Medical Marijuana Program

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Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]		
Home Address (including Apartment or Suite #): [redacted]		
City: [redacted]	State: CT	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]	

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

Huntington's disease

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

see attached

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

see attached

Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

see attached

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

see attached

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

see attached

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

see attached

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

see attached

Section J: Submission of Petition
In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so. • Attach additional pages as necessary.
see attached

I hereby certify that the above information is correct and complete.	
My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration.	
Signature: ▶ [redacted]	Date Signed: 12/4/2020

Attachment to Medical Marijuana Program

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

Section C: Background

Huntington Disease (HD) is an inherited progressive neurodegenerative disorder characterized by choreiform movements, psychiatric problems, and dementia. It is caused by a CAG trinucleotide repeat expansion in the huntingtin (HTT) gene on chromosome 4p and inherited in an autosomal-dominant pattern. There is no known cure, and the treatment is focused only on alleviating the symptoms of the disease. The estimated prevalence of HD is 5 to 8 per 100,000 population in Europe and North America. HD causes chorea (involuntary writhing movements of the head, body, and limbs), psychiatric illness, and dementia. Additional symptoms include depression, anxiety, behavioral changes, gait and coordination difficulties, weight loss, cachexia, and impairment of insight or judgement.[i]

Section D: Negative Effects of Current Treatment

There is no cure for HD, and there is no treatment that will reverse or stop the course of the disease. The treatments that exist only help to alleviate some symptoms and provide supportive care for patients and their families. Tetrabenazine and deutetrabenazine are the only medications that have been FDA-approved for use in HD to reduce choreiform movements associated with the disease. Side effects include depression, suicidality, drowsiness, fatigue, insomnia, restlessness, anxiety, irritability, nausea, diarrhea, loss of appetite, headache, bruising, and parkinsonism.[ii] [iii]

[ii] https://medlineplus.gov/druginfo/meds https://medlineplus.gov/druginfo/meds/a618009.html https://medlineplus.gov/druginfo/meds/a617022.html

iii Koch J, Shi WX, Dashtipour K. VMAT2 inhibitors for the treatment of hyperkinetic movement disorders. *Pharmacol Ther*. 2020;212:107580. doi:10.1016/j.pharmthera.2020.107580

Section E: Negative Effects of Condition or Treatment

Negative Effects of Condition- Huntington disease is a debilitating, rapidly progressive neurodegenerative condition that is inevitably fatal. Average life expectancy from the time of onset of symptoms is 10-20 years. People with HD live with involuntary twitching of the arms, legs, trunk and face, referred to as chorea, as well as sustained painful muscle contractions and spasms called dystonia. These involuntary spasms and movements are incessant, relentless, and get worse over time. Furthermore, HD also causes gait, balance and coordination problems that can lead to an inability to maintain activities of daily living, such as dressing, toileting, feeding oneself, and even walking independently. Eventually, many people with HD become wheelchair or bed bound. In addition to these physical abnormalities, people with HD also suffer from significant depression, anxiety, decreased motivation or apathy, trouble sleeping, loss of appetite, nausea, weight loss and suicidality, which can all further hasten disability and death.[iv]

Negative Effects of Treatment- See section D. There is poor evidence in management of HD today. The analysis of the twenty level-I studies fails to result in any treatment recommendation of clinical relevance. High-quality RCT are highly warranted to advance HD treatment in clinical practice. [v]

Section F: Conventional Therapies

See Section D on medications that are used to treat symptoms of HD. In additional to medications listed, other interventions used to manage the symptoms of HD include antidepressants to help with depression and anxiety, physical therapy to improve strength, balance, and walking, occupational therapy to try to help with dexterity and activities of daily living, speech therapy for communication and swallowing difficulties, acupuncture to alleviate pain and muscle strain, botulinum toxin injections into muscles affected by dystonic muscle contractions, and psychotherapy and counseling to address mood problems and assist patients and their family members navigate the challenges inherent to the disease. [vi]

Section G: General Evidence of Support for Medical Marijuana Treatment

THC's chemical structure is similar to the brain chemical anandamide. Because of this similarity, THC is able to attach to structures called cannabinoid receptors on neurons in specific brain areas and activate them. In early research, THC binding to the cannabinoid receptors has been shown to improve motor function and slow disease progression in animal models of HD. THC, acting through cannabinoid receptors, also activates the brain's reward system, which includes regions that govern the response to healthy pleasurable behaviors such as sex and eating. Like most other drugs that people misuse, THC stimulates neurons in the reward system to release the signaling chemical dopamine, and can improve a person's mood, appetite and overall sense of enjoyment and well-being.[vii]

The impression in the general population is that cannabis is helpful for a few of the symptoms that can be debilitating in Huntington disease: loss of appetite, nausea, anxiety, and insomnia. There are a number of articles online supporting its use for these symptoms, but not necessarily specifically in HD. A few of these articles are referenced here. There is an extensive discussion of the potential role of medical cannabis to stimulate appetite and decrease nausea by inhibiting the production of leptin which contributes to suppressing appetite, and by activating CB1 receptors, respectively.[viii] As regards anxiety, it is reported that cannabidiol helps to reduce anxiety, but tetrahydrocannabinol can exacerbate this.[ix] As such, it is important to use regulated formulations of medical marijuana when trying to manage anxiety. Lastly, cannabis as a medicinal herb has been widely used for sleep induction for decades. One study published in 2019 found that among cannabis users who said they were using cannabis to improve sleep, 84% said it was "very" or "extremely" helpful. And 83% of people who reported having used over-the-counter sleep medications in the past were able to either reduce or eliminate those drugs from their routines, when they began using cannabis for sleep.[x]

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

According to "Medical Marijuana in Huntington's Disease: Report of Two Cases" by Meisel and Friedman, the authors hypothesized that marijuana provided psychological or physical relief of the patient's HD symptoms. Patients were assessed while taking medical marijuana, and then reassessed after not taking medical marijuana for 48 hours. The study showed that subjects had less anxiety, less depression, and minor improvement in their motor examination while using medical marijuana.[xi]

THC has also been investigated as a potential treatment for dystonia (sustained painful muscle contractions, which can be present in HD). According to an article titled "Marijuana as Medicine? The Science Beyond the Controversy" published in the journal Marijuana and Neurological Disorders: No

controlled study of marijuana in patients with dystonia has yet been published. Cannabidiol, a chemical component of marijuana was tested in a preliminary open trial in which patients knew they were receiving the experimental drug. The five participants showed only modest improvements, which increased with the amount of drug they received. Better results occurred in a study of an animal model for dystonia—a mutant strain of hamsters—in which researchers tested a synthetic cannabinoid that activates the same cellular receptors as THC. The hamsters exhibited a type of dystonia that produces either sudden spasms of rapid, jerky motions or slow, repetitive writhing movements, both of which decreased under the influence of the cannabinoid.[xii]

One important application of the use of medical marijuana in treating HD patients could be its role as an appetite stimulant. According to Huntington's Disease Society of America website, "Research has shown that people with Huntington's Disease often have a lower than average body weight for height and may have higher than average calorie needs. This may be due to chorea, metabolic changes, or some other factor yet undiscovered. There is also some evidence that maintaining a body weight slightly above "desirable" weight will facilitate control of the disease. Therefore, people with HD should be encouraged to eat and every effort should be made to make eating enjoyable. When it is no longer possible for the person with HD to meet his or her nutritional needs with an oral diet, enteral feedings (tube feeding) may be considered. Tube feedings may be given as a supplement to an oral diet, to provide extra fluids in case of swallowing difficulty, or as a sole means of nutritional support."

Medical cannabis is well known as an appetite stimulant. The exact mechanism is unknown, but it is thought to increase food intake by boosting appetite, tricking the brain into thinking that one is hungry, and increasing appreciation of food. Regardless of the mechanism, medical marijuana can increase caloric intake in HD patients, increasing their quality of life, and delaying the need for a feeding tube, which can create numerous complications (surgical procedure, risk of infection, and risk of tube displacement due to the increased movements of HD.) FDA approved formulations of cannabidiols are used extensively for weight loss, nausea and cachexia associated with cancer.[xiii]

As regards anxiety, a study of 24 people with social anxiety disorder found that they had less anxiety in a simulated public speaking test after taking CBD than after taking a placebo. Four studies have suggested that cannabinoids may be helpful for anxiety in people with chronic pain; the study participants did not necessarily have anxiety disorders.

On the other hand, lastly, as regards the use of medical marijuana for the motor symptoms of HD, only 3 studies were noted in a systematic review of the literature with small number of study participants, and these showed conflicting results regarding benefit.[xiv]

Section I: Professional Recommendations for Medical Marijuana Treatment

See attached letter of support from petitioner's primary neurologist, Dr. [redacted], a Movement Disorders specialist with extensive experience in caring for people with Huntington disease.

Section J: Submission of Petition

There is little scientific data in terms of large-scale double-blind placebo-controlled studies studying the effect of medical marijuana in HD patients. It is difficult to find physicians who are able to provide letters of evidence of proof that medical marijuana helps patients with HD simply because there

are so few HD patients overall, and due to the lack of scientific data. Letters would mostly be able to provide anecdotal support. According to the AAN (American Academy of Neurology), medical marijuana for neurologic conditions has been more extensively studied in multiple sclerosis and epilepsy. Patients with HD exhibit many of the same symptoms as patients with MS including muscle spasticity, weakness, fatigue, anxiety, and decreased appetite. It is possible that given the similarity of symptoms, patients with HD may also benefit from the effects of medical marijuana in terms of increasing appetite, reducing pain, reducing muscle spasms, and decreasing anxiety, all of which would potentially improve the quality of life for patient who suffer from this debilitating, progressive neurodegenerative disease.

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[i] Paulson HL, Albin RL. Huntington's Disease: Clinical Features and Routes to Therapy. In: Lo DC, Hughes RE, editors. Neurobiology of Huntington's Disease: Applications to Drug Discovery. Boca Raton (FL): CRC Press/Taylor & Francis; 2011. Chapter 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56000/

[ii] https://medlineplus.gov/druginfo/meds https://medlineplus.gov/druginfo/meds/a618009.html https://medlineplus.gov/druginfo/meds/a617022.html

[iii] Koch J, Shi WX, Dashtipour K. VMAT2 inhibitors for the treatment of hyperkinetic movement disorders. *Pharmacol Ther*. 2020;212:107580. doi:10.1016/j.pharmthera.2020.107580

[iv] Suchowersky, O., 2020. *Uptodate*. [online] Uptodate.com. Available at: <https://www.uptodate.com/contents/huntington-disease-clinical-features-and-diagnosis> [Accessed 19 August 2020].

