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Abstract

Significant advances have increased our understanding of the molecular mechanisms of amyotrophic lateral sclerosis (ALS), yet this has not translated into any greatly effective therapies. It appears that a number of abnormal physiological processes occur simultaneously in this devastating disease. Ideally, a multidrug regimen, including glutamate antagonists, antioxidants, a centrally acting anti-inflammatory agent, microglial cell modulators (including tumor necrosis factor alpha [TNF- α] inhibitors), an antiapoptotic agent, 1 or more neurotrophic growth factors, and a mitochondrial function-enhancing agent would be required to comprehensively address the known pathophysiology of ALS. Remarkably, cannabis appears to have activity in all of those areas. Preclinical data indicate that cannabis has powerful antioxidative, anti-inflammatory, and neuroprotective effects. In the G93A-SOD1 ALS mouse, this has translated to prolonged neuronal cell survival, delayed onset, and slower progression of the disease. Cannabis also has properties applicable to symptom management of ALS, including analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction. With respect to the treatment of ALS, from both a disease modifying and symptom management viewpoint, clinical trials with cannabis are the next logical step. Based on the currently available scientific data, it is reasonable to think that cannabis might significantly slow the progression of ALS, potentially extending life expectancy and substantially reducing the overall burden of the disease.

Keywords

cannabis, endocannabinoids, amyotrophic lateral sclerosis, clinical trials, motor neuron disease

Introduction

Amyotrophic lateral sclerosis (ALS), with an incident rate of 5 to 7 per 100 000 population, is the most common form of adult motor neuron disease.¹ Amyotrophic lateral sclerosis is a rapidly progressive neuromuscular disease that destroys both upper and lower motor neurons, resulting in weakness, spasticity, and ultimately death from respiratory failure. The vast majority of ALS cases are acquired and occur sporadically. Emerging evidence suggests that increased oxidative stress from free radical toxicity and/or excessive glutamate activity is what leads to motor neuron cell death in the brain and spinal cord.²⁻⁵ Inherited forms of the disease, which occur in approximately 5% to 10% of all patients with ALS, are largely because of mutations in the superoxide dismutase gene, presumably producing a marked increase in oxidative stress. Presentations of familial ALS have more variability than in sporadic ALS and are mutation specific with the most aggressive form because of the A4V mutation.⁵ Recent results have established that ALS also involves other nonneuronal cells including astroglia and microglia.^{6,7} Other putative mechanisms involved in motor neuron degeneration in ALS include

mitochondrial dysfunction, neuroinflammation, growth factor deficiency, and glutamate excitotoxicity.^{2,3}

Significant advances have been made regarding our understanding of the molecular mechanisms of ALS.⁸⁻¹² However, this has not yet translated into an effective therapeutic treatments. To date, the only food and drug administration- (FDA) approved therapy available for ALS is the antiglutamatergic agent Riluzole, which has limited therapeutic efficacy.¹⁰ Given

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this perspective, there remains an ongoing search for novel therapeutic approaches. There is increasing evidence that cannabinoids and manipulation of the endocannabinoid system may have beneficial disease-modifying potential in ALS.¹³⁻²¹ Moreover, the clinical effects of cannabis, the principal cannabinoid-producing botanical agent, have been reported to be useful in managing the symptomatology in ALS, as well as many other neurodegenerative disorders.²²⁻³⁴ Thus, significant efforts are now being directed at evaluating the role of the endocannabinoid system in the pathophysiology of ALS. In addition, there is an emerging body of science that points to a role of exogenous cannabinoids in both clinical symptom management and a positive disease-modifying effect.¹³⁻²¹

The Physiology and Pharmacology of Cannabinoids

Prior to the last decade, there was little known about the specific pharmacological and molecular effects of cannabis. However, important advances have taken place recently, which have greatly increased the understanding of the receptors and ligands composing the endogenous cannabinoid system.³⁵⁻⁵⁴ Research has shown that 2 major cannabinoid receptor subtypes exist, including the cannabinoid receptor, type 1 (CB1) subtype, which is predominantly expressed in the brain, and the cannabinoid receptor, type 2 (CB2) subtype, which is primarily found on the cells of the immune system.^{35,49,50} A variety of ligands for these receptors based on the cannabinoid structure have been synthesized and studied. Experiments performed with several types of neural cells that endogenously express the CB1 receptor suggest that activation of protein kinases may be responsible for some of the cellular responses elicited by these receptors.⁵¹ The discovery of the endocannabinoids, that is, endogenous metabolites capable of activating the cannabinoid receptors, and the understanding of the molecular mechanisms leading to their biosynthesis, release, and inactivation, have created a new area in research on the pharmaceutical applications of cannabinoid-based medicines.⁵² The characterization of endocannabinoids such as anandamide and the detection of widespread cannabinoid receptors in the brain and peripheral tissues suggest that the cannabinoid system represents a previously unrecognized ubiquitous network in the nervous system.

