Amyotrophic Lateral Sclerosis

ISSN: 1748-2968 (Print) 1471-180X (Online) Journal homepage: https://www.tandfonline.com/loi/iafd19

ALSUntangled No. 16: Cannabis

The ALSUntangled Group

To cite this article: The ALSUntangled Group (2012) ALSUntangled No. 16: Cannabis, Amyotrophic Lateral Sclerosis, 13:4, 400-404, DOI: 10.3109/17482968.2012.687264

To link to this article: https://doi.org/10.3109/17482968.2012.687264

Published online: 28 May 2012.

Amyotrophic Lateral Sclerosis, 2012; 13: 400–404

informa
healthcare

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Introduction

In a widely viewed series of Internet videos called "Surviving ALS," Cathy Jordan reports that regularly smoking cannabis has dramatically slowed her ALS progression, and improved her mood and appetite (see for example http://www.youtube.com/watch?v = -kf8wTBiUDU). Indeed, cannabinoids and manipulation of the endocannabinoid system may well have disease-modifying potential in ALS (1–9). Moreover, cannabis could potentially be useful in managing the symptomatology in ALS (10–13). Here, on behalf of PALS who are asking about it, we critically review the evidence for cannabis in ALS.

What Is Cannabis?

Cannabis is a remarkably complex plant. There are several existing phenotypes, with each containing over 400 distinct chemical moieties (14–22). Approximately 70 are chemically unique and classified as plant cannabinoids (14–17). Cannabinoids are lipophilic 21 carbon terpenes, biosynthesized predominantly via a recently discovered deoxyxylulose phosphate pathway (14). Delta-9 tetrahydrocannabinol (THC) and delta-8 THC appear to produce the majority of the psychoactive effects of cannabis (18,19). Delta-9 THC, the active ingredient in dronabinol (Marinol) is the most abundant cannabinoid in the plant and this has led researchers to hypothesize that it is the main source of the drug's impact. However, other major plant cannabinoids, including cannabidiol and cannabinol, may 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 effects at moderate, mid range doses. Cannabidiol becomes THC as the plant matures and THC over time breaks down into cannabinol. Up to 40% of the cannabis resin in some strains is cannabidiol (16). The amount varies according to plant. Some varieties of Cannabis sativa have been found to have no cannabidiol (16). Cannabidiol appears to modulate and reduce untoward effects of THC (18). Cannabidiol breaks down to cannabinol as the plant matures. Much less is known about cannabinol, although it appears to have distinct pharmacological properties from cannabidiol. Cannabinol has anticonvulsant, sedative, and other pharmacological activities likely to interact with the effects of THC (19–22). Cannabinol may induce sleep and may provide some protection against seizures for epileptics (22).

Cannabis Receptors and Endogenous Ligands

Recent advances have increased understanding of the receptors and endogenous ligands composing the cannabinoid system (23–36). Two major cannabinoid receptor subtypes exist: CB1 is predominantly expressed in the brain, and CB2 is primarily found on the cells of the immune system (23,37–39). Both receptors are G protein-coupled, 7-segment transmembrane proteins, similar to the receptors of dopamine, serotonin, and norepinephrine (39,40). Dense cannabinoid 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 (41–43). Low concentrations are found in the brainstem, perhaps accounting for the low potential for lethal overdose with cannabinoid-based medicines (44–47).

The discovery of endocannabinoids, (i.e. endogenous metabolites capable of activating the cannabinoid receptors), and an improved understanding of the molecular mechanisms leading to their biosynthesis, release, and inactivation, have inspired research on the pharmaceutical applications of cannabinoid-based medicines (40). 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. Ligands have been developed that are potent and selective agonists for CB1 and CB2 receptors, potent CB1 selective antagonists, and inhibitors of endocannabinoid uptake or metabolism (48). Distinct varieties of cannabis contain different combinations of partial cannabinoid agonists and antagonists, which could be utilized in designing synthetic cannabinoid

ISSN 1748-2968 print/ISSN 1471-180X online
DOI: 10.3109/17482968.2012.687264

agonists and antagonists as well as cannabis strains with high therapeutic potential.

Why Might Cannabis Work in ALS?

The fact that CB2 receptors have been found on immune cells suggests that cannabinoids play a role in the regulation of the immune system. Indeed, recent studies show that cannabinoids can down regulate cytokine and chemokine production, which in turn suppresses inflammatory responses (49–52). Since the pathophysiology of ALS may involve neuroinflammation (53,54), agents such as cannabinoids that modulate this process could potentially be useful.

Alternatively, or in addition, cannabinoids might act similarly to tamoxifen, a Food and Drug Administration (FDA)-approved drug used to treat breast cancer (55–57). Both cannabinoids and tamoxifen are terpenes, organic, lipid soluble compounds that readily penetrate the CNS (55). In a 60 patient pilot study, PALS taking tamoxifen reportedly had improved survival and no significant side effects (56); unfortunately this study has yet to be published so it cannot be peer reviewed. A follow up study is underway (http://www.clinicaltrials.gov/ct2/show/NCT01257581? term = tamoxifen + als&rank = 1). Tamoxifen may affect ALS by modulating inflammation, or by altering glutamate uptake (55). Endocannabinoids can also modulate glutamatergic neurotransmission indirectly via NMDA receptors (33,34,36).

What Relevant Animal Data Exists in ALS?

Beyond the theoretical, observations in mice support the idea that the endocannabinoid system might be involved in the pathophysiology of ALS. Endogenous cannabinoids are elevated in spinal cords of symptomatic G93A-SOD1 mice (9). mRNA levels, receptor binding, and function of CB2, but not CB1, receptors are dramatically and selectively up-regulated in spinal cords of G93A-SOD1 mice in a temporal pattern paralleling disease progression (2). The sensitivity of CB1 receptors in controlling both glutamate and GABA transmission is potentiated in the striatum of symptomatic G93A-SOD1 ALS mice (5).

