and 10 suggest severe pain.

Its simplicity allows the NRS to be used even in subjects with limited communication skills [30, 69, 87].

Another one-dimensional scale often used to measure pain intensity is the visual analog scale (VAS) [24]. It corresponds to the visual representation of the amplitude of the pain felt by the patient and consists of a predetermined line 10 cm long, where the left extremity corresponds to “no pain,” while the right extremity corresponds to the “worst possible pain.” The patient is asked to draw a sign on the line that represents the level of pain felt.

The scale, as a one-dimensional measure, is used to assess current pain or possibly pain felt in the past 24 hours.

The score is calculated in millimeter, by measuring with a ruler the length of the line between the extreme corresponding to the minimum intensity and the mark placed by the patient. Based on several studies, the following cut-off values have been suggested: from 0 to 4 mm, “no pain”; from 5 to 44 mm, “mild pain”; 45 to 74 mm, “moderate pain”; and 75 to 100 mm, “intense pain.”

The VAS has the advantage of having a high sensitivity but has the disadvantage of requiring a paper support and is difficult to use in patients with visual, physical, or cognitive deficits [24].

Other one-dimensional scales available to clinicians are the Verbal Assessment Scale (VRS), the Faces Pain Scale (FPS), and the Wong-Baker Faces Pain Rating Scale (WBFPRS).

The Verbal Assessment Scale (VRS) associates the level of pain present (no pain, mild, moderate, strong, and unbearable) to a number from 0 to 4. It has a simple use and does not require a paper support but has a low sensitivity.

The Faces Pain Scale (FPS) has several versions. The original version uses the association of six expressive mimic faces, arranged on a horizontal line. The left extremity corresponds to no pain, and the right extremity indicates the worst pain, with a score ranging from 0 to 5. It is easily intuitive but not very sensitive.

The Wong-Baker Faces Pain Rating Scale (WBFPRS) has a similar structure of the six-face FPS, but the score ranges from 0 to 10.

The multidimensional scales instead evaluate pain as a complex sensory experience, and they also analyze the impact of pain on the quality of life of patients, considering different aspects such as the quality of sleep, the ability to carry out normal daily activities, the impact on mood, and the interference of pain at work, on interpersonal relationships.

The Brief Pain Inventory (BPI) is a multidimensional scale structured as a qualitative and quantitative questionnaire that investigates the intensity of pain experienced in the last week and at the time of the interview (with scales numbered 0, “no pain,” to 10, “the most horrible pain imaginable”) and localization of pain. The BPI also provides information on the treatments performed and the relief obtained by the patient, on a scale ranging from 0% (no improvement) to 100% (improvement). Furthermore, BPI evaluates the interference of pain with daily functions, asking the patient to indicate the level of interference on a scale numbered from 0 (no interference) to 10 (total interference). Obviously, this questionnaire is structured for chronic pain in general; therefore, not being specific for ALS, some functions are not considered, such as the ability to walk and interaction with work [16, 21–23, 28, 30, 88, 89].

The McGill Pain Questionnaire (MPQ) is a pain assessment tool developed in 1975 by Melzack and Torgerson. The original version included 102 verbal pain descriptors, which were then reduced to 78 in later versions. The McGill Pain Questionnaire (MPQ) is a multidimensional pain scale used to assess both the quality and intensity of pain self-described by patients [28, 90].

The PAINAD (Pain Assessment IN Advanced Dementia) is a multidimensional scale for pain assessment. It was designed and used for uncooperative patients with significant cognitive impairment.

The final score ranges from 0 (painless) to 10, where the score from 1 to 3 indicates mild pain, the score from 4 to 6 indicates moderate pain, and the score from 7 to 10 indicates severe pain.

We have not found any studies in which this scale has been used to assess pain in ALS patients [91].

In addition to aforementioned pain assessment scales, there are specific questionnaires to assess the possible neuropathic component of pain. These tools are especially useful for the correct pharmacological management of pain in ALS patients.

The first specific instrument developed to measure and analyze pain caused by lesion of the nervous system was the Neuropathic Pain Scale (NPS), developed in 1997 [92, 93].

Later, other scales were developed such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale [94, 95], the Neuropathic Pain Questionnaire (NPQ) [96, 97], the painDETECT (PD-Q) [98], and the Douleur Neuropathique 4 (DN4) [99, 100].

The Neuropathic Pain Scale (NPS) is the first scale designed to qualify and quantify neuropathic pain, and it is also useful for determining the effectiveness of different treatments.

Obviously, the NPS has not been validated in the ALS population; in fact, this represents a limitation in the studies that have used it [39, 92, 93].

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) is a scale developed by Bennett that provides immediate clinical information and helps distinguish nociceptive pain from neuropathic pain.

The maximum score that the patient can receive is 24.

A score of less than 12 points makes it unlikely that the patient's symptoms have neuropathic mechanisms, while a

score of 12 or higher makes it possible that the neuropathic mechanisms contribute to the pain in the patient. The LANSS scale had a sensitivity of 85%, a specificity of 80%, and a predictive value of 82%.

We have not found in literature any studies on pain in ALS patients that have used this scale [94, 95].