[v] Bonelli RM, Wenning GK. Pharmacological management of Huntington's disease: an evidence-based review. *Curr Pharm Des*. 2006;12(21):2701-2720. doi:10.2174/138161206777698693

[vi] Bachoud-Lévi, Anne-Catherine, et al. International Guidelines for the treatment of Huntington's Disease. *Frontiers in neurology* 10 (2019): 710.

[vii] Jaffe, Adi. THC for Huntington's disease? CB1 receptors important for more than drug use. https://www.psychologytoday.com/ca/blog/all-about-addiction/201102/thc-huntingtons-disease-cb1-receptors-important-more-drug-use. Posted Feb 25 2011

[viii] Verbora, D., 2020. *How Does Medical Cannabis Stimulate Appetite? - Canabo Medical Clinic*. [online] Canabo Medical Clinic. Available at: <https://www.canabomedicalclinic.com/how-does-medical-cannabis-stimulate-appetite/> [Accessed 31 August 2020].

[ix] Salerno L, Lieblich S, et al. https://www.anxiety.org/is-cannabis-an-effective-treatment-for-anxiety-what-research-shows. Sept 3 2019.

[x] Breuss, Michael. https://thesleepdoctor.com/2020/02/04/does-cannabis-help-insomnia/. Feb 4 2020.

[xi] Meisel, K. and Friedman, J., 2012. Medical Marijuana in Huntington's Disease: Report of Two Cases. *Medicine and Health Rhode Island*, 95(6), p.178.

[xii] Mack A, Joy J. Marijuana as Medicine? The Science Beyond the Controversy. Washington (DC): National Academies Press (US); 2000. 8, MARIJUANA AND NEUROLOGICAL DISORDERS. Available from: https://www.ncbi.nlm.nih.gov/books/NBK224385/

[xiii] Kasvis P, Vigano M, Vigano A. Health-related quality of life across cancer cachexia stages. *Ann Palliat Med*. 2019;8(1):33-42. doi:10.21037/apm.2018.08.04

[xiv] Lim K, See YM, Lee J. A Systematic Review of the Effectiveness of Medical Cannabis for Psychiatric, Movement and Neurodegenerative Disorders. *Clin Psychopharmacol Neurosci*. 2017;15(4):301-312. doi:10.9758/cpn.2017.15.4.301

**** See attached PDF files for actual references ****

Hartford HealthCare

Ayer Neuroscience Institute

Chase Family Movement Disorders Center

Section I: Professional Recommendations for Medical Marijuana Treatment

September 18, 2020

Board of Physicians
Medical Marijuana Program, State of Connecticut
450 Columbus Blvd, Suite 901,
Hartford, CT 06103-1840

Dear Sirs/Madams:

This letter is written in support of the petition filed with the Medical Marijuana Program by my patient, [redacted], who seeks to add Huntington disease (HD) to the list of debilitating conditions for which medical marijuana is approved for use in the State of Connecticut. I helped Mr. and Mrs. [redacted] prepare the information and references necessary to fill out the application form for the Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions in the Medical Marijuana Program of the State of Connecticut. As would be noted in that application, there have been a number of scientific papers published in peer-reviewed medical journals that would support the potential utility of medical marijuana in the treatment of the symptoms of HD.

Keeping in mind that HD is a relentlessly disabling and inevitably fatal neurodegenerative condition with no cure, any treatment option that can relieve even just some of the debilitating symptoms associated with the disease would have a significant impact on the patient's quality of life. Further considering that the life expectancy of someone who has been diagnosed with HD is 10 to 20 years from the onset of symptoms, there is a definite urgency to this request on behalf of Mr. [redacted] and many other Connecticut residents who are living with this terrible disease. I implore this committee to look favorably upon this petition and consider Mr. [redacted] request.

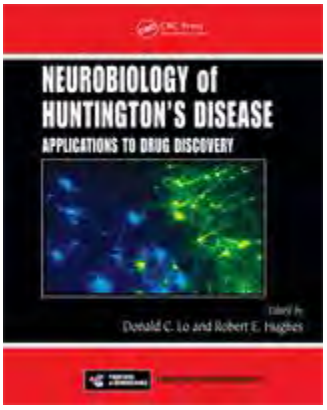
Please feel free to contact me with any further questions or concerns.

Respectfully,

[redacted], *M.D.*

[redacted], M.D.

Section C i



Neurobiology of Huntington's Disease: Applications to Drug Discovery.

Chapter 1Huntington's Disease

Clinical Features and Routes to Therapy

Henry L. Paulson and Roger L. Albin.

OVERVIEW

In 1872, physician George Huntington reported a familial form of chorea noted previously on Long Island by his father and grandfather, also physicians. More than a century later his comments about the disease now carrying his name, Huntington's disease (HD), remain a clear description of its major clinical features (Huntington, 1872; reprinted in Huntington, 2003). Huntington described chorea in general as the "dancing propensities of those … affected," in whom there "seems to exist some hidden power, something that is playing tricks, as it were, upon the will." The familial form started "as an ordinary chorea might begin, by the irregular and spasmodic action of certain muscles as of the face, arms, etc. These movements gradually increase when muscles hitherto unaffected take on the spasmodic action…."

The disease, he further noted, "seems to obey certain fixed laws." It is "confined to … a few families, is attended generally by all the symptoms of common chorea, hardly ever manifesting itself until adult or middle life, and then coming on gradually but surely, increasing by degrees, and often occupying years in its development, until the hapless sufferer is but a quivering wreck of his former self." The "tendency to insanity," Huntington observed, progresses so that the "mind becomes more or less impaired, in many amounting to insanity while in others, mind and body both gradually fail until death relieves them of their sufferings."

The inheritance pattern was also clear to Huntington: "When either or both the parents have shown manifestations … one or more of the offspring almost invariably suffer from the disease … but if by any chance these children go through a life without it, the thread is broken…." Finally, he noted the relentless, fatal course: "I have never known a recovery … it seems at least to be one of the incurables." Commenting later on Huntington's description,

Sir William Osler noted that "there are few instances in which a disease has been more accurately, more graphically, and more briefly described" (Stevenson, 1934).

The cardinal features of HD so aptly described by Huntington are even clearer to us now, nearly 140 years later. It is a dominantly inherited, neuropsychiatric disorder that affects successive generations of afflicted families. It progresses slowly over years with symptoms typically, but not always, beginning in adulthood. Although HD usually involves chorea and other abnormal movements, the progressive cognitive impairment and behavioral problems are perhaps even more disabling. The remarkable clinical variability and wide range in age of onset, even among affected members in the same family, are now recognized to stem directly from the type of mutation in HD, a dynamic repeat expansion in a polyglutamine-encoding CAG tract. Likewise, the clinical phenomenon of anticipation—the tendency for disease to begin earlier in successive generations—is the result of the propensity for further expansion of the disease-causing repeat on transmission to offspring. We now also recognize that not *all* HD is familial, as a small percentage of cases arises sporadically from newly expanded alleles. Naturally, such sporadic HD cases then constitute the first generation of new HD families.

The HD mutation, a CAG repeat expansion in the *HTT* gene (Huntington's Disease Collaborative Research Group, 1993), is present in all affected persons. The high sensitivity and specificity of genetic testing for the mutation ensure that molecular confirmation of HD is straightforward in the clinic (Davis et al., 1994; Kremer et al., 1994). For persons in whom HD is clinically suspected, a gene test can quickly prove or disprove the diagnosis. For those who are known to be at risk for disease, presymptomatic testing is available after appropriate counseling (WFN Research Group on Huntington's Chorea, 1994). Currently, in the absence of a preventive medication or disease-modifying therapy, only a small minority of at-risk persons choose to undergo presymptomatic testing (Quaid and Morris, 1993). But the ability to track presymptomatic HD gene carriers in long-term observational studies has greatly improved researchers' and clinicians' ability to chart the course of disease symptoms and signs, both before and after diagnosis. This knowledge will be crucial to the success of future preventive and symptomatic trials.

The discovery of the HD mutation has also shed light on possible disease mechanisms (Gatchel and Zoghbi, 2005; Nakamura and Aminoff, 2007; Todi et al., 2007). The CAG repeat expansion encodes a polymorphic stretch of the amino acid glutamine in the disease protein, a large polypeptide known as huntingtin (htt). This expanded polyglutamine tract is widely believed to be the key molecular culprit in HD (Mangiarini et al., 1996). Although the mechanism by which expanded polyglutamine in huntingtin causes brain dysfunction and neuronal cell death remains uncertain, growing knowledge about both the aberrant properties of the disease protein and the havoc it wreaks on cells has provided new insight into potential rational therapies (Di Prospero and Fischbeck, 2005), as discussed elsewhere in this book.

Although HD is a clinically distinctive neurodegenerative disease, polyglutamine expansions are not unique to HD. At least eight other neurodegenerative disorders are caused by polyglutamine expansions (Table 1.1) (Gatchel and Zoghbi, 2005; Riley and Orr, 2006; Todi et al., 2007). In many important ways, HD can be considered a flagship for other

polyglutamine diseases. It is the most common among them: roughly 30,000 people are diagnosed with HD in the United States and Canada, with another ~150,000 at risk for disease. More than any other polyglutamine diseases, HD is studied by a vast array of clinicians and scientists who explore disease mechanisms, the natural course of disease, and potential therapies. In particular, the highly organized HD clinical research community is driving the push toward biomarkers and quantifiable clinical measures that will serve as the basis for successful human trials. Importantly, because all polyglutamine diseases may share common elements of pathogenesis, insights from the HD field could prove valuable for the thousands of people affected by other polyglutamine diseases.

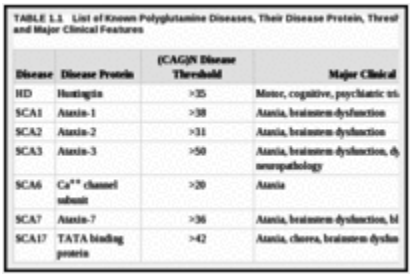


TABLE 1.1 List of Known Polyglutamine Diseases, Their Disease Protein, Threst and Major Clinical Features

Disease	Disease Protein	(CAG)N Disease Threshold	Major Clinical
HD	Huntingtin	>35	Motor, cognitive, psychiatric sy
SCA1	Ataxin-1	>39	Ataxia, brainstem dysfunction
SCA2	Ataxin-2	>31	Ataxia, brainstem dysfunction
SCA3	Ataxin-3	>50	Ataxia, brainstem dysfunction, dy neuropathology
SCA6	Ca^{++} channel subunit	>20	Ataxia
SCA7	Ataxin-7	>36	Ataxia, brainstem dysfunction, bl
SCA17	TATA binding protein	>42	Ataxia, chorea, brainstem dysfun

TABLE 1.1

List of Known Polyglutamine Diseases, Their Disease Protein, Threshold Disease Repeat, and Major Clinical Features.