Other animal studies suggest that treatment with cannabinoids could be useful. Treatment with Delta(9)-THC at onset of tremors delayed motor impairment and prolonged survival in G93A-SOD1 mice (58). Daily injections of the selective CB2 agonist AM-1241, initiated at symptom onset in G93A-SOD1 ALS mice, increased survival after disease onset by 56% (2). Treatment of post symptomatic, 90-day-old G93A-SOD1 mice with a synthetic cannabinoid, WIN55,212–2, improved motoneuron survival and muscle force at 120d although this did not improve overall survival (6). Genetic ablation of the (Fatty Acid Amide Hydrolase) FAAH enzyme, which results in raised levels of the endocannabinoid anandamide by preventing its breakdown, delayed disease onset in G93A-SOD1 ALS mice but did not affect survival (6). Ablation of the CB1 receptor had no effect on disease onset in G93A-SOD1 ALS mice but significantly extended life span. These animal studies all have significant methodological flaws, including small sample size, lack of randomization and lack of blinding.

What Are the Efficacy, Safety and Costs of Cannabis in Human ALS?

A small randomized, double-blind placebo-controlled crossover trial of oral THC at 5mg twice daily was conducted in PALS, with the goal of improving cramps. (59). While this was well-tolerated, there was no effect on cramp frequency or intensity, or on secondary outcome measures including fasciculation frequency, quality of life, sleep or depression. This 27 patient trial may well have been underpowered for some of these outcomes. A small trial of dronabinol in PALS was previously published as an abstract and indicated good tolerability (11). However Dronabinol is 100% Delta-9 THC, the most psychoactive ingredient in cannabis. Natural cannabis contains, at best, 20% THC. There are varying physiological effects when the other cannabinoid forms are present, as is the case with natural cannabis plant material. Moreover, while glutamate toxicity is reduced by both CBD (cannabadiol - nonpsychoactive), and THC, the neuroprotection observed with CBD appears greater than THC (60–62). Most patients find dronabinol too sedating and associated with too many psychoactive effects (63–66). Dronabinol is not an appropriate substitute for cannabis in this setting.

Within the PatientsLikeMe online community, 48 members with ALS reported taking cannabis in a variety of forms, durations and dosages. Benefits described included improved speech, swallowing, secretions, fasciculations, appetite, sleep and mood. Side effects included dry mouth, clumsiness, dizziness, pneumothorax and sore throat.

What Would be Needed to Test Cannabis in Human ALS Clinical Trials?

Doing multi-center clinical research trials for PALS using cannabis would pose many unique barriers. First of all there is no commercial manufacturer of cannabis, thus these studies would have to be funded either by the federal government or privately, as it is not likely there would be 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). Unfortunately NIDA provides low-potency material, and makes the cannabis available only to projects it approves.

NIDA supplies cannabis with a THC content, by weight, of 2–4% typically, although it has supplied cannabis with an 8% by weight THC content on occasion (67). Although THC is not the ideal target compound per se, it is a relative indicator of potency and quality. For comparison, the average THC content of cannabis at randomly surveyed medical cooperatives in California is approximately 15 to 20% (68). 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 (69,70). Nonetheless, it is possible, with coordinated effort, to effectively do double-blind, randomized, placebo controlled clinical trials with cannabis. 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. Mode of drug delivery could be via vaporization, which would allow for dosing standardization (71,72).

Another interim option would be clinical trials with Sativex®, a product from GW Pharmaceutical company in the UK. Sativex is a natural cannabinoid pharmaceutical product, administered as an oral spray absorbed by the patient's mouth. The drug is obtained from natural cannabis and standardized by weight to be 50% THC and 50% cannababidiol (CBD)(73). This makes it a much better choice than Marinol (dronabinol). Yet this is not as desirable as natural cannabis, which contains a multitude of other therapeutic cannabinoids, many of which are not psychoactive, such as cannabinol (CBN). One of the ALSUntangled team (GTC) has tried to get GW to pursue this but has not had success to date, with the company decision being based on financial information. GW Pharma openly acknowledges that it needs a large patient base to be financially viable and is thus targeting multiple sclerosis (MS). Finally Sativex is not available as of yet in the United States.

Conclusions

Cannabis has biological properties including immunomodulation and effects on excitototoxicity that suggest it could be useful in ALS. Evidence from small, non-randomized, unblinded animal studies suggest that it could potentially slow ALS progression, and anecdotal reports suggest that it could ameliorate troubling ALS symptoms. Given all this, ALSUntangled supports further careful study of cannabis and cannabinoids, the active ingredients contained therein. Natural cannabis, as a single agent, provides advantages similar to a multiple drug trial given its numerous mechanisms of action. A possible next step would be a small case series of well-characterized PALS using cannabis at controlled dosages that could potentially be monitored by blood levels of cannabinoids, compared to matched controls, performed in a geographic area where it would be legal.

The ALSUntangled Group currently consists of the following members: Gregory Carter, Richard Bedlack, Orla Hardiman, Lyle Ostrow, Edor Kabashi, Tulio Bertorini, Tahseen Mozaffar, Peter Andersen, Jeff Dietz, Josep Gamez, Mazen Dimachkie, Yunxia Wang, Paul Wicks, James Heywood, Steven Novella, LP Rowland, Erik Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Alex Sherman, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Marigakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Terry Heiman-Patterson, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula. Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

Disclosures: ALSUntangled is sponsored by the Packard Center and the Motor Neurone Disease Association.

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