The Neuropathic Pain Questionnaire (NPQ) is another questionnaire designed to differentiate patients with neuropathic pain from patients with no neuropathic pain. Subjects with scores below 0 are predicted to have non-neuropathic pain, while those with scores at or above 0 are predicted to have neuropathic pain. The NPQ can differentiate patients with neuropathic pain from patients with non-neuropathic pain with a sensitivity of 66.6% and a specificity of 74.4% and an accuracy of 71.4%.

The same research group developed the NPQ-Short Form which has 64.5% sensitivity, 78.6% specificity, and 73% accuracy.

We have not found in literature any studies on pain in ALS patients that have used this questionnaire [96, 97].

Freyenhagen et al. developed the painDETECT questionnaire (PD-Q), in 2006, during a prospective multicenter study involving 392 patients. The PD-Q proved to be a reliable screening tool with 85% sensitivity and 80% specificity. The PD-Q showed slightly higher sensitivity and specificity than other screening questionnaires for neuropathic pain such as DN4, LANSS, NPQ, or NPS. The painDETECT was initially developed and validated in patients with back pain but has shown applicability to patients with other types of neuropathic pain as well. An important advantage of this questionnaire is that it is easy for the patient to fill in, without first needing any clinical medical examination. Maximum achievable score is 38. A score  $\leq 12$  indicates that pain is unlikely to have a neuropathic component (probability  $< 15\%$ ), while a score  $\geq 19$  suggests that pain is likely to have a neuropathic component (probability  $> 90\%$ ). A score between 13 and 18 correlates to an unclear cause for pain [16, 98].

The Douleur Neuropathique 4 (DN4) is a questionnaire used in several studies to evaluate the predominant type of pain in ALS [28–30, 99, 100].

Respondents with a total score  $\geq 4/10$  are considered to have neuropathic pain. A cut-off score of 4 has a predictive value of 86%, a sensitivity of 82.9%, and a specificity of 89.9%.

Beswick et al. conducted a systematic review of the assessment of nonmotor symptoms in clinical trials for amyotrophic lateral sclerosis [101].

They evidenced that nonmotor symptoms, including pain, should have been evaluated with ALS-specific assessment tools or validated for use in people with ALS. For these patients, with progressive physical and speech impairment, traditional measures might not be effective in detecting the change in symptoms correctly. Instead, this could be done using validated tools specifically for this type of patients.

The assessments of the prevalence and severity of pain were done using scales and questionnaires that were not specific to ALS patients, which might not be objective enough to detect changes that occur during disease progression or

assessment of a pharmacological improvement of symptoms. Using specific or tailored assessment tools for patients with ALS, we could better determine the prevalence and progression of nonmotor symptoms, including pain [47–102].

**3.4. Pain Treatments in ALS.** The insufficient understanding of ALS physiopathology, the few data in the literature, and the absence of guidelines still make difficult to set up a pharmacological therapy in patients with ALS. There is the necessity to establish new therapeutic strategies universally accepted.

The Food and Drug Administration approved two possible disease-modifying therapies that can slow ALS progression, riluzole and edaravone, but they are used in a few countries [103–107].

In Italy, for example, riluzole remained the only drug paid by the National Health System (NHS); instead, edaravone since 2020 is no longer disburseable by the NHS due to a poor proven risk-benefit ratio.

In fact, there is a consensus in the scientific community on the modest efficacy of riluzole in prolonging survival, particularly when taken in the early stages of the disease, while there are still debates regarding the efficacy of edaravone in slowing the progression of the disease [108–111].

Riluzole has a neuroprotective action against glutamatergic excitotoxicity. It inhibits the release of glutamate and was the first drug approved by the FDA for the treatment of ALS in 1995 [108].

A long-term follow-up study evaluated the efficacy of riluzole in a cohort of 415 patients with ALS. Long-term use of riluzole was found to be associated with a better prognosis in patients with ALS, whereas short-term use had little impact on survival [112].

Edaravone scavenges free radicals thereby reducing oxidative stress and thus cell damage. It has been approved for the treatment of ALS in some countries (approved in Japan in 2015, South Korea in 2015, United States in 2017, Canada in 2018, Switzerland in 2019, China in 2019, and Indonesia in 2020) [110, 113].

There are conflicting studies about its ability to modify disease progression [114–116].

The FDA recently approved two new disease-modifying drugs: tofersen [117] and AMX0035 (sodium phenylbutyrate and taurursodiol) [118].

Tofersen is an antisense oligonucleotide for the treatment of ALS patients who have a mutation in the superoxide dismutase 1 (SOD1) gene. The significant decline in neurofilament light chain (NfL) after tofersen treatment confirmed its disease-modifying ability [119], given the proven correlation between the biomarker NfL and ALS progression [120].

AMX0035 is a combination of sodium phenylbutyrate (PB) and taurursodiol designed to reduce neuronal death by mitigating both endoplasmic reticulum (ER) stress and mitochondrial dysfunction. The CENTAUR trial has demonstrated a longer median survival of 6.5 months in patients treated with AMX0035 compared to placebo [121].

Regarding the ALS symptoms like pain, spasticity, cramps, sialorrhea, fatigue, depression, and insomnia, they could be alleviated by pharmacological and nonpharmacolo-

gical interventions, with a multidisciplinary approach mostly based on good clinical practice [122, 123].

The pharmacological treatments of pain are depending on its different origin.