Although HD and other polyglutamine disorders are relatively uncommon, they have an impact disproportionate to their prevalence. In populations of European descent, the estimated prevalence of HD is approximately 4–9/100,000. Prevalence rates are much lower in populations of non-European ancestry. The aggregate prevalence of all other polyglutamine diseases, primarily spinocerebellar ataxias, may approach the lower bound of prevalence estimates for HD. Because HD and other polyglutamine diseases tend to strike in middle age and are slowly progressive, the economic impacts as a result of lost earnings and costs of care are enormous. The personal suffering and family disruption imposed by HD are devastating. The combination of usual midlife onset and dominant inheritance tends to pull HD families down the social scale, compromising the lifetime opportunities of both mutant allele carriers and their unaffected relatives.

Despite the many advances in our understanding of HD since discovery of the disease gene, HD remains, in Huntington's words, "one of the incurables." As the existence of this book attests, however, the knowledge gained since the gene discovery puts us in a position where this incurable status may soon change. Here we review HD, focusing on its major clinical features, neuropathological hallmarks, and current and possible future therapies. We emphasize literature from the past 15 years. Earlier studies are reviewed thoroughly in other books and chapters (Harper, 1991; Marshall, 2004). In keeping with this book's purpose, we stress clinical and neuropathological aspects of HD that should be kept in mind as the field moves toward preventive therapy.

Go to:

CLINICAL FEATURES

HD is, in every sense of the word, a "neuropsychiatric" disorder. No other disease so firmly bridges the disciplines of psychiatry and neurology. The classic clinical triad in HD is (1) progressive movement disorder, most commonly chorea; (2) progressive cognitive disturbance culminating in dementia; and (3) various behavioral disturbances that often precede diagnosis and can vary depending on the state of disease.

LEARNING FROM WOODY

Physicians who run HD clinics are continually astonished by the diverse array of symptoms and signs that affected persons can develop. In one respect or another, each person with HD is clinically unique. But if there is a "typical" case of HD, it would be adult-onset disease manifested by chorea and behavioral changes that, over a 15–20-year period, slowly rob the affected person of his or her professional skills and social graces. Woody Guthrie, the famous activist and folksinger who died from HD in 1967, was by no means a typical person. Yet the course of his HD fits the description above (Arevalo et al., 2001). Reviewing his life story may help readers gain a personal perspective on this devastating disease.

Born in 1912, Guthrie proved to be a precocious boy and later a creative and prolific folksinger (among his thousands of songs are "This Land Is Your Land" and "So Long, It's Been Good to Know You"). By the time Guthrie was a young adult, his mother had passed away from progressive dementia accompanied by disruptive behavior that led to her institutionalization. When Guthrie was 39, he was admitted to a detoxification center after an angry outburst toward his wife. This was the first of many institutions he would enter in the final 15 years of his life. At that time, Guthrie's own notes described his various symptoms and his psychological state very well (Arevalo et al., 2001). He felt "terribly restless always. I get here and I want to be yonder. I get over yonder and I want to be back over here … I don't trust anybody I see." Later the same year he wrote:

Here's my funny feeling over me again. That lost feeling. That gone feeling. That old empty whipped feeling. Shaky. Bad control. Out of control. Jumpy. Jerky. High tension. Least little thing knocks my ego down below zero mark. Everything cuts into me and hurts me several times more than it should … no bodily (physical) pains; just like my arms and legs and hands and feet and my whole body belongs to somebody else and not to me; so ashamed of myself … I spend every drop of my bodily strength trying to hide my trouble away so you can't see it; trying to keep you from reading it in my face, or my eyes, or in any words I'd say … or in that stumbly way I walk around.

A short time later Guthrie wrote, "My chorea sure isn't kidding these days. I feel it as a nervous fluttery heart condition along with a slight lack of control over my body at times." As his disease progressed, the diagnosis was soon established as HD based on his progressive clinical signs (including chorea) and his mother's illness. Eleven years later, Guthrie's wife Marjorie described his now advanced symptoms at age 51:

Woody's muscular condition continues to deteriorate. I find it more and more difficult to understand him when he speaks and this is when his fiery temper jumps out. His memory

remains uncanny, but he just hasn't got the muscular control to mouth the words. His balance is very poor … forever lighting up a new cigarette because the old one fell out of his mouth.

By age 53, Guthrie had stopped speaking entirely and could only communicate by pointing a wildly flailing arm at "yes" and "no" cards that Marjorie made for him. Eight months before he died in 1967 at 56 years of age, the folksinger Pete Seeger visited him. Woody was, Seeger noted,

in a wheelchair. He couldn't walk anymore so the hospital attendant wheeled him out under a porch where it was warm…. You could see how much he wanted to be part of our little [group] … he tried to get his arms going but they were just flailing around like a windmill. He got to the point where it looked as though he might hurt himself so the attendant said, "You'd better quit playing." (Arevalo et al., 2001)

Age of Onset, Natural History, and Diagnosis

Onset of manifest HD is defined conventionally by the presence of a motor disorder, usually the involuntary movements known as chorea (see "Movement Disorder" below). In some patients, other motor abnormalities may lead to a diagnosis of HD (Louis et al., 2000). Because the motor features of HD are often preceded by cognitive or behavioral features (see "Movement Disorder" below), the diagnostic criterion of a discernible motor disorder is a fairly conservative standard. In the earlier stages of HD, motor abnormalities may be subtle and may fluctuate depending on the state of arousal of the patient. Median age of diagnosis is approximately 40 years of age with a wide range in ages of onset. Onset before age 20 or after age 65 is relatively rare, but both very young and elderly new-onset HD patients are seen in tertiary referral clinics. Death generally occurs 15–20 years after diagnosis.

When the characteristic motor disorder is present in an individual from a well-characterized HD pedigree, diagnosis of manifest HD is straightforward (Kremer et al., 1994). Circumstances may arise, however, where information about the family history is limited or absent. In some individuals without an apparent family history of HD, covert adoption or nonpaternity, as well as a new mutation, may have occurred. Molecular testing is invaluable in these situations.

Movement Disorder

Although the range of movement disorders in HD extends beyond chorea, it remains the classic motor sign of HD. Derived from the Greek word for "dance," chorea often begins as fleeting, suppressible movements that may appear as fidgetiness. Over the course of disease, chorea becomes more overt as it involves larger muscle groups. Patients often will incorporate chorea into purposeful movements, something known as parakinesia. Motor impersistence, the inability to sustain a voluntary muscular effort, is common in HD and often goes hand in hand with chorea. The "fly-catcher's tongue" describes the difficulty many moderately advanced HD patients have in keeping their tongue from protruding beyond the lips.

By itself, chorea is usually not greatly disabling. For many HD clinicians chorea is not something that becomes a major target of treatment. However, flailing and continual chorea can be disabling or physically harmful, requiring treatment with dopamine-depleting agents such as tetrabenazine. In past decades, potent dopamine-blocking neuroleptic medications (e.g., haloperidol) were routinely used to control chorea in HD patients. More recently, however, clinicians have tended first to use newer atypical antipsychotic drugs in persons who experience severe chorea, especially when it is accompanied by psychiatric symptoms warranting antipsychotic use, such as delusions.

Dystonia, the involuntary contraction of muscles, is seen in most persons with HD but is especially prominent in younger-onset individuals. As "typical" adult-onset HD progresses, straightforward chorea can evolve into a more complicated constellation of movement disorders that increasingly include dystonia (Feigin et al., 1995). In addition, clumsiness and slowness of movements (bradykinesia) are common in those with HD, the latter especially in earlier-onset disease. Indeed, the juvenile-onset form of disease that manifests initially with bradykinesia, rigidity, and little or no chorea has been given its own name, the "Westphal variant." Very early-onset cases also have a high incidence of epilepsy. The distinctive phenotype of very early-onset HD probably reflects the effects of the mutant allele on developing brains. Rather than single out one clinical subset of HD, it is perhaps better to think of motor signs in HD as spanning a spectrum—earlier-onset cases tending to have more bradykinesia and dystonia and later-onset cases tending to have more chorea (Louis et al., 2000). In many adult-onset HD patients, chorea will gradually progress and then begin to subside as dystonia and bradykinesia become more prominent motor features. The combination of chorea, bradykinesia, and dystonia sometimes leads to very unusual gait patterns that leave patients highly prone to falls. Ataxia and marked postural instability are common in those with more advanced HD.

Eye movement abnormalities occur early and persist throughout the course of disease. Persons with HD have difficulty maintaining fixation and develop slowed initiation and velocity of the rapid eye movements known as saccades (Lasker et al., 1987). As this worsens, they may need to thrust their head or blink to break fixation and move their eyes to gaze at a new target.

In summary, HD manifests with a remarkably wide range of movement disorders, partly because of the phenotypic heterogeneity stemming from differences in expanded repeat lengths and partly reflecting the fact that disease symptoms and signs change over time. The progressive movement disorder and increasingly widespread failure of the motor system contribute greatly to the physical disability and decreased life expectancy of individuals with HD. In particular, difficulties with swallowing (dysphagia), speech (dysarthria), and balance (frequent falls) become very debilitating. A common cause of death in those with advanced HD is aspiration pneumonia, reflecting severe dysphagia and general immobility (Sorensen and Fenger, 1992).

Cognitive Disorder

It was once suspected that cognitive decline only began when, or soon before, manifest HD was apparent. Recently, however, large-scale observational studies of HD gene carriers before diagnosis make it clear that subtle cognitive impairment is among the earlier manifestations in the disease process and is associated with progressive caudate atrophy (Aylward, 2007; Aylward et al., 2000). By the time of diagnosis, most subjects with HD have significant cognitive impairment readily measurable by neuropsychological testing. These early signs do not impede most activities of daily living, but individuals with demanding jobs requiring sustained concentration often find work increasingly stressful and difficult. The cognitive impairment progresses slowly over many years to frank dementia in most persons with HD.