Cannabinoid receptors are G protein-coupled, 7-segment transmembrane proteins, similar to the receptors of other neurotransmitters such as dopamine, serotonin, and norepinephrine.^{51,52} Dense receptor concentrations are found in the cerebellum, basal ganglia, and hippocampus, likely accounting for the effect of exogenously administered cannabinoids on motor tone and coordination as well as mood state.⁵³⁻⁵⁵ Low concentrations are found in the brain stem, accounting for the low potential for lethal overdose with cannabinoid-based medicines.⁵⁶⁻⁵⁹ A growing number of strategies for separating sought-after therapeutic effects of cannabinoid receptor agonists from the unwanted consequences of CB1 receptor activation are emerging. Recently, ligands have been developed that

are potent and selective agonists for CB1 and CB2 receptors, as well as potent CB1—selective antagonists and inhibitors of endocannabinoid uptake or metabolism.⁶⁰ In addition, varieties of cannabis are known to contain a mix of partial cannabinoid agonists and antagonists, which can be rationally used. This knowledge may lead to the design of synthetic cannabinoid agonists and antagonists as well as cannabis strains with high therapeutic potential. The fact that both CB1 and CB2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system. Recent studies show that cannabinoids downregulate cytokine and chemokine production, both mechanisms that suppress inflammatory responses.⁶¹⁻⁶⁴ Manipulation of endocannabinoids (ie, via the use of exogenous cannabis) has great potential treatment viability against inflammatory disorders, including the inflammation seen in the central nervous system (CNS) of the patients with ALS. The potential use of cannabinoids as a novel class of anti-inflammatory agents may become one of the predominant indications, as that includes not only neuro-modulation but pain as well.^{65,66} Indeed, any number of inflammatory processes that are at least partially triggered by activated T cells or other cellular immune components could be treated with cannabis and other cannabinoid-based medicines.

Cannabinoids are chemically classified as terpenes. These are lipid-soluble hydrocarbons that function as major biosynthetic cellular messengers in many forms of life. Terpenes are widespread in plants and most species of animals as well, including humans. Any compound that resembles the basic terpenes structure, yet may be modified chemically via oxidation or other processes, is termed a terpenoid. Many hormones, including estrogens, are terpenoids, and share the same basic organic chemical structure as cannabinoids.^{53,54} All terpenes are organic, readily penetrate the highly lipophilic CNS.

Interestingly, tamoxifen, which is an antagonist of the estrogen receptor in breast tissue, is terpenoid and chemically resembles cannabinoids. Tamoxifen's primary use is as a FDA-approved drug for the treatment of breast cancer.⁶⁷⁻⁶⁹ However, phase II clinical trials of tamoxifen in ALS have now demonstrated preliminary efficacy and safety.⁶⁸ A phase 2B study demonstrated increased survival after 2 years in patients with ALS taking higher doses of tamoxifen, with no effect seen in 2 lower dose groups.⁶⁸ The 3 higher dose groups experienced a 4- to 6-month prolongation of survival over a 24-month trial, with no significant side effects observed.⁶⁸ Interestingly, glutamate uptake in cultured retinal cells is inhibited by tamoxifen, thus this mechanism may be part of a possible beneficial effect in ALS.⁶⁷ The chemical similarity between cannabinoids and tamoxifen points to a possible shared mechanism of action for neural protection.⁶⁹

The cannabis plant is a remarkably complex plant, with several phenotypes, each containing over 400 distinct chemical moieties.⁷⁰⁻⁷³ Approximately 70 of these are chemically unique and classified as cannabinoids.⁷⁰⁻⁷³ Delta-9 tetrahydrocannabinol (THC) and delta-8 THC appear to produce the majority of the psychoactive effects of cannabis.^{74,75} Delta-9 THC, the active ingredient in dronabinol (Marinol), is the most abundant