For neuropathic pain, the use of gabapentin, pregabalin, and tricyclic antidepressants is recommended [50, 124, 125].

The nociceptive pain can be relieved by NSAIDs and paracetamol. In case of joint pain, the intra-articular injections of corticosteroids, alone or combined with lidocaine, are useful [55].

Opioids are second-line drugs for refractory pain. Opioids are used primarily in the advanced stages of ALS to control increased pain associated with insomnia. O'Brien et al. conducted a retrospective analysis of oral morphine use and identified the best tolerated effective dose: a mean 30 ( $\pm 2.34$ ) mg/24 h oral morphine equivalent, with mean treatment duration of 58 ( $\pm 18.51$ ) days [126].

An additional one study about oral morphine use, lasted 95 days, suggested that strong opioids could be used safely in palliative care [127].

Despite these analgesic effects, the opioids are associated with notorious side effects like respiratory depression, constipation, antitussive effect, and dependence.

Perhaps, for these side effects, the opioid use is more frequent in a hospice or palliative care unit rather than at home [128, 129].

Furthermore, there are differences between countries in opioid use [129].

Another common source of pain is cramps, which improve with the intake of quinine, benzodiazepine, magnesium, and carbamazepine [23].

Symptomatic treatment of muscle cramps includes sufficient hydration of the patient with correction of any electrolyte imbalances and, if possible, elimination of any causative drugs. A new effective and safe therapeutic option has recently been introduced in patients with ALS: mexiletine, a Na<sup>+</sup> channel blocker that reduces persistent sodium currents. A multicenter double-blind placebo-controlled crossover trial of mexiletine 150 mg twice daily was conducted in ALS patients complaining of painful muscle cramps. The frequency and severity of muscle cramps were reduced in 18 of 20 patients, and no serious adverse event occurred [130, 131].

A less safe drug is quinine sulfate because its long-term use might be associated with severe thrombocytopenia, cinchonism, hypoglycemia, hypotension, hearing and visual disturbances, gastrointestinal symptoms, cutaneous effects, conduction abnormalities, arrhythmias, hemolysis, and cardiotoxicity [50, 132, 133].

Due to various adverse events reported, the FDA (Food and Drug Administration) in 2010 launched a risk management plan about its off-label use for leg cramps [134, 135].

A survey on palliative care in the clinical management of ALS patients was conducted among members of the European ALS Study Group. Of the 110 centers consulted, 73 (66%) have completed the questionnaire, getting information from 18 European countries.

For fasciculations and cramps, quinine sulfate is used in 58% of centers, benzodiazepines in 40%, magnesium in 25%, and carbamazepine in 23%.

For spasticity, baclofen is the drug of first choice (93%), followed by tizanidine (38%), dantrolene (36%), and benzodiazepines (36%) [50].

The initial treatment approach for spasticity includes stretching exercises and drugs to reduce pain associated with spasms and stiffness. Muscle relaxants such as baclofen and tizanidine unfortunately have several side effects including aggravation of muscle weakness and the sedative effect [27, 122].

Furthermore, some patients are resistant to treatment or experience side effects that force the reduction of the therapeutic dose of these drugs [136, 137].

In these cases, placement of an intrathecal baclofen pump might be an efficient treatment option [138].

A small study was performed to evaluate the results obtained from the placement of an intrathecal baclofen pump (ITB). Eight patients with intractable spasticity-related pain underwent this treatment, six patients described a pain score reduction, and three of them had a complete resolution of pain. The average reduction in pain scale was 54% after placement of the pump. This result is limited, however, by the small cohort of patients involved and the lack of follow-up which precludes long-term evaluation of the efficacy of intrathecal baclofen for pain [139].

Ashworth et al. [140] systematically reviewed in literature treatments for spasticity in amyotrophic lateral sclerosis, but they identified only one RCT (randomized controlled trial), in which spasticity (as measured by the Ashworth Spasticity Scale) was improved at 3 months following a list of exercises involving most muscle groups of the four limbs and trunk [75].

Precisely, twenty-five ALS patients were randomized to receive a daily exercise program (14 patients) or to perform no physical effort beyond the normal daily activities (11 patients).

Patients were evaluated for one year, every three months. In addition to spasticity, muscle strength, functional status, severity of fatigue, pain, and quality of life were also assessed.

At 3 months, patients who exercised regularly showed less worsening of spasticity and functional status, but not of other parameters. At 6 months, there was no significant difference between groups. At 9 and 12 months, there were too few patients in each group for a statistically significant assessment.

This study has a high risk of bias due to a very small sample size ( $N = 25$ ). It is not possible to conclude whether the exercise program is beneficial, but further research is needed because no additional randomized controlled clinical trials have been conducted on the efficacy of pharmacological and nonpharmacological therapy for the treatment of spasticity in ALS patients [75].

About the nonpharmacological analgesic strategies, the therapeutic ultrasounds, the laser therapy, the transcutaneous electrical nerve stimulation (TENS), and the acupuncture are also mentioned in literature [13, 23, 141, 142].

**3.5. New Therapeutic Perspectives: Cannabis.** In recent years, research has been directed towards new therapeutic strategies, and among these, our review focused on the use of cannabis.