In contrast to the dementia of Alzheimer's disease (AD), HD results in a largely "subcortical" dementia characterized by slowness in initiating thought processes, difficulties with executive function, and problems with attentional and sequencing tasks (Paulsen et al., 1995; Rohrer et al., 1999). Although episodic memory is impaired, memory in general is relatively well preserved compared with, for example, AD. Because a battery of cognitive tests can detect abnormalities before diagnosis, elements of cognitive impairment likely will serve as important quantifiable measures in future clinical trials of candidate preventive agents in prediagnosis individuals.

One intriguing feature of the cognitive impairment in HD is the lack of insight subjects may have regarding their own symptoms (Hoth et al., 2007). Some individuals with overt signs of HD, evident to other family members, deny that they experience any motor or cognitive difficulties. Lack of insight is a typical sign of impaired frontal lobe function and may reflect early dysfunction of striatal neurons receiving prominent frontal lobe inputs.

Behavioral Disorder

The behavioral problems arising in HD can be the most vexing to the patient, family, and physician. These range from affective illness, most notably depression and apathy, to delusional behavior that can include, rarely, hallucinations (Caine and Shoulson, 1983; Paulsen et al., 2001). As is true of other progressive neurodegenerative diseases, the behavioral disorders of HD evolve during the course of illness. Most HD gene carriers will experience some behavioral symptoms before establishing the diagnosis (Close Kirkwood et al., 2002; Duff et al., 2007; Kirkwood et al., 2002). These may include depression, obsessive–compulsive behaviors (OCBs), irritability, and behavioral outbursts (Duff et al., 2007; Kirkwood et al., 2002). Family members often comment that patients' personalities change in the years leading up to diagnosis, although this may be apparent only in retrospect.

Depression is particularly common in those with HD: between 30% and 50% of patients will develop depressive symptoms in the course of disease. The depression often responds very well to treatment, with selective serotonin reuptake inhibitor antidepressants commonly being the first agents tried. Often, however, there is superimposed apathy that is difficult to treat. Personality changes can occur that impair work performance and social interactions well before the diagnosis is established. This can lead to behavioral agitation, anxiety, alcohol abuse, marital problems, and antisocial behavior. Also common in HD patients are

OCBs. These may overlap with features of rigidity and perseveration that also can be seen in individuals with frontal lobe dysfunction. OCBs, rigidity, and perseverative features probably all reflect striatal dysfunction.

The severity of psychiatric symptoms varies greatly in those with HD and does not correlate with dementia and chorea (Paulsen et al., 2001). Recent findings suggest that psychiatric problems are especially problematic in juvenile-onset cases (Ribai et al., 2007).

Some psychiatric symptoms tend to run in specific HD families. For example, overt psychotic behavior more likely will occur in someone from a family where one or more affected persons also suffer from psychosis (Tsuang et al., 2000).

An important cautionary note is the high rate of suicide in patients with HD (Almqvist et al., 1999; Lipe et al., 1993). The risk is significantly higher for those with HD gene-positive status, including both those with diagnosed HD and those who are prediagnosis. The risk may also be higher for family members who are *not* carriers of the gene, underscoring the tremendous stress and burden placed on families with HD (Lipe et al., 1993). Factors that increase the risk of suicide in gene-positive individuals include being single, lacking children, living alone, having depression, and already having manifest signs of HD. Degeneration of striatal neurons involved in limbic circuits is a possible substrate of depression in those with HD (Tippett et al., 2007).

Clinical Heterogeneity

In patients with HD, the remarkable range in symptoms and age of onset largely reflects differences in the length of the repeat expansion. As shown in Figure 1.1 (Langbehn et al., 2004) and documented in many publications, repeat length inversely correlates with age of onset (Andrew et al., 1993; Ashizawa et al., 1994; Duyao et al., 1993; Kieburtz et al., 1994; Stine et al., 1993). Because earlier- versus later-onset forms of disease typically manifest different motor symptoms, the differences in repeat length also explain, in part, the heterogeneous phenotype.

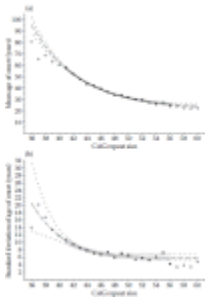


FIGURE 1.1

HD disease onset as a function of repeat length. Shown are population estimates based on an analysis of nearly 3,000 individuals seen at 40 HD centers. (a) Inverse correlation between mean age of onset and CAG repeat length. (b) Standard deviation of (more...)

Expanded repeat length accounts for approximately 50% of variability in age of onset. However, also note in Figure 1.1b that the *variance* in age of onset for a given repeat length is much greater with small expansions (e.g., 39) than with the rarer, large expansions (e.g., ~56). In other words, the range in age of disease onset for a repeat of 39 can span four decades or more, whereas a repeat of 56 has a narrow range. Clearly other genetic and environmental factors contribute to age of disease onset, particularly for the more common, smaller expansions (<45). Indeed, genetic modifiers of disease onset have already been identified. For example, Meyers and colleagues (Li et al., 2006) and Rubinsztein and colleagues (Rubinsztein et al., 1997; Zeng et al., 2006) separately have identified loci that influence the rate of onset. As mentioned earlier, familial aggregation of certain symptoms (e.g., psychosis) occurs in HD, and this too likely reflects genetic modifiers. It is hoped that further success in defining genetic risk factors/modifiers will shed light on biological pathways that contribute to disease.

Given the relationship of repeat length to age of onset, one can generate "probability curves" that, for a given repeat length, plot the probability of developing manifest disease by a particular age (Langbehn et al., 2004). A series of such probability curves is shown in Figure 1.2. For larger expansions, the narrower range of disease onset is again clear (i.e., steeper slope). An important point illustrated by this figure is that rather modest expansions (≤40) may *not* lead to manifest disease until very late in life, and in some cases, HD symptoms may not surface before one dies from other age-related causes. In other words, shorter HD expansions are not fully penetrant alleles (Quarrell et al., 2007). There is also an underappreciation of the fact that HD manifesting after age 50 years is not as rare as once thought. Because a higher percentage of late-onset cases will be sporadic cases from newly expanded alleles, clinicians need to keep in mind that late-onset HD often does *not* have the typical positive family history (Falush et al., 2001).

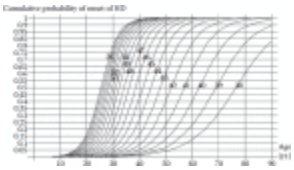


FIGURE 1.2

Cumulative probability curves of HD onset for various CAG repeat lengths. Numbers shown indicate repeat length for a given curve. (From Langbehn, D. R., Brinkman, R. R., Falush, D., Paulsen, J. S., and Hayden, M. R., *Clin Genet* 65, 267, 2004. With permission.) (more...)

Unlike age of *onset*, which strongly correlates with repeat length, rate of disease *progression* is not convincingly linked to repeat length. Some studies have found no correlation (Kieburtz et al., 1994), whereas others have, especially with late-stage outcomes (Marder et al., 2002). Ongoing, large observational studies of gene carriers may provide new data that resolve this uncertainty.

HUNTINGTON'S DISEASE MIMICS

HD is a distinctive phenotype, but mimics of HD are encountered occasionally in clinical practice (Rosenblatt et al., 1998; Schneider et al., 2007). The list of choreiform disorders in the differential diagnosis is extensive. Many can be excluded based on the history or features of the physical examination. In doubtful cases, molecular testing is invaluable for identifying or excluding HD. More difficult to evaluate are a few inherited neurodegenerations that can mirror HD. These include other dominant disorders such as the polyglutamine diseases dentatorubral-pallidoluysian atrophy (DRPLA) and SCA17; Huntington's disease-like 2, which is another expanded repeat disorder; and members of the neurodegeneration with brain iron accumulation spectrum such as neuroferritinopathy. Recessive and X-linked disorders in the neuroacanthocytosis family of diseases can also mimic HD. Molecular diagnoses are available for all of these diseases. Because among these disorders HD is by far the most common, a reasonable strategy is first to test for the presence or absence of the HD mutation. If absent, more extensive testing will be needed to establish a diagnosis. Establishing an accurate diagnosis is crucial for the family and the patient. The clinical implications are vastly different for a dominant versus a recessive disorder, and appropriate presymptomatic testing in other family members can be pursued only with an accurate diagnosis.

Go to:

NEUROPATHOLOGICAL FEATURES

NON–CENTRAL NERVOUS SYSTEM CHANGES

As with the other polyglutamine disorders, HD is primarily a disorder of the central nervous system (CNS). Huntingtin is expressed in many tissues, but the clinical features of HD reflect CNS dysfunction, and almost all histopathologic abnormalities are restricted to the brain. It is important to note that although clinical features and traditional histopathologic analyses point to HD as a CNS disease, investigations with more sensitive measures point to widespread, albeit subclinical, effects of expanded htt. Studies of peripheral blood and lymphoblasts derived from HD subjects have revealed aberrant gene regulation and mitochondrial abnormalities (Borovecki et al., 2005; Sawa et al., 1999). A recent study of urea cycle metabolites suggests a subclinical but detectable effect of expanded htt on hepatic function (Chiang et al., 2007). Several studies suggest abnormalities of another long-lived postmitotic tissue, muscle. Gene regulation studies, magnetic resonance spectroscopic studies, and biochemical studies suggest muscle mitochondrial abnormalities in HD, and muscle biopsy histology indicates the presence of significant but nonspecific abnormalities (Arenas et al., 1998; Lodi et al., 2000; Saft et al., 2005; Strand et al., 2005). An interesting recent observation is the description of testis abnormalities in HD. Testes are characterized by high-level expression of *HTT* mRNA. Van Raamsdonk et al. (2007) describe reduced numbers of germ cells and abnormal seminiferous tubule morphology.

GROSS CNS PATHOLOGY

CNS changes, however, drive the mortality and morbidity associated with HD. A plausible explanation for the CNS selectivity of HD is that cell populations with limited lifespans do not live long enough to experience the damage caused by expanded polyglutamine htt. In this

model, neurons are preferentially susceptible to the toxicity of expanded htt because of their long lifespan. Although this could explain the selective CNS pathology of HD, it explains neither the regional selectivity within the CNS nor the midlife onset of HD. Some unexplained interaction between expanded polyglutamine htt effects and normal aging phenomena must be invoked to explain the relatively late onset of HD.