cannabinoid in the plant, which historically led researchers to erroneously hypothesize that it was the main source of the drug's impact. It is now known that other major plant cannabinoids, including cannabidiol and cannabinol, modify the pharmacology of THC and have distinct effects of their own. Cannabidiol is the second most prevalent of cannabis's active ingredients and may produce most of its therapeutic effects. Cannabidiol becomes THC as the plant matures and this THC over time breaks down into cannabinol. Up to 40% of the cannabis resin in some strains is cannabidiol.⁷² The amount varies according to plant. Some varieties of *Cannabis sativa* have been found to have no cannabidiol.⁷² Cannabidiol breaks down to cannabinol as the plant matures. Much less is known about cannabinol, although it appears to have distinct pharmacological properties that are quite different from cannabidiol. Cannabinol has significant anticonvulsant, sedative, and other pharmacological activities likely to interact with the effects of THC.⁷⁵⁻⁷⁸ Cannabinol may induce sleep and may provide some protection against seizures for epileptics.⁷⁸

Hypothetical Applications

Preclinical Studies of the Endocannabinoid System in ALS

The primary murine model for human ALS is the G93A-SOD1 mutant mouse, which is genetically engineered to replicate familial ALS.⁴ There is strong evidence in the G93A-SOD1 mouse model of ALS that the endocannabinoid system is involved, both directly and indirectly, in the pathophysiology of the disease. Several recent studies have highlighted this. Rossi et al¹⁷ investigated both excitatory and inhibitory synaptic transmission in the striatum of symptomatic G93A-SOD1 ALS mice, along with the sensitivity of these synapses to CB1 receptor stimulation. They reported a reduced frequency of glutamate-mediated spontaneous excitatory postsynaptic currents and increased frequency of GABA-mediated spontaneous inhibitory postsynaptic currents in recordings from striatal neurons in ALS mice. This is likely due to some presynaptic defects in transmitter release. The sensitivity of CB1 receptors in controlling both glutamate and GABA transmission was potentiated in ALS mice. This provides good evidence that adaptations of the endocannabinoid system might be involved in the pathophysiology of ALS. This is not inconsistent with current theories on pathophysiological mechanisms of ALS, which still remain largely a pathophysiologic enigma.⁷⁹⁻⁸³

Bilsland et al¹⁸ showed that treatment of postsymptomatic, 90-day-old SOD1G93A mice with a synthetic cannabinoid, WIN55,212-2, significantly delayed disease progression. Furthermore, genetic ablation of the fatty acid amide hydrolase (FAAH) enzyme, which results in raised levels of the endocannabinoid anandamide by preventing its breakdown, prevented the appearance of disease signs in 90-day-old SOD1G93A mice. Surprisingly, elevation of cannabinoid levels with either WIN55,212-2 or FAAH ablation had no effect on life span. Ablation of the CB1 receptor, in contrast, had no effect on disease onset in SOD1G93A mice but significantly extended life

span. Together, these results indicate that cannabinoids have significant neuroprotective and disease-modifying effects in this model of ALS and suggest that these beneficial effects may be mediated by non-CB1 receptor-based mechanisms.

It is now known that during active neurodegeneration from disease or trauma in the CNS, the concentration of tumor necrosis factor alpha (TNF- α) rises well above normal levels during the inflammatory response. Addition of exogenous TNF- α , both in vitro and in vivo, to neurons has been shown to significantly potentiate glutamatergic excitotoxicity. Thus, the discovery of drug targets reducing excess TNF- α expression may help protect neurons after injury. Zhao et al⁸⁴ investigated the neuroprotective role of the CB1 receptor after TNF- α exposure in the presence or absence of CB1 agonists. They demonstrated that CB1 activation blocks the TNF- α -induced increase in inflammation, thus protecting the neurons from damage. Thus, neuroprotective strategies which increase CB1 activity may help to reduce damage to motor neurons in ALS that are mediated by CNS inflammation.

Additionally, CB2 receptors are dramatically upregulated in inflamed neural tissues associated with CNS disorders, including ALS.⁸⁵ In G93A-SOD1 mutant mice, endogenous cannabinoids are elevated in spinal cords of symptomatic mice.²¹ Furthermore, treatment with nonselective cannabinoid partial agonists prior to, or on, symptom appearance minimally delays disease onset and prolongs survival through undefined mechanisms. Shoemaker et al¹⁴ demonstrated that messenger RNA (mRNA) levels, receptor binding, and function of CB2, but not CB1, receptors are dramatically and selectively upregulated in spinal cords of G93A-SOD1 mice in a temporal pattern paralleling disease progression. Daily injections of the selective CB2 agonist AM-1241, initiated at symptom onset, increased the survival interval after disease onset by 56%.¹⁴