In truth, the use of cannabis for medical purposes has been widespread for thousands of years in different areas of the world [143, 144].

Cannabis is one of the oldest known psychotropic drugs. Its use is estimated as early as around 4000 BC in China to treat emesis, parasitic contaminations, and hemorrhage. Even in India, the properties of cannabis were known, which was used since 1000 BC as an anesthetic and anti-inflammatory [145].

Lately, research has focused on the therapeutic use of cannabis especially for neurological diseases; in fact, cannabis relieves pain and spasticity both in people with multiple sclerosis (MS) than amyotrophic lateral sclerosis (ALS) patients and acts positively on tremor, stiffness, and pain in people with Parkinson's disease (PD) [146, 147]. Cannabinoids are a group of chemical compounds capable of binding to the two receptors of our endocannabinoid system known as CB1 and CB2 [148].

Based on their origins, cannabinoids are classified into three groups.

The first group includes phytocannabinoids or natural cannabinoids such as THC and over 100 other cannabinoid compounds contained in *Cannabis sativa* [149, 150].

$\Delta^9$ -Tetrahydrocannabinol (THC) is the main psychoactive component present in the female inflorescences of *Cannabis sativa* (marijuana), and it was isolated in 1964 [151, 152].

Cannabidiol (CBD) is the main nonpsychoactive component of cannabis, and it was isolated in 1940 [153].

The presence of cannabidiol diminishes the psychotropic effects of THC [154, 155].

Other known phytocannabinoids, with minor or no psychoactive properties, are tetrahydrocannabivarin (THCV), cannabinol (CBN), cannabichromene (CBC), cannabicyclol (CBL), and cannabigerol (CBG) [156].

The second group consists of synthetic cannabinoids that bind the CB receptors. These are a diverse set of compounds which include HU-210, Win-55212-2, CP-55,940, JWH-073, JWH-018, and other substances much more potent than THC [157].

Among the synthetic cannabinoids, two important drugs should be mentioned: dronabinol and nabilone, synthetic analogs of  $\Delta^9$ -THC.

Dronabinol and nabilone were both approved by the FDA in 1985 for nausea and emesis in patients undergoing chemotherapy. Dronabinol was approved also for wasting syndrome associated with HIV/AIDS. Several clinical studies have confirmed the benefits of this drug in other pathologies including chronic pain, multiple sclerosis, amyotrophic lateral sclerosis (ALS), fibromyalgia, and dementia [158–160].

The third group of cannabinoids consists of endogenous cannabinoids, derived from arachidonic acid. Anandamide was first identified in 1992 [161] and subsequently 2-arachidonoylglycerol (2-AG) in the CNS [162–164].

The endocannabinoid system is an important endogenous system of intercellular communication involved in many physiological processes, including motor control, pain perception, modulation of the immune system, and neuroprotection.

There are two receptors in this system, CB1 and CB2, both coupled to inhibitory G protein.



CB1 receptor is one of the most common in the central nervous system, especially in the hippocampus, basal ganglia, prefrontal cortex, and cerebellum [165] highlighting the critical role of the endocannabinoid system in motor and cognition function [166].

CB2 receptor is mainly found expressed in immune system's cells but has also been detected in the cerebellum and brainstem [167].

It has been demonstrated that the upregulation of CB2 receptors occurs in the CNS due to injury and inflammatory processes [168, 169], specially on activated microglia, involved in the removal of damaged neurons through mechanisms of phagocytosis and cytotoxicity [170].

Activation of the CB2 receptor gives neuroprotection reducing glial activation and downregulating cytokine and chemokine production [171–176].

Several studies have shown the neuroprotective effects of the endocannabinoid system, such as the reduction of excitotoxicity, oxidative damage, and neuroinflammation through the inhibition of microglia by activating CB1 and especially CB2 receptors [177–181].

The endocannabinoid system (ECS) has multiple connections with the other transmission pathways present in the CNS, suggesting that it might be an interesting therapeutic target especially in neurodegenerative diseases [182–184].

CB1 is expressed in the glutamatergic and GABAergic presynaptic terminals in the brain, spinal cord, and peripheral nerves. The activation of cannabinoid receptors inhibits the release of the excitatory neurotransmitter glutamate and potentiates the effect of the inhibitory neurotransmitter GABA [185–188].

Neurodegenerative diseases show common changes in endocannabinoid levels and CB receptor expression as result of neuroinflammation [189].

Any type of CNS injury or disease is also characterized by increased levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) which determines the neuronal upregulation of AMPA-type glutamatergic receptors (AMPA $\alpha$ s), enhancing significantly glutamatergic excitotoxicity. Therefore, a neuroprotective effect could be achieved by avoiding the increase in TNF- $\alpha$  concentration [190–195].

Interestingly, this was obtained with activation of the CB1 receptor. The neuroprotective role of the CB1 receptor was demonstrated by measuring the change in AMPAR receptor expression after exposure to TNF- $\alpha$  in the presence or absence of CB1 agonists. CB1 activation blocks TNF- $\alpha$ -induced upregulation of AMPAR receptors, thereby protecting neurons from excitotoxic neuroinflammatory death (END) [196].

The pharmacological action on the endocannabinoid system therefore could have an important potential role not only on neuromodulation but also on pain [197–199].