Within the CNS, htt is expressed by neurons throughout the neuraxis without dramatic regional differences. Despite this, there is a definite regional pattern to HD pathology (Vonsattel and DiFiglia, 1998). Classic descriptions emphasize that HD is a striatal degeneration. This is true to a first approximation, but this traditional teaching point should not be exaggerated. Gross striatal atrophy is a prominent feature of HD. Careful pathologic analyses, performed usually on specimens of advanced HD, reveal a more complex picture (Figure 1.3). Thinning of the cortical mantle and decreased brain weights and volumes are common as well. Consistent with diffuse loss of neurons is the diffuse loss of cerebral white matter. Careful studies reveal neuronal loss in many regions, including the neocortex, cerebellum, hippocampal formation, substantia nigra, and brainstem nuclei. These findings reflect the widespread expression of htt and correlate well with the profound and diffuse clinical deficits found in patients with advanced HD, including pyramidal signs, ataxia, severe bulbar dysfunction, marked incoordination, and profound dementia.

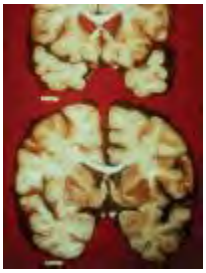


FIGURE 1.3

Gross neuropathology of HD. The top section is from an HD subject, whereas the lower section is from a control without neurologic disease. There is marked striatal atrophy with corresponding ventriculomegaly. There is also diffuse thinning of the cortical (more...)

An important question to consider is what structures are affected earlier in the course of HD. Identifying neuronal populations that are relatively susceptible to expanded polyglutamine htt effects might provide important clues to pathogenic mechanisms. The prevailing impression is that the striatal complex is affected early in HD, although there is also increasing evidence of early neocortical degeneration (Vonsattel and DiFiglia, 1998; see discussion of imaging results under “Striatal Pathology” below). An important development in the study of postmortem changes in HD was the introduction by Vonsattel et al. (1985) of a pathologic grading system based on the degree of striatal pathology. In earlier (lower) Vonsattel grades of pathology, the striatum does seem to be more affected than other brain regions. Vonsattel and colleagues also documented subregional differences in HD pathology in the striatal complex. In the extensive series of specimens examined by Vonsattel and colleagues, neurodegeneration within the striatal complex progressed in caudalto-rostral and dorsal-to-ventral gradients.

Striatal Pathology

Initial explorations of HD striatal pathology beyond classic histopathology involved biochemical assessments of neurotransmitter systems. These initial studies revealed loss of γ-aminobutyric acid (GABA)ergic and cholinergic markers with relative sparing of dopaminergic markers. These results suggested loss of intrinsic GABAergic and cholinergic neurons with relative sparing of extrinsic dopaminergic terminals. The similarity of these changes to the results of experimental excitotoxic lesions gave rise to the still popular excitotoxic hypothesis of neuronal death in HD.

The identification of striatal neuron subpopulations made it possible to pursue a finegrained analysis of striatal changes in HD. Striatal neuron populations are divided into two major groups: (1) aspiny interneurons whose projection arbors are restricted to the striatum; and (2) medium spiny projection neurons whose primary axons synapse in the downstream targets of the striatal complex. Striatal interneurons are further subdivided based on the morphology and neurochemical phenotype. Well-studied populations of striatal interneurons include the large aspiny cholinergic interneurons, which are probably synonymous with the tonically active neurons described in extracellular recording studies. These neurons are virtually spared in HD striatum (Ferrante et al., 1987). Interestingly, although there is solid evidence that cholinergic neuron perikarya persist even in those with advanced HD, striatal choline acetyltransferase (ChAT) levels decrease markedly. The discrepancy between decreasing ChAT activity and preserved perikarya suggests significant striatal cholinergic interneuron dysfunction, as opposed to neurodegeneration, in HD. Another spared subpopulation of striatal interneurons are those containing somatostatin, neuropeptide Y, and nitric oxide synthase, which persist even in advanced HD striatum (Ferrante et al., 1985).

Subpopulations of striatal projection neurons, all of which are GABAergic, are defined by their primary projection targets, coexpressed neuropeptides, and neurotransmitter receptors. Striatal neurons projecting to the different segments of the globus pallidus (external [GPe] and internal [GPi]) and the different components of the substantia nigra (dopaminergic pars compacta [SNc] and GABAergic pars reticulata [SNr]) form relatively segregated pools of neurons. Striato-GPe neurons are distinguished by the expression of enkephalins, dopamine D2 receptors, and adenosine A2a receptors, whereas the other striatal projection neuron pools tend to express tachykinins and dopamine D1 receptors. Some recent studies in nonhuman primates using sensitive tract tracing methods have cast doubt on the idea of segregated striatal projection neuron pools (Levesque and Parent, 2005). However, recent data from mice engineered to express green fluorescent protein under the control of the D1 or D2 promoters strongly support the existence of distinct pools of striatal projection neurons (Lobo et al., 2006). The existence of different pools of striatal projection neurons overlaps to some degree with another important aspect of striatal organization: the patch (striosome)–matrix differentiation. A variety of neurochemical markers differentiate the striatum into two compartments: (1) patches (striosomes), a geometrically complex interconnected tubular compartment; and (2) the surrounding matrix compartment. Striato-SNc neurons are disproportionately represented within the patch compartment.

Examination of postmortem HD material across a full spectrum of pathologic grades suggests a specific temporal order in degeneration of striatal projection neuron subpopulations. The early changes appear to be loss of striato-GPe neurons and perhaps striato-SNr neurons (Albin et al., 1992; Deng et al., 2004; Reiner et al., 1988). In contrast, striato-GPi neurons are relatively spared until later in the course of HD. This sequential pattern of neuronal loss correlates broadly with certain features of the natural history of HD. Oculomotor abnormalities, particularly abnormalities of saccadic eye movements, are early features of HD. As basal ganglia inputs to the superior colliculus come from SNr, the early loss of striato-SNr projection neurons correlates nicely with early saccadic abnormalities. The evolution of involuntary movements in HD correlates also with the evolution of striatal projection neuron changes. One predicted downstream consequence of initial degeneration of striato- GPe neurons is inhibition of the subthalamic nucleus. Decreased subthalamic activity is associated with choreoathetoid movements. In many patients, disease progression is associated with gradual worsening of choreoathetoid movements, which then peak in intensity and gradually decrease. The decrease in choreoathetosis is accompanied by worsening dystonia and bradykinesia. The apparent correlate in striatal pathology is generalized loss of striatal projection neurons and probably neurons within other nuclei of the basal ganglia (Albin et al., 1990). In a recent, interesting study, Tippett et al. (2006) looked specifically at a marker of striosomal striatal projection neurons in a broad spectrum of HD postmortem specimens. This work suggests a correlation between mood disorders in HD and striosomal pathology.

Neocortex is also affected significantly in HD. Recent neuroimaging data (see "Neuroimaging" below) suggest that this may be an early event in HD. Some data suggest that neocortical atrophy proceeds in tandem with striatal atrophy (Halliday et al., 1998; Macdonald and Halliday, 2002). As in the striatum, there is evidence for differential involvement of different cortical neuron populations in HD. Careful studies looking at changes in cortical laminae reveal differential loss of neurons in different layers. Pyramidal neurons of deeper cortical layers appear to be more affected in HD, although this may vary by cortical field (Hedreen et al., 1991; Sieradzan and Mann, 2001; Sotrel et al., 1991, 1993).

Unlike the neurofibrillary tangles of AD or the Lewy bodies of Parkinson's disease, HD was believed historically not to exhibit characteristic abnormalities at the cellular level. This perception changed radically with the discovery in the R6/2 transgenic mouse model of neuronal intranuclear and cytoplasmic aggregates containing expanded polyglutamine htt, ubiquitin, and other proteins. These types of inclusions were also found in HD brain and in most other polyglutamine disorders. Although inclusions are found in the HD brain, their frequency is less than that seen in many of the murine genetic models (DiFiglia et al., 1997; Gutekunst et al., 1999). Perhaps because of the relatively short lifespan of mice, neuronal loss in murine genetic models is less severe than that seen in end-stage HD. It is possible that neuronal loss in HD is accompanied by a corresponding loss of neuronal inclusions.

Debate has arisen about the role, if any, of neuronal inclusions in disease pathogenesis. Suggestions for the role of inclusions include that they are (1) directly pathogenic structures; (2) markers of failed clearance of abnormal disease protein; (3) protective "sinks" for toxic

polyglutamine proteins and associated factors; and (4) epiphenomena of the disease process (Ross and Poirier, 2005). A relevant fact from postmortem analysis is that neuronal inclusions are more readily found in some of the spared striatal interneuron populations than in the vulnerable striatal interneurons (Kuemmerle et al., 1999).

NEUROIMAGING

Whereas imaging methods were pursued originally to improve diagnosis of HD, recent studies have pursued imaging methods as part of efforts to develop biomarkers for HD. The hope is that novel imaging methods will provide sufficiently precise measures of disease state and progression to serve as state markers, as response markers, or even as surrogate endpoints in trials.

Computed tomography, magnetic resonance imaging (MRI), and positron emission tomography (PET) imaging methods have all been applied to HD. Most recent studies have concentrated on MRI morphometric analyses of regional brain volumes in the hope of establishing changes over time that will be useful as a marker of disease progression in symptomatic or presymptomatic HD subjects. Using observer-identified volumes of interest, Aylward and colleagues presented data suggesting progressive decrease in striatal volume well before the onset of manifest HD (Aylward, 2007). In their dataset, approximately 50% of the striatum had degenerated by onset of manifest HD. This approach seems promising for the development of a surrogate marker of disease progression that could be applied in both prediagnosis and manifest HD populations. On the other hand, the relatively small volume of the striatum and the apparent fact that considerable striatal atrophy occurs early in the course of HD may limit the dynamic range of striatal volume as a biomarker in studies of manifest HD. For presymptomatic subjects, the imaging arm of the PREDICT-HD observational study (Paulsen et al., 2008) will provide definitive data about the potential use of this approach as a biomarker.

Improved MRI morphometry analysis methods may provide additional or even superior biomarkers. Cortical mantle atrophy is a significant feature of HD pathology. The large extent of the cortex and the possibility of assessing many cortical regions offer the theoretical hope of a morphometric marker with very wide dynamic range. Improved morphometry methods make it possible to measure cortical thickness of many regions simultaneously. Rosas and colleagues pursued cortical morphometry in both symptomatic and presymptomatic HD subjects (Rosas et al., 2002, 2005). Their work suggests that cortical atrophy is an early event in HD, that it occurs in presymptomatic subjects, and that the magnitude of changes over relatively short intervals (e.g., 2–3 years) is sufficiently great to provide a biomarker of disease progression. In addition, this group's work suggests that cortical degeneration is not uniform throughout the cortical mantle but occurs in a stereotyped sequence, with some cortical fields affected earlier than others (HD Rosas, personal communication). This exciting work awaits validation in suitable prospectively collected large datasets.