Disease-Modifying Treatment of ALS

Clinical trials for ALS have been largely based on preclinical work using the G93A-SOD1 mouse. Unfortunately, translation of therapeutic success in mice to humans has proven quite difficult and a cure for ALS is not yet known. Many factors have been implicated in explaining the predominantly negative results of numerous randomized clinical trials in ALS, including methodological problems in the use of animal-drug screening, the lack of assessment of pharmacokinetic profile of the drugs, and methodological pitfalls of clinical trials in patients with ALS. Riluzole is currently the only agent approved by the FDA for the treatment of ALS.¹⁰ This drug inhibits the presynaptic release of glutamate and reduces neuronal damage in experimental models of ALS. Four controlled trials of a total of 974 riluzole-treated and 503 placebo-treated patients showed that it prolonged survival opposed to placebo, although the benefit was fairly modest.¹⁰ Because oxidative stress is one of the proposed pathogenic factors in ALS, antioxidants have been extensively tested, including vitamin E, vitamin C, coenzyme Q, B-carotene, *N*-acetylcysteine, and creatine, an amino acid naturally found in skeletal.¹¹ To date, trials of

neurotrophic factors, antioxidants, glutamate antagonists, and creatine have all failed to show any significant benefit in humans, although most had significant benefit shown in mice.¹¹ It is currently felt that a cocktail approach may be the ideal treatment strategy, including glutamate antagonists, antioxidants, and neurotrophic factors.⁶⁸ Recently, the kynurenine pathway (KP) has emerged as a potential target for ALS treatment.⁸ The KP is a major route for the metabolism of tryptophan, generating neuroactive intermediates in the process. These catabolites include the excitotoxic *N*-methyl-D-aspartate (NMDA) receptor agonist, quinolinic acid (QUIN), and the neuroprotective NMDA receptor antagonist, kynurenic acid (KYNA). These catabolites appear to play a key role in the communication between the nervous and immune systems and also in modulating cell proliferation and tissue function. Targeting the KP, hence, could offer a new therapeutic option to improve ALS treatment, and several drugs that block the KP are already under investigation.

Although other potential neuroprotective agents have been evaluated in randomized clinical trials, none have shown unequivocal benefit for the treatment of ALS. Thus, there remains an enormous need for more trials to test other putative disease-modifying therapies. As the effectiveness of such drugs can only be definitively established by large, costly, phase III randomized controlled studies, it is imperative that researchers target compounds that have potential benefit based on demonstrated pharmacological and physiological mechanisms.

There remains the possibility that ALS could represent a state of clinical endocannabinoid deficiency (CED).^{28,31} The endocannabinoid anandamide demonstrates dopamine-blocking and anti-inflammatory effects and is also tonically active in the periaqueductal gray matter.⁸¹ Endocannabinoids also modulate glutamatergic neurotransmission indirectly via NMDA receptors, and these pathways can be modulated to produce a clinical effect, such as reduction in motor tone, seizure threshold, and perception of pain and mood state.⁸²⁻⁹³ These clinical, biochemical, and pathophysiological patterns could reflect an underlying abnormality in the endocannabinoid system in ALS that could be potentially treated with exogenous cannabinoids, that is, via clinical use of cannabis or some derivative thereof.

Practical Applications

Symptom Management in ALS

As discussed previously, animal studies strongly suggest that the endocannabinoid system is implicated in the pathophysiology of ALS, either directly as part of the underlying disease mechanisms, or indirectly, inasmuch as this system plays a role in the homeostatic functioning of the neuromuscular system. Irrespective, it is clear that cannabinoids are able to slow down the progression of ALS in mice, likely by acting as an antioxidant, among other mechanisms.¹⁵⁻¹⁸ In addition to the neuroprotective effect, patients report that cannabis helps in treating symptoms of the disease, including alleviating pain

and muscle spasms, improving appetite, diminishing depression, and helping to manage sialorrhea (excessive drooling) by drying up saliva in the mouth.²⁴ Indeed, in a large survey it was noted that patients with ALS who were able to obtain cannabis found it preferable to prescription medication in managing their symptoms. However, this study also noted that the biggest reason patients with ALS were not using cannabis was their inability to obtain it, due to legal or financial reasons or lack of safe access.^{24,26}