Cannabinoid receptor agonists cause analgesic effects in acute and chronic pain states via spinal and supraspinal pathways, similarly to opioids [200, 201].

Many studies indicate that cannabinoids systemically or topically administered enhance the antinociceptive properties of opioids. Additionally, the antiemetic effect of cannabis can alleviate the nausea associated with opioids [202, 203].

The synergy between  $\Delta$ 9-tetrahydrocannabinol and morphine has been demonstrated in many animal models. CB2 receptor agonists produce antinociceptive effects in inflammatory pain models, with activation of the opioid system as well. Furthermore, CB receptor agonists enhance the effect of  $\mu$ -opioid receptor agonists in a variety of animal models, and combinations of cannabinoids and opioids can produce synergistic effects [204, 205].

A double-blind, placebo-controlled study has evaluated the direct effects of opioids combined with cannabis in humans. Cannabis and oxycodone were coadministered to understand the influence of smoked cannabis on the opioid's antinociceptive effect and to evaluate its interaction. Subtherapeutic doses of oxycodone (2.5 mg) and cannabis, if administered individually, did not cause analgesia in the patients, while if administered together, a significant reduction in pain responses was recorded during the cold pressor test (CPT), thanks to the synergistic action of cannabis and opioids [206].

Moreover, there is evidence of CB2 receptor expression in keratinocytes, which, in presence of CB2 agonists, release endogenous  $\beta$ -endorphins to activate opioid receptors in the peripheral nerve endings of sensory neurons [207].

A randomized, double-blind, placebo-controlled crossover study evaluated the analgesic efficacy of vaporized cannabis in patients with pain syndromes caused by nervous system lesions or disease refractory to traditional treatment.

42 patients underwent a standardized inhalation procedure of 4 puffs of vaporized cannabis containing placebo, 2.9% or 6.7% delta-9-tetrahydrocannabinol. This first administration was followed by a second administration at 240 minutes, during which patients inhaled four to eight mouthfuls of cannabis (or placebo). Pain intensity, the primary outcome variable, was rated by patients with a one-dimensional scale ranging from 0 (no pain) to 10 (worst possible pain). It was found that vaporized cannabis had conferred relief from neuropathic pain with decrease in the pain intensity [208].

This is a prospective nonrandomized study of 338 patients who suffered of various chronic pain conditions treated with a decoction of Cannabis Flos 19% for 12 months, in addition to their traditional analgesic drug therapy. Pain intensity, pain disability, anxiety, and depression were recorded at 1, 3, 6, and 12 months. After 12 months of therapy, the data showed a substantial improvement [209].

A recent analysis showed that the legalization of medical cannabis was associated with a reduction in both the prescribing (30%) and dosage of Schedule III opioids in the United States. The data was collected during the period in which the legalization of medical cannabis at the state level was implemented, from 1993 to 2014 [210].

A retrospective mirror-image study enrolled twenty-nine patients who suffered from chronic pain to investigate whether medical cannabis could improve quality of life and pain. After 3 months of treatment, data suggested improvement in QoL, pain reduction, decrease of opioid use, and cost savings [211].

There is also evidence that cannabinoids enhance the analgesic effect of nonsteroidal anti-inflammatory drugs

(NSAIDs), allowing the reduction of the NSAIDs required dose and their side effects [212].

Although the pathogenetic mechanisms of ALS are yet unknown, it is believed that an important role in the development and progression of the disease concerns neuroinflammation, oxidative damage, alteration of axonal transport by neurofilaments, and glutamatergic excitotoxicity [6–8, 213].

Furthermore, several studies on animal models have demonstrated the presence of alterations of the endocannabinoid system in symptomatic ALS transgenic mice [214].

CB2 receptors, that have a role in neuroprotection, are upregulated in a mouse model for ALS (G93A-SOD1 mutant mice) [215].

Treatment with the synthetic CB1 and CB2 receptor agonist (WIN55, 212-2) and the synthetic selective CB2 agonist (AM-1241) delays the progression of ALS in animal models [215–221].

Moreover, the neuroprotection of THC is decreased by blockade of the CB1 receptor [222].

A human postmortem study confirmed the data obtained in mouse models: patients with ALS have an overexpression of CB2 receptors on spinal cord microglia following neuronal damage [223, 224].

These data suggest that ALS is associated with changes in the endocannabinoid system and the iatrogenic increase of endocannabinoid tone could slow the disease progression due to the neuroprotective action [179, 225, 226].

In addition, cannabis can relieve the multiplicity of ALS symptoms. The different pharmacological properties, the synergy with various endogenous systems, and the several mechanisms of action highlight that cannabis can manage the heterogeneous symptomatology of ALS patients like pain, spasticity, cramps, dyspnea, sialorrhoea, cachexia, insomnia, anxiety, and depression [227–230].

Approximately 50% of patients with ALS experience significant sialorrhoea due to inability to swallow and to close the mouth and head postural difficulties with the risk of coughing and choking. Excessive saliva causes facial irritation and social embarrassment [231].

Cannabis can cause dry mouth by acting on the CB1 and CB2 receptors present on the salivary glands allowing to avoid the use of anticholinergic drugs which can cause sedation and delirium as side effects [232].