There has been less activity with PET imaging in HD research, but this remains an interesting potential imaging modality for HD. PET availability was limited historically to

research centers with cyclotrons, but PET imaging has become a standard modality for many medical applications, and both scanner availability and the number of easily used tracers is expanding rapidly. The theoretical advantage of PET is its ability to image specific molecular targets. In HD, several PET studies have demonstrated decreases in striatal neurotransmitter markers, particularly striatal dopamine receptors. Changes in these markers appear to be an early feature of HD, consistent with the MRI morphometry data of Aylward and colleagues (Ginovart et al., 1997; van Oostrom et al., 2005; Weeks et al., 1996). Counterintuitively, some PET studies also demonstrate loss of striatal dopamine terminal markers in HD (Backman et al., 1997; Bohnen et al., 2000). This loss seems to be associated with more severe disease. It may reflect the loss of nigrostriatal dopaminergic neurons as a result of direct effects of perikaryal nigral polyglutamine toxicity or the loss of trophic support from striatal neurons.

Ongoing studies with MRI morphometry are likely to provide the critical data within the next 4–5 years. There is a very good chance that MRI morphometry will provide adequate biomarkers for evaluating progression and treatment response in HD.

Go to:

THERAPY: PRESENT AND FUTURE

SYMPTOMATIC THERAPY

Although HD may not yet be curable, some features are amenable to therapy (Bonelli and Hofmann, 2007). These include depression, which responds often to antidepressants, most commonly selective serotonin reuptake inhibitors or other, newer antidepressants. OCBs may also respond to antidepressants, as may agitation and irritability. Irritability and impulsive behavior are sometimes treated with anticonvulsants, such as valproic acid or carbamazepine. Anxiety can benefit from anxiolytic medications. When HD is accompanied by delusions or paranoid thoughts, atypical antipsychotic drugs are frequently used (less so the classic neuroleptic agents), and appropriate antipsychotic medications can improve behavioral outbursts. Thus far, limited trials of cognitive-enhancing agents used primarily in patients with AD, such as memantine (Beister et al., 2004), rivastigmine (de Tommaso et al., 2007), and donepezil, have shown only modest benefit. Bradykinesia and rigidity in younger-onset individuals can respond to dopaminergic agents used in parkinsonism (Jongen et al., 1980).

Chorea will respond to dopamine-blocking agents; for example, a recent well-controlled clinical trial proved that tetrabenazine reduces chorea in a dosedependent manner (Huntington Study Group, 2006). Many other medications have shown modest benefit for chorea (Bonelli et al., 2002; de Tommaso et al., 2005; Huntington Study Group, 2003; Kremer et al., 1999; O'Suilleabhain and Dewey, 2003; Verhagen Metman et al., 2002), but not all have been tested in well-controlled trials. Suppressing chorea per se is not an endpoint sought by many physicians who treat HD unless the chorea is disabling or so severe as to increase risk of injury. Although traditional neuroleptic agents or dopamine blockers such as tetrabenazine can be effective in reducing chorea, these medications are not without their side effects, including parkinsonism, gait disturbance, somnolence, and depression.

Myoclonus, which is rare in HD and sometimes mistaken for chorea, can respond to valproic acid (Saft et al., 2006).

Assistive therapies such as physical, occupational, and speech therapy play an important role in the care of HD patients. In many cases, these are the primary therapeutic interventions and can be very useful for some patients. The efficacy of assistive interventions is often limited, however, by the cognitive and behavioral impairments of HD patients. As with many aspects of HD, the burden of maximizing benefits from assistive interventions falls on caregivers.

Although the focus of this book and the HD research community is on identifying a preventive medicine for HD, we must also continue efforts to seek out symptomatic medications and enhance practical measures (Nance, 2007) that can improve the lives of those currently affected by HD.

Toward Preventive Therapy

As our understanding of the molecular basis of HD becomes clearer, routes to preventive therapy are being considered (Di Prospero and Fischbeck, 2005; Feigin and Zgaljardic, 2002; Nakamura and Aminoff, 2007). Potential contributing factors to HD include perturbations in protein homeostasis, mitochondrial dysfunction, excessive or aberrant corticostriatal input, transcriptional dysregulation, loss of neurotrophic support, and impairments in axonal trafficking. Correspondingly, potential compounds or strategies considered for preventive treatment include histone deacetylase inhibitors (e.g., phenylbutyrate [Gardian et al., 2005]); antioxidants, mitochondrial enhancers, and energy substrates (e.g., coenzyme Q_{10} [Huntington Study Group, 2001] and creatine [Hersch et al., 2006]); neuroprotective compounds (e.g., lithium [Wei et al., 2001]); antiapoptotic compounds (e.g., minocycline [Huntington Study Group, 2004]); transglutaminase inhibitors (Dubinsky and Gray, 2006); reagents that block protein aggregation or assist protein folding; compounds to enhance autophagic clearance of mutant protein (Sarkar et al., 2007); inhibitors of the kynurenine 3-monooxygenase pathway (Giorgini et al., 2005); cell or gene replacement therapy (Bachoud-Levi et al., 2000; Bloch et al., 2004; Keene et al., 2007); and RNA interference reagents that "knock down" disease gene expression (Harper et al., 2005). The availability of numerous mouse models of HD in which disease progression can reliably be measured has allowed researchers to identify more than 20 compounds or reagents that slow disease in these models and therefore may warrant human trials (reviewed in Beal and Ferrante, 2004; Hersch and Ferrante, 2004). Two challenges at hand are (1) determining which molecules and compounds should be tried in human trials and (2) refining quantitative measures of HD in humans so that clinical trials can be performed faster and in fewer subjects without sacrificing statistical power.

To date, human clinical trials testing candidate preventive compounds have been discouraging. In the largest published study to date, the CARE-HD study, in which both coenzyme Q_{10} and remacemide were tested, coenzyme Q_{10} (600 mg) showed a statistically insignificant trend toward slowing disease (Huntington Study Group, 2001). A similar study of a higher dose of coenzyme Q_{10}, the 2CARE trial (also sponsored by the Huntington Study

Group), recently began. This study tests the effects of 2,400 mg/day on the progression of functional decline in HD subjects.

The field is now witnessing human trials that include potential biomarkers of disease as outcome measures. For example, a short-term study of creatine in a small number of HD subjects led to a reduction in a marker of DNA damage, 8-OH- deoxyguanosine (Hersch et al., 2006). We caution the reader that even though reducing levels of a peripheral marker of DNA damage sounds promising, we do not know that doing so would alter the disease process or disease progression in any way. As more potential biomarkers of disease surface, it will be vitally important to correlate changes in them with disease progression and with the clinical response to any preventive medication that does surface.

Search for Quantifiable Measures

This latter study points to the growing interest in identifying biomarkers for HD—for example, changes in brain imaging (reviewed earlier), metabolic/proteomic profiles (Dalrymple et al., 2007; Gomez-Anson et al., 2007), or gene expression (Borovecki et al., 2005) that might one day serve as reliable proxies for clinical benefit. To get there, however, we first need to know more about disease progression.

In the HD research community, efforts to define disease progression and response to medications have been aided greatly by a widely used standardized clinical rating scale, the Unified Huntington's Disease Ratings Scale (UHDRS) (Huntington Study Group, 1996; Siesling et al., 1998). The UHDRS has four major components: motor function and cognitive, behavioral, and functional ability. It has been used by the large consortium of HD investigators known as the Huntington Study Group for 15 years and serves as the data collection base for two ongoing, large-scale observational trials: PREDICT-HD (Paulsen et al., 2006) and PHAROS-HD (Huntington Study Group PHAROS, 2006). The movement disorder of HD has classically been the barometer by which neurologists establish the diagnosis. Reliance on movement disorder as the *sine qua non* of HD diagnosis may change as these studies identify a nonredundant set of cognitive, psychiatric, and functional measures that are associated with motor scores.

With respect to developing therapeutics, it is important to recognize that clinical progression in HD and accompanying brain changes detectable by imaging can be quantified both before and after diagnosis. Studies have shown measurable decreases in total functional capacity, particularly in the early to middle years after diagnosis (Marder et al., 2000). Because the limited dynamic range of these measures in advanced disease makes it much more difficult to assess progression late in disease, effective preventive trials will almost certainly be carried out in early HD or prediagnosis subjects who are relatively close to the predicted age of onset. A subset of measures in the full UHDRS, perhaps supplemented with additional cognitive tests, likely will constitute a reliable, straightforward battery of tests with which clinicians in future trials can measure changes in rate of progression and more accurately pinpoint phenoconversion to manifest disease. As shown in Figure 1.4, an effective preventive medication would slow the rate to "phenoconversion."

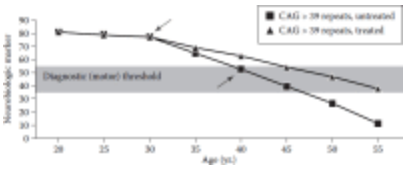


FIGURE 1.4

Intervention model for adult-onset HD. In this illustrated scenario, the downward-pointing arrow indicates administration of an effective neuroprotective agent in a treated individual, whereas the upward-pointing arrow indicates the point of clinical (more...)

Ongoing observational studies likely will generate the longitudinal data that allow the HD research community to establish associations between specific biomarkers and either conversion to manifest disease or progression of disease. Biochemical markers like 8-OH-deoxyguanosine or other metabolomic or genomic markers are being sought as state markers, progression markers, and response markers. Imaging markers look directly at brain changes and may prove to be particularly useful as progression/response markers and even prove to be suitable as surrogate endpoints. All putative biomarker methods will need to be validated against the well-developed clinical dataset and carefully evaluated to ensure that they have suitable statistical properties. Certain such markers may then become true surrogates for a clinical endpoint and thus permit trials of shorter duration in smaller numbers of subjects to identify preventive medications or experimental treatments. In short, “one of the incurables” might just become treatable after all.

Go to:

SUMMARY

HD is a complex and clinically demanding disorder. Work over the past two decades has defined the clinical phenotype and neuropathology with increasing precision. This essential descriptive work provides the platform for an increasingly sophisticated body of clinical research aimed at developing tools for characterizing clinical, imaging, and other features of HD. These new tools will facilitate researchers’ ability to translate insights from the laboratory into rigorous clinical research and potential therapies for HD.