There are many other clinical problems faced by patients with ALS that could be helped by cannabis. The majority of patients with ALS experience significant pain.²⁴ The pain is largely due to immobility, which can cause adhesive capsulitis, mechanical back pain, pressure areas on the skin, and more rarely, neuropathic pain.^{24,31} Pain in ALS is a frequent symptom especially in the later stages of disease and can have a pronounced influence on quality of life and suffering.⁹⁴⁻⁹⁸ Treatment of pain, therefore, should be recognized as an important aspect of palliative care in ALS. A recent Cochrane review of the evidence for the efficacy of drug therapy in relieving pain in ALS revealed no randomized or quasi-randomized controlled trials showing significant benefit. Despite the major pain problems encountered by patients with ALS, there are no clear guidelines and few randomized clinical trials about how to manage pain in ALS. However, as noted previously, the cannabinoids have been shown to produce an anti-inflammatory effect by inhibiting the production and action of TNF and other acute phase cytokines.³⁵ Additionally, cannabis may reduce pain sensation, likely through a brain stem circuit that also contributes to the pain-suppressing effects of morphine.⁹⁹ Cannabinoids produce analgesia by modulating rostral ventromedial medulla neuronal activity in a manner similar to, but pharmacologically distinct from, that of morphine.^{100,101} This analgesic effect is also exerted by some endogenous cannabinoids (anandamide) and synthetic cannabinoids (methanandamide) and may be prevented by the use of selective antagonists.¹⁰²⁻¹⁰⁴ Thus, cannabinoids are centrally acting analgesics with a different mechanism of action than opioids, although the analgesia produced by cannabinoids and opioids may involve similar pathways at the brain stem level.¹⁰³⁻¹⁰⁵

There are now multiple, well-controlled clinical studies using cannabis to treat pain, showing ample evidence of analgesic efficacy.¹⁰⁶ A recent systematic review and meta-analysis of double-blind randomized controlled trials that compared any cannabis preparation to placebo among participants with chronic pain showed a total of 18 completed trials. The studies indicate that cannabis is moderately efficacious for the treatment of chronic pain.¹⁰⁶ In the setting of ALS, the medications should be titrated to the point of comfort. Concomitant use of narcotics may also be beneficial because, as noted above, the opioid receptor system is distinct from the cannabinoid system. In that regard, the antiemetic effect of cannabis may help with the nausea sometimes associated with narcotic medications.

In addition to pain, spasticity is also a major problem for patients with ALS. Spasticity in ALS is induced both at the

motor cortex and at the spinal cord level through the loss of motor neuron inhibition.¹⁰⁷⁻¹¹⁰ Cannabis has an inhibitory effect via augmentation of γ -amino-butyric acid (GABA) pathways in the CNS.¹¹¹ This produces motor neuron inhibition at spinal levels in mice. Several past studies have suggested that cannabinoid therapy provide at least a subjective reduction of spasticity, although virtually all of the studies have been done in patients with multiple sclerosis (MS).^{29,112} A survey study has shown that patients with ALS do subjectively report that cannabis helps alleviate symptoms of spasticity.²⁴

In addition to pain and spasticity, there are other pharmacological effects of cannabis that may be useful for patients with ALS. Patients with ALS and bulbar symptoms also usually have difficulty controlling and swallowing the saliva that is normally present in the oral cavity.¹¹³ Cannabis is a potent anti-salivatory compound that swiftly dries the oral cavity and upper airway, potentially reducing the risk of aspiration pneumonia and increasing patient comfort.^{22,24}

Cannabis also increases appetite and may help prevent "ALS cachexia," a phenomenon experienced by some patients where weight loss occurs in excess of that caused by muscle atrophy and reduced caloric intake.¹¹⁴⁻¹¹⁶ In addition to improving appetite, cannabis appears to also help with mood state and sleep. Patients with ALS previously have reported that cannabis is at least moderately effective at reducing symptoms of pain, spasticity, drooling, appetite loss, and depression.²⁴

Cannabinoids will vaporize at temperatures in the range of 200°F and can be inhaled via a hot mist.¹¹⁷⁻¹¹⁹ This delivers the cannabinoids rapidly, allowing for ease of titration and letting patients with ALS having severe dysarthria rapid access to the drug's effects. Vaporizing also helps dry up oral secretions.²⁴ Cannabis may also be ingested orally or through a feeding tube, although absorption is much slower. Cannabis can be titrated to desired effect, with individual, patient-specific dosing.¹²⁰⁻¹²² In terms of clinical trials for disease-modifying effects, dosing paradigm would be more complex. Fortunately, the low toxicity of cannabis would allow for trail and error. Based on the available studies, a typical dosing range for clinical effects would likely be 1 to 2 g/d of cannabis, with an average THC content of 20% by weight.¹²²