Cannabis can also improve “ALS cachexia” by increasing appetite and reducing catabolism. The CB1 receptor is capable of modulating appetite through presynaptic regulation on orexigenic and anorexigenic neurons [233].

This receptor is abundantly expressed both in areas of the CNS involved in the control of food intake (hypothalamus and brainstem) and in gratification (nucleus accumbens), as well as in the peripheral nervous system, and organs involved in metabolism such as the gastrointestinal tract, liver, and adipose tissue [234, 235].

Moreover, cannabis has a bronchodilator action on the airways as reflected by increases in both PEFR and FEV1, which may be beneficial in ALS patients with respiratory insufficiency [236–240].

Several clinical studies indicate that ALS is associated with high levels of anxiety and depression [241–243].

Cannabis could also act on these symptoms, improving the quality of life of ALS patients [244, 245].

In recent years, academic and industrial efforts have focused on the search for new substances capable of increasing the endocannabinoid tone such as selective inhibitors of the main ECS degradative enzymes, namely, fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MAGL) [246–249].

Inhibition of the hydrolyzing enzymes FAAH and MAGL could allow to obtain the desired therapeutic effect without the negative side effects associated with the use of exogenous cannabinoid agonists [250].

Simultaneous inhibition of FAAH and MAGL is known to effectively reduce inflammatory pain by increasing 2-AG and AEA [251] and represents a valid therapeutic strategy to reduce opioid doses in pain treatment [252–254].

Spasticity, a debilitating problem for ALS patients [255], is induced by the lack of inhibition of motor neurons both in the motor cortex and in the spinal cord. Cannabis relieves this symptom by acting mainly on the CB1 receptors located on the synapses of the CNS, with the consequent inhibition of the presynaptic calcium influx and therefore a reduced release of glutamatergic neurotransmitters [256, 257].

Several clinical studies conducted in patients with multiple sclerosis have shown the safety and efficacy of tetrahydrocannabinol (THC) and cannabidiol (CBD); indeed, nabiximols, a combination of THC and CBD, has been approved in Europe for the treatment of spasticity in MS patients since 2010, and it is already used in 15 countries [258–264].

These promising results have encouraged the scientific research to evaluate the use of nabiximols for spasticity in ALS patients too [87, 265].

Riva et al. conducted the first one randomized controlled clinical trial to evaluate the safety and efficacy of nabiximols in ALS patients. They included 59 eligible patients who were asked to complete a diary of their daily levels of spasticity, pain, spasm frequency, and sleep disturbances. Nabiximols was delivered via an oromucosal spray, and each 100  $\mu$ L actuation delivered 2.7 mg of  $\Delta^9$ -THC and 2.5 mg of cannabidiol. The primary outcome was the change in the score on modified Ashworth Scale (MAS) scores in the active group compared with the placebo group.

After 6 weeks, the MAS score significantly improved in the nabiximols group compared to the control group. Additionally, there was a significant reduction in pain, but no significant differences were noted between groups for sleep quality, muscle strength, and scores on ALSFS-R. Nabiximols was overall well tolerated. No participants permanently discontinued treatment during the double-blind phase of the study, and no serious adverse events occurred in either group [265].

An observational study was conducted as a retrospective, single-center, cross-sectional cohort study with the aim of assessing the level of satisfaction with the use of an oromucosal spray containing THC:CBD for the symptomatic management of spasticity in 32 ALS patients [87].

Each 100  $\mu$ L actuation contained 2.7 mg of THC and 2.5 mg of CBD. The patient's perception of spasticity and associated pain and cramps was recorded with the one-dimensional NRS scale [266, 267].

The NPS has also been used to examine patients' attitudes towards their THC:CBD treatment. Patients were asked the question, "How likely is it that you would recommend THC:CBD to a friend or colleague who suffers from ALS and spasticity?" The answers were evaluated on a numerical scale ranging from 0 (absolutely improbable recommendation) to 10 (highest probability of recommendation).

THC:CBD treatment satisfaction was assessed using the TSQM-9 (Medication Treatment Satisfaction Questionnaire), a validated rating scale containing nine questions [268].

Most patients rated spasticity as severe (24.2%,  $n = 8$ ) or moderate (48.5%,  $n = 16$ ). Of the ALS patients surveyed, 70% ( $n = 23$ ) reported pain.

The overall NPS score was +4.9 points, which translates into a moderately positive recommend rate. In particular, patients with moderate to severe spasticity ( $\text{NRS} \geq 4$ ) were highly likely to recommend (NPS: +28) treatment with THC:CBD, unlike patients with mild spasticity ( $\text{NRS} < 4$ ) which were unwilling to recommend THC:CBD to other patients (NPS: -44). Another interesting data is the correlation found between the severity of the symptoms and the dose of THC:CBD applied. A mean number of 7.3 ( $\pm 6.0$ ) actuations was used in patients with severe spasticity, while 3.5 ( $\pm 2.2$ ) actuations per day were used in patients with mild spasticity.

Evaluation of TSQM-9 showed a high general level of satisfaction with THC:CBD treatment in the majority of ALS patients studied (84% of patients).

Unfortunately, this study evaluated a small sample of patients ( $n = 32$ ), and 40% of them ( $n = 16$ ) discontinued THC:CBD treatment during the study [87].