Go to:

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Section E iv

Huntington disease: Clinical features and diagnosis

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INTRODUCTION

Huntington disease (HD) is an inherited progressive neurodegenerative disorder characterized by choreiform movements, psychiatric problems, and dementia. It is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the huntingtin (HTT) gene on chromosome 4p and inherited in an autosomal-dominant pattern. The pathophysiology of HD is not fully understood, although it is thought to be related to toxicity of the mutant huntingtin protein. As there is no known cure, treatment is symptomatic and remains supportive.

This topic will review the clinical features and diagnosis of HD. Other aspects of HD are discussed separately. (See "Huntington disease: Genetics and pathogenesis" and "Huntington disease: Management".)

ETIOLOGY/GENETICS

The genetics and pathogenesis of HD are reviewed here briefly and discussed in detail separately. (See "Huntington disease: Genetics and pathogenesis".)

Huntington disease is an autosomal dominant disorder caused by an expansion of the cytosine-adenine-guanine (CAG) trinucleotide in the huntingtin (HTT) gene (also known as the HD gene) that encodes the protein huntingtin, resulting in an expanded polyglutamine tract. Huntingtin is present in a large number of tissues throughout the body. However, pathology mainly involves the central nervous system, with atrophy of the caudate and putamen (the neostriatum) being most prominent. At the cellular level, protein aggregates are seen both in the cytoplasm and nucleus. The pathophysiology of neuron loss is incompletely understood. The huntingtin protein is thought to become toxic with the CAG expansion ("gain of function") but continues to serve a function that is critical to survival in early development.

The main determinant of age of onset is the number of CAG repeats in the HTT gene. The normal number of repeats is 28 or less. Repeats between 28 and 35 will not develop symptoms but the next generation is at a small risk to develop expansion which may or may not be into the disease-causing range. Repeats between 36 and 39 are incompletely penetrant – individuals may develop symptoms but typically with a late age of onset. When repeats are equal or greater than 40, the disease is fully penetrant and symptoms of the disease will occur. Those individuals with the earliest onset tend to

have the largest expansion in the number of repeats, while onset late in life correlates with a lower expansion of the repeat number. Rate of disease progression is also inversely related to repeat size. Additional factors predicting age of onset are thought to be environmental and/or other genetic determinants.

Literature review current through: **Nov 2020.** | This topic last updated: **Sep 09, 2019.**

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Section E v

Pharmacological management of Huntington's disease: an evidence-based review

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Abstract

Introduction: Despite the increasing body of published reports on pharmacological interventions in Huntington's disease (HD), an evidence based review (EBR) of treatment studies has not yet been published.

Method: Systematic literature searches were done using Medline (1965-August 2005), the central database in the Cochrane Library (1969-August 2005), and reference lists published in review articles and other clinical reports. Randomized controlled trials (RCTs) were classified as level-I-studies in this paper. Level-II evidence was assigned to non-randomized, controlled clinical studies. Level-III-studies comprised open label trials excluding case reports. Measures of efficacy as well as safety and tolerability were considered for each compound.

Results: We identified 218 publications on pharmacological interventions in HD since 1965. Among them were 20 level-I, 55 level-II, 54 level-III trials, and 89 case reports. All these papers are listed and analyzed. Chorea was the primary end point in all level-I and level-II symptomatic intervention trials. There is some evidence for treating chorea with haloperidol or fluphenazine, and less evidence for olanzapine. These three drugs have been considered "possibly useful" for the treatment of chorea in this analysis. Other substances (e.g. amantadine, riluzole, and tetrabenazine) are considered "investigational" for chorea. There is very low evidence for the treatment of other problems: "possibly useful" drugs are L-dopa and pramipexole for rigidity; amitryptiline and mirtazapine for depression; risperidone for psychosis; and olanzapine, haloperidol, and buspirone for behavioral symptoms in HD. Three substances are considered "investigational" for possible neuroprotection: coenzyme Q10, minocycline, and unsaturated fatty acids.

Conclusion: There is poor evidence in management of HD today. The analysis of the twenty level-I studies fails to result in any treatment recommendation of clinical relevance. High-quality RCT are highly warranted to advance HD treatment in clinical practice.

Section F vi

POLICY AND PRACTICE REVIEWS ARTICLE

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International Guidelines for the Treatment of Huntington's Disease

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The European Huntington's Disease Network (EHDN) commissioned an international task force to provide global evidence-based recommendations for everyday clinical practice for treatment of Huntington's disease (HD). The objectives of such guidelines are to standardize pharmacological, surgical and non-pharmacological treatment regimen and improve care and quality of life of patients. A formalized consensus method, adapted from the French Health Authority recommendations was used. First, national committees (French and English Experts) reviewed all studies published between 1965 and 2015 included dealing with HD symptoms classified in motor, cognitive, psychiatric, and somatic categories. Quality grades were attributed to these studies based on levels of scientific evidence. Provisional recommendations were formulated based on the strength and the accumulation of scientific evidence available. When evidence was not available, recommendations were framed based on professional agreement. A European Steering committee supervised the writing of the final recommendations through a consensus process involving two rounds of online questionnaire completion with international multidisciplinary HD health professionals. Patients' associations were invited to review the guidelines including the HD symptoms. Two hundred and nineteen statements were retained in the final guidelines. We suggest to use this adapted method associating evidence base–medicine and expert consensus to other rare diseases.

Introduction

HD is a rare neurodegenerative disorder of the central nervous system, with a genetic autosomal-dominant inheritance, that first involves basal ganglia (caudate nucleus and putamen) and results from expansion of a CAG trinucleotide repeat in the HTT (huntingtin) gene: alleles with 40 or more repeats are fully penetrant. The disease is characterized by motor, cognitive

and psychiatric disorders, and a range of somatic symptoms. Progressive worsening leads to a bedridden state with cognitive deterioration. Death occurs about 20 years after the onset of symptoms.

More than a century after the first description of Huntington's disease (HD), there is still no curative treatment of the disease; however, symptomatic treatments are thought to be efficacious in controlling some of its troublesome symptoms. Yet, symptomatic management of HD remains inadequately documented (1–4), which may lead to variations in care mainly based on clinical experience and not on scientific evidence (5–7).

This document provides scientifically supported and consensual pharmacological, surgical and non-pharmacological recommendations for the treatment of HD.

Materials and Methods

Methodology

The EHDN guidelines task force developed guidelines between 2015 and 2018 based on a formalized consensus method, adapted from the 2015 French Health Authority recommendations (HAS) (https://www.has-sante.fr/portail/jcms/c_272505/recommandations-par-consensus-formalize-rcf). This method combines exhaustive review of the literature, experts' proposals, and external scoring of the proposals until agreement (Figure 1). This is particularly suitable when at least two of the following conditions are met (1) absence or insufficiency of high-level evidence specifically addressing the questions asked; (2) possibility of declining the theme in easily identifiable clinical situations; (3) controversy, with the need to identify by an independent group situation in which a practice is deemed appropriate. Its main advantages are (1) its ability to identify the degree of agreement or indecision among experts (2) the strict independence between the steering group, which formulates the proposals to be put to the vote, and the rating group which judges the appropriateness.

FIGURE 1

Figure 1. Guidelines' developing stages.

Search Strategy

First, we conducted a search of scientific evidence published between 01/01/1965 and 01/08/2015 in the following databases: Cochrane Library, Embase, MEDLINE, PASCAL, BMJ Clinical Evidence, Current Contents, Infobanque AMC, National Guidelines Clearinghouse, PEDro, and BDSP (Public Health Database) as well as in the following websites: CEBAM, EBM sources, OMS Réseau de bases factuelles en santé, CBEM Oxford, Center for Evidence based child health, Center for health evidence, Center for reviews and Dissemination, Evidence based neurology, National institute for health and clinical excellence, Orphanet, ClinicalTrials.gov, OpenSIGLE (System for Information on Gray Literature in Europe). We also hand searched abstracts of international congresses of the Movement Disorders Society. Search terms were chosen based on a list of symptoms to focus on determined following discussions within the guidelines committee and working groups (neuroprotective, rehabilitation, and cognitive) of the European Huntington's Disease Network. Search terms were: “Huntington disease,” “drug therapy,” and symptoms (Huntington chorea, drug therapy, Chorea, Dystonia, Falls, Chokes, Bradykinesia, Rigidity, Depression, Apathy, Irritability, aggression, Obsessions, perseverations, Anxiety, Agitation, Hallucinations, delusions, paranoia, Impatience, Impulsivity, Suicidal Ideation, Memory, Loss of fluency, speech, Dysarthria, Attention disorders, Social cognition impairments, Disorientation, Bradyphrenia, Indecision, Weight loss, Incontinence, Sleep disorders, Diarrhea, Sweating, Constipation, Vomiting, Swallowing, Pain, Dental decay, and Surgery).

Drug manufacturers and authors were also contacted in order to obtain additional information on unpublished trials. In total 637 publications were collected.

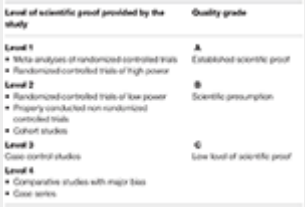
Data Extraction and Analysis

The Task Force committees reviewed the 637 collected publications with the French and UK committees focusing on pharmacological/surgical and non-pharmacological interventions, respectively. First, two members of each national committee conducted independently a screening of the collected publications and retained results from clinical trials, observational studies, meta-analysis, systematic reviews, case studies, previous recommendations, or conference and congress summaries. Studies including patients with HD clinical features and a confirmatory genetic diagnosis or a compatible family history (mostly for studies published before gene discovery in 1993) were also included 288 and 88 papers on pharmacological/surgical and non-pharmacological interventions, respectively, were retained for further analysis. The remaining members of the Task force validated the list of excluded publications. Second, a pair of members from each national committee summarized the key elements of the retained studies by filling a table with the following columns: authors, date of publication, type of intervention, daily dose (both of the active drug and the placebo), genetic characteristics of the patients (genetically diagnosed), study design, number of participants, duration of the study, primary and secondary endpoints, outcome, scales used, conclusion of the reviewers, and level of proof. Then they analyzed independently each study by assessing the methods (quality of the study) and results (the contents of the study) and assigned a level of scientific evidence according to the HAS classification (see below).