A Call for Clinical Trials

In terms of symptoms management, cannabis is a substance with many pharmacological properties that are directly applicable to the clinical care of patients with ALS. These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, sleep induction, and mood elevation.²⁴ From a pharmacological perspective, cannabis is remarkably safe with realistically no possibility of overdose or frank physical addiction. There is a valid, logical, scientifically grounded rationale to support the use of cannabis in the pharmacological management of ALS. Indeed, cannabis, as a single compound, could potentially replace and provide the benefits of multiple standard medications, including analgesics, antispasmodics, anxiolytics, antidepressants, appetite stimulants, and agents

used to dry the mouth (typically anticholinergic medications). There is ample clinical evidence to warrant the empiric use of cannabis to manage the symptoms of ALS.

From an experimental, disease-modifying perspective, it is not likely that a single mechanism agent would treat all of the abnormal physiological processes occurring simultaneously in this devastating disease.¹²³⁻¹²⁷ Thus, some experts are now advocating for a combination drug approach to slowing the progression of ALS.⁸⁰ Based on what is known about the pathophysiology of ALS, a multidrug regimen would include glutamate antagonists, antioxidants, a CNS anti-inflammatory agent, a microglial cell modulators, including TNF- α inhibitors, an antiapoptotic agent, 1 or more neurotrophic growth factors, and a mitochondrial function-enhancing agent.^{127,128} Remarkably, cannabinoids appear to have at least some activity in all of those categories.¹²⁹⁻¹³¹ Moreover, there is a particularly strong, growing, body of preclinical data indicating that cannabis has powerful antioxidative, anti-inflammatory, and protective neuromodulatory effects.¹³²⁻¹³⁵ In the G93ASOD1 ALS mouse, this has translated to prolonged neuronal cell survival.^{15,16,18,43}

There is an overwhelming amount of preclinical and clinical evidence to warrant initiating a multicenter randomized, double-blind, placebo-controlled trial of cannabis as a disease-modifying compound in ALS. Secondary outcome measures could include clinical management, with end points such as pain scores, quality-of-life measures, and so on. Developing a multicenter clinical research trial using cannabis would pose many unique barriers that would have to be overcome. Inasmuch as there is no commercial manufacturer of cannabis, the study would have to be funded either by the federal government or privately. Presumably, there would be no industry funding. Obtaining the trial drug would require the investigators to gain access to a large, reliable supply of cannabis that is legal for medical research. At present, the only source of cannabis that can be legally used in research in the United States is through the National Institute on Drug Abuse (NIDA). National Institute on Drug Abuse provides low-potency material and makes the cannabis available only to projects it approves. National Institute on Drug Abuse supplies cannabis with a THC content, by weight, of 2% to 4% typically, although it has supplied cannabis with an 8% by weight THC content on occasion.^{136,137} The average THC content of cannabis at randomly surveyed medical cooperatives in California is approximately 15% to 20%.^{26,117,121} Thus, an independent source of cannabis would be needed to ensure a consistently high cannabinoid content that may be strong enough to possibly alter the disease progression. An independent cannabis source would also allow investigators to avoid NIDA's arbitrary and lengthy review process that it mandates before providing any cannabis for research. Historically, NIDA has derailed clinical trial plans by refusing to supply cannabis, even after the research protocols were approved by the FDA.¹¹⁷ Nonetheless, it is possible, with coordinated effort, to effectively do double-blind, randomized, placebo-controlled clinical trials with cannabis.¹³⁸⁻¹⁴¹ To properly evaluate both subjective and objective

effects, cannabinoid blood levels should be followed as well, to further ensure adequate data for a dose–response curve.

Clinical trials with cannabis would also address the issue of single versus multiple drug clinical trials. Arguable, multiple drug trials would increase the chances of success but also exponentially increase the difficulty of completing the trial and analyzing the data. Cannabis, as a single agent, in essence provides the advantages of a multiple drug trial due to its multiple mechanisms of action. Cannabis is a unique compound that possesses significant internal therapeutic synergy. The search for the underlying cause of ALS continues.^{142,143} With respect to treatment, from both a symptom management and disease modifying viewpoint, the logical next step, based on the available science, would be clinical trials with cannabis. Although not expected to be necessarily curative, it is not unreasonable to think that cannabis might significantly slow the progression of ALS, potentially extending life expectancy and substantially reducing the overall burden of the disease.

Declaration of Conflicting Interests

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