Cannabis use has also been evaluated for cramps in ALS patients. In fact, the distribution of CB1 receptors in the pre-synaptic terminals in the brain, spinal cord, and peripheral nerves suggests that its use could be more advantageous than drugs that act only centrally (gabapentin) or only peripherally (quinine sulfate) [269, 270].

Weber et al. conducted a randomized, double-blind, placebo-controlled crossover study of 22 ALS patients who suffered from moderate or severe daily cramps. Adult patients with a mean daily cramp severity score of 4 or greater were eligible. The patients were randomly assigned to receive 5 mg THC twice daily followed by placebo or vice versa. Each treatment period lasted 2 weeks and was preceded by a 2-week drug-free observation period. The primary outcome was the change in cramp intensity assessed with the VAS. Secondary outcome measures included the number of cramps per day, the intensity of fasciculations (VAS) as well as the quality of life (ALSAQ-40), the quality of sleep (SDQ), the appetite (FAACT), and the depression (HADS). THC was well tolerated, but there was no evidence for a treatment effect on cramp intensity, cramp frequency, fasciculation intensity, or any of the other secondary outcome measures. This may be, in part, due to the limited 2-week treatment period and poor knowledge of the pharmacokinetics of THC in ALS patients so with consequent difficulty to determine the correct length of the wash period. Another confounding factor is the natural course of cramps, which is unknown [271].

Amtman et al. [228] conducted a survey with 131 ALS patients. This study is the first anonymous survey of ALS patients regarding cannabis use, published in 2004, well before the official legalization of cannabis in the United States. Only 10% of 131 patients ( $n = 13$ ) reported having used cannabis in the last 12 months, and all of them had already used cannabis in their own life before to have the ALS diagnosis.

Respondents were asked to rate the relief obtained from cannabis use for each symptom on a scale numbered from 0 (not at all) to 4 (completely relieves the symptom). Respondents reported that cannabis use helped moderately with depression, loss of appetite, spasticity, sialorrhoea, and pain.

Duration of symptom relief was also rated using a scale from 0 (no relief) to 6 (more than nine hours). Relief for depression was the longest lasting (averaging two to three hours), while other symptoms were relieved for an average of about an hour or less.

Unfortunately, the survey has several limitations: the 13 cannabis users may not represent the true percentage of ALS patients who use cannabis. Furthermore, 75% of respondents were male and 25% female; therefore, the female percentage is slightly lower than the real one estimated in the general ALS population because men develop ALS at 1.3-1.56 times the rate of women [272, 273].

In 2023, Lacroix et al. published a study on the use of therapeutic cannabis in ALS patients in France. The study analyzed online questionnaires compiled by ALS patients about their "real-life" situation to better understand patients' opinions on medical cannabis. There were 129 respondents and 28 reported using cannabis (21.7%) to relieve ALS symptoms. All cannabis users were men. Regarding frequency of use, 12 participants reported daily use (42.9%), seven weekly use (25%), and seven occasional use (25%). Oral or sublingual administration was the most reported route ( $n = 19$ , 67.9%), followed by smoking ( $n = 5$ , 17.9%) and vaping ( $n = 2$ , 7.1%). One participant reported applying a skin cream. The concentration of the cannabinoids was not well known by users. Regarding the different purchasing methods, 13 participants reported having purchased products in shops (46.4%), 11 on the Internet (39.3%), six in the street (dealer) (21.4%), two self-cultivation (7.1%), one in another European country, and one in a hospital pharmacy because he was a participant in the ANSM experimentation campaign. The majority of patients declared benefits on both motor symptoms (stiffness, cramps, and fasciculations) and nonmotor symptoms (sleep quality, pain, emotional state, quality of life, and depression). Only eight patients reported minor adverse reactions like drowsiness, euphoria, and dry mouth. Furthermore, 15 participants reported an overall positive impression of the change (53.6%). From this study, it emerges that cannabinoids could be an important treatment options for the symptoms of ALS, but at the same time, there is the need to conduct studies on a larger number of patients, to have formulation pharmaceuticals and precise dosages, and the possibility of accessing cannabis through safer routes [274].

The bioavailability and pharmacokinetics of cannabis change depending on the chosen mode of administration.

Besides the concentration of THC and other phytocannabinoids in marijuana varies considerably depending on the genetic characteristics of the plant, on the different methods of cultivation and processing [275].

The most common and traditional use of cannabis is through rolled cigarettes or pipes, used to smoke dried cannabis flowers [276].

The main advantage of smoking is the rapid onset of effect and easy dose titration. Cannabinoids present in inhaled smoke are rapidly absorbed and easily cross the blood-brain barrier due to their fat solubility. Obviously, this route of administration carries risks for the respiratory system [277].

To date, healthier formulations are available: vaporized, ingested orally, applied topically, or administered via other routes.

Oral cannabis products are available as both foods and beverages with varying percentages of THC and CBD [278–280].

In addition, cannabis oils and tinctures are also edibles. This mode of administration is preferred by women, the elderly, and patients who use cannabis for medicinal purposes [281–283].

The vaporization of cannabinoids is possible as they are volatile compounds that vaporize at a temperature much lower than combustion, exposing cannabis users to fewer toxicants as carbon monoxide [284, 285].

Heated air is drawn in, and the vaporized active compounds are inhaled and rapidly absorbed [286].