Quality Appraisal and Data Synthesis

Following the HAS recommendations, a quality grade was attributed to each study according to the level of scientific proof they provided (Table 1) (Appendix 1).

TABLE 1



Level of scientific proof provided by the study	Quality grade
Level 1 • Meta-analyses of randomized controlled trials • Randomized controlled trials of high power	**A** Established scientific proof
Level 2 • Randomized controlled trials of low power • Properly conducted non-randomized controlled trials • Cohort studies	**B** Scientific presumption
Level 3 Case-control studies	**C** Low level of scientific proof
Level 4 • Comparative studies with major bias • Case series	

Table 1. Level of scientific evidence and gradation of studies.

Method for Reaching a Consensus

The subsequent steps for developing the guidelines are displayed in Figure 1. First, the experts of the national committees formulated provisional recommendations for each HD symptom, classified in four categories of disorders (motor, psychiatric, cognitive, and “others”). Recommendations were based on the synthesis of information from the studies, i.e., quality grade, accumulation of scientific evidence, and professional expertise. Recommendations were rated according to the quality grades of the studies on which they are based, with the highest quality grade determining the score. When scientific evidence was lacking, best clinical practice (professional agreement) was formulated, based on the experience of the National committees. The International Steering Committee reviewed the initial recommendations before initiating process to reach a consensus with the International Multidisciplinary HD Health Professionals group (Table 2). This involved two rounds of online questionnaire completion. After the first round, only appropriate recommendations with strong consensus were retained (Table 3). Those without strong consensus were reviewed and modified by the International Steering Committee prior to the second round of ranking (Table 3). After the second round, all recommendations were deemed appropriate, and agreed as such, except two of the motor chapter and two of the psychiatric chapter. Two hundred and nineteen statements were retained in the final guidelines. The steering committee added a rider considered important by the multidisciplinary group to the four recommendations that did not reach a consensus. Whereas, the literature basis scored through survey monkey ends in 2015, experts' and knowledge input were provided through the survey

scoring and comments as well as the last face-to-face meeting until October 2018.

TABLE 2

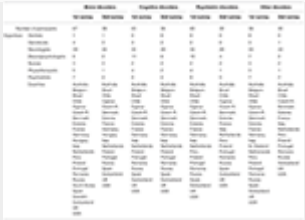


Table 2. Composition of the international multidisciplinary HD health professionals.

TABLE 3

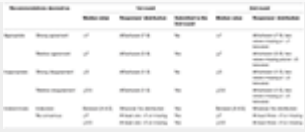


Table 3. Rules to determine the strength of the consensus of the multidisciplinary experts.

Patients' Associations Involvement

European, Chinese and French HD associations as well as the Italian League for Research on Huntington and related diseases Foundation were invited to review the guidelines.

Results

A condensed version of HD symptoms and recommendations is provided in the main text. A full version is available in Appendix 2. Publications justifying the grades of the recommendations are cited in the text. Recommendations provided without specific grading are underpinned by professional agreements.

Given that any HD symptoms may be worsened by stress, fatigue, and intercurrent disorders (e.g., anxiety, digestive disorders, infectious or painful conditions, etc.), these aspects must be assessed and should be treated with appropriate measures alongside managing the Huntington's symptoms.

Motor Disorders

The wide spectrum of motor manifestations are the best known and the most visible symptoms in HD. Among them, involuntary movements (i.e., chorea) are the most obvious. However, while the diagnosis of manifest HD is based on the presence of motor symptoms, these are frequently preceded by cognitive and behavioral symptoms (8). While motor symptoms are easily detected, and might be the source of anxiety and ostracism, they are often well-tolerated by the patients and their proxies in contrast to cognitive and behavioral symptoms that often lead to family and social/professional's issues.

Chorea

Chorea is characterized by abnormal, involuntary, spontaneous, uncontrollable, irregular, intermittent, non-rhythmic and aimless movements affecting the trunk, the face, and the limbs.

Drug treatment should be considered if chorea causes the patient distress or discomfort.

Tetrabenazine is one of the first-line treatments for this symptom (Grade A) (9) unless the patient suffers from not well-managed depression or suicidal thoughts. Second generation neuroleptics (Grade B) (10, 11) are first-line treatments for this symptom in particular when the patients have associated personality and/or behavioral or psychotic disorders. Monotherapy to treat chorea is preferred because combination therapy increases the risk of adverse effects and may complicate the management of non-motor symptoms. In the presence of disturbing chorea, appropriate protective measures (especially during meal times and during the performance of instrumental activities of daily living) should be put in place to avoid traumatic injury or chokes. Rehabilitation specialists can help identify appropriate assistive technology devices and positioning techniques.

Dystonia

Dystonia is characterized by abnormal postures that may affect all body segments and is frequently associated with rigidity (12). Dystonia intensity varies from a slight intermittent abnormal posture to severe twitch of muscles with major impact on movements and functions of daily living.

Both active and passive physiotherapy approaches are recommended as a preventive measure to maintain the range of joint motion, limit postural and musculoskeletal deformities and, prevent the development of contractures. Injection of botulinum toxin in the case of focal dystonia or to prevent secondary deformities should be performed by a trained professional. Customized chairs can provide a comfortable environment in view of the dystonia-related deformities.

Rigidity

Rigidity is an increase in muscle tone leading to a resistance to passive movement that can induce joint stiffness and limited range of motion, which might be distressing for patients.

Rigidity may be increased or induced by the use of neuroleptics or tetrabenazine. If this impacts the functional capacity of the patient, a reduction in dosage or the withdrawal of neuroleptics and/or tetrabenazine should be considered considering overall benefit on chorea and/or behavioral symptoms vs. severity of rigidity.

Levodopa may provide partial and temporary relief of the akinetic–rigid symptoms of HD, especially in juvenile forms (Grade C) (13–18). Treatment with levodopa should be started gradually and the total daily dose is usually lower than in Parkinson's disease.

Physiotherapy is recommended to improve or maintain mobility and prevent the development of contractures and joint deformity (Grade C) (19).

Akathisia

Akathisia is a syndrome characterized by unpleasant sensations of “inner” restlessness that manifests as an inability to sit still.

An iatrogenic cause of akathisia should be investigated as the priority.

Tetrabenazine (Grade C) (20, 21), neuroleptics and Selective serotonin reuptake inhibitors (SSRI) may cause akathisia in HD and reducing the dose or changing the treatment may be helpful.

Swallowing Disorders

Swallowing disorders can occur in patients at the early stages of the disease and become a major problem in later stages by inducing repeated choking and leading to secondary bronchopulmonary infections or even cardiac arrest.

Regular assessment of swallowing disorders should be provided throughout the progression of the disease (Grade C) (22) and referral to a Speech and Language Therapist is recommended as soon as the disorders appear (Grade C) (22–24).

Ancillary assessments that may help in managing swallowing disorders include: generalized motor skills, respiratory status, dental health, mood, behavior and emotional status, cognition, nutrition, and hydration status. Provision of information and advice on safe swallowing procedures, on posture and positional changes can help to avoid aspirations and leads to improvement of swallowing disorders. Oral-facial exercise with swallow sequence individualization and cough post swallow may also improve swallowing difficulties. In some cases, treating chorea might help in improving swallowing problems. However, side effects of treatments for chorea (e.g., sedation, attention, and parkinsonism) might also negatively impact swallowing capacities.

The education of carers is important as they are often managing the eating, drinking, and swallowing regime.

For severe swallowing disorders impacting nutrition and quality of life of the patient, the use of a gastrostomy device Percutanous Endoscopic Gastrostomy (PEG) may be considered and should be discussed on a case-by-case basis with the patient and the caregivers. PEG should be anticipated and discussed with relatives and patients still able to understand the benefits and burdens of the methods. Before advanced stages of the disease, patients should be educated to make an informed choice concerning the PEG methods even if they can change their decision at any time.

Myoclonus

Myoclonus refers to sudden muscle contractions, brief and involuntary, axial, in extremities or generalized, similar to spams and jerks in epileptic seizures but not related epilepsy. In HD, myoclonus can be observed in a predominant akineto-rigid phenotype and can be associated with an at rest or action tremor, especially in the juvenile forms but also in later-onset forms. In juvenile forms, non-epileptic myoclonus can coexist with epilepsy.

In case of myoclonus impacting the functional capacity of the patients, treatment with sodium valproate or clonazepam, used alone or in combination, and in escalating doses, is recommended (Grade C) (25–32). Levetiracetam is a therapeutic alternative for the same indication. In case of myoclonus of cortical origin that is not associated with epileptic seizures, piracetam has a marketing authorization (Grade C) (29). Benzodiazepines, in particular clonazepam, may be used to manage myoclonus whilst remaining vigilant with regard to adverse effects such as somnolence and increasing falls, and the risk of drug-dependence.

Gait and Balance Disorders

Gait and balance disorders impairments include disruption of cadence regulation, increased variability of step width and length, disturbed initiation

and increased postural sway (33). These develop as a result of the progressive complex movement disorder seen in HD adding to the overall burden of motor morbidity with falls and loss of independence in HD (34).

Generally, interventions for gait and balance should start as early as possible and be continued and adapted throughout the progression of the disease (Grade C) (33, 35–38). Physiotherapy interventions (Grade B) (39–42) and the introduction of falls prevention programs, gait, core stability, and balance interventions (Grade C) (35, 43–45) as well as attentional training are recommended.

Pharmaceutical management of chorea may improve walking and balance as they can be affected by chorea (Grade C) (46–49). However, they should always be used cautiously and regularly reassessed as their adverse effects may also aggravate walking disorders.

Maintaining physical activity and low impact exercises is recommended.

The use of assistive devices such as four-wheeled walker (Grade B) (50) as recommended by Physiotherapist or Occupational Therapist should be considered to improve stability and reduce fall risk.

Bruxism

Bruxism is an involuntary clenching with excessive contraction of the jaw muscles. It typically causes lateral movements (or front to back) responsible for gnashing and can lead to tooth damage.

Injecting botulin toxin A into the masseter muscles is proposed as the first-line treatment of bruxism (Grade C) (51). Customized protective mouth guards may be used to reduce the complications of bruxism on a case-by-case basis, mostly in early stage patients.

Bruxism may occur as a side effect of neuroleptics (Grade C) (51, 52) and serotonin reuptake inhibitors, thus reducing their dose should be considered.

Manual Dexterity

Manual dexterity can be impaired secondary to chorea/dystonia/akinesia/rigidity but also occur in their absence—due to abnormal motor planning and sequencing