Cannabis vaporizers can heat dried buds or aerosolize the cannabinoids/terpenes for inhalation. Vaporizers represent the ideal choice for patients using medical cannabis as they pose a lower risk to health by not creating combustion products [282, 283, 287].

Patients describe better taste, stronger effects, and greater confidentiality in use (for example, reduced odor) compared to smoked cannabis [288, 289].

The data demonstrate that vaping results in fewer respiratory symptoms than conventionally smoked cannabis, but the long-term effects are still unclear [290].

Another available route of administration is the transdermal one. Topical products can be THC or CBD-dominant, with several possible formulations as lotions, gels, creams, ointments, and patches. Finally, new products have been introduced such as sublingual sprays which have the advantage of bypassing liver metabolism and rectal and vaginal suppositories [276, 279].

Medical cannabis has great therapeutic potential, but its use in clinical practice presents several problems.

First, pharmaceutical companies have little incentive to support large clinical trials because medical cannabis is not protected by any patent [291].

Obviously, the lack of clinical data discourages many clinicians from prescribing it, opting for other drugs. The forms of cannabis that have been approved for medical use are very expensive, and sometimes the pills are difficult for patients with dysphagia and nausea to consume. It has been argued that smoked cannabis is more effective as it crosses the blood-brain barrier quickly. Unfortunately, with this method of administration, it is difficult to determine the effective concentration of the active component [292, 293].

Scientific literature on appropriate dosing regimens for the medicinal use of cannabis is lacking. Carter et al. conducted a study highlighting the need for guidelines on the rational dosing of cannabis. They used the FDA-accepted guidelines on dronabinol prescribing as the basis for making natural cannabis dosing recommendations. The prescribed dose of dronabinol for appetite stimulation is 2.5 mg twice daily, to be taken before lunch and dinner. For nausea, vomiting, and pain, the dosage is 5 mg/m<sup>2</sup>. If the 5 mg dose is ineffective, incremental increases of 2.5 mg are recommended, up to a maximum of 15 mg. The same dose can be taken every 2–4 hours for a maximum of 4–6 doses per day. Regardless of the clinical problem, the maximum total recommended dose of dronabinol is 15 mg/m<sup>2</sup> four to six times per day or approximately 100 to 120 mg/day. Applying the known pharmacokinetics of cannabis, compared to a conservative dronabinol dosing model of 2.5 to 60 mg/day, they calculated doses for cannabis containing particular percentages of THC [294].

In addition to the problems mentioned above, often the medical use of cannabis is avoided due to the skepticism that can interest both uninformed patients and doctors. Indeed, a common obstacle to the use of cannabis is the fear of adverse effects on the nervous system, cardiorespiratory system, and mental health [295].

Long-term cannabis use is most closely related to risk of addiction [296, 297], dose-related cognitive changes, and possible long-term morpho functional brain alterations. Obviously, as happens with any drug, a conscious and accurate assessment of the risk-benefit ratio is necessary [298–300].

Furthermore, government restrictions and different laws in force between states can hinder its use [301].

A large survey of cannabis use in patients with ALS found that the main reason ALS patients did not use it was their inability to obtain it, whether for legal or financial reasons or lack of safe access [228].

In this review, we have examined the various therapeutic properties of cannabis to encourage its use where conventional therapies are not applicable.

Standardized and safe protocols are needed, which can only be obtained by increasing scientific research [302].

## 4. Limitations

There are several limitations in our review. Many aspects of the ALS pathophysiology and associated pain are not yet fully understood to enable therapeutic progresses. Furthermore, the different types of conducted studies may have created important evaluation biases. A longitudinal approach is needed in these patients to better understand the impact of ALS and pain from the earliest stages. Another major limitation in the progress of research in this medical-scientific field is the impact of the frailty of ALS patients on the ethically correct design of RCTs with placebo. Obviously, the nature of this pathology and the painful complex associated pain symptomatology prevents these fragile patients from being subjected to the use of placebos or from denying multidisciplinary assistance.



## 5. Conclusion

Patients with ALS can experience pain of various etiologies. Based on the available published works, pain should be considered as a symptom to be valued from the early stages of the disease. Fundamental is the development of standardized and specific pain assessment tools for patients with ALS. The heterogeneity of the pathophysiological mechanisms of pain requires at the same time a personalized and multidisciplinary clinical approach. Pain management also has positive psychological effects on ALS patients, thereby influencing the patient's and caregiver's quality of life. However, specific guidelines on pain management in ALS patients are not available, and the different potential pain treatments have not been subjected to randomized trials. Only full knowledge of this disease might allow to use the right pharmacological and nonpharmacological approaches, with the creation of guidelines uniformly accepted by the scientific community.

## Conflicts of Interest

The authors declare no financial or other conflict of interests.

## Authors' Contributions

VP, SDS, and MCP were responsible for the conceptualization. VP, SDS, PS, CA, MCP, FB, and MB wrote the manuscript. FC, MF, GC, and MBP reviewed and edited the manuscript.

## Acknowledgments

The authors wish to thank the support of the Dept. of Women, Child, General and Specialistic Surgery, University of Campania "L. Vanvitelli".

## Supplementary Materials

Table 1: pain assessment tool. (*Supplementary Materials*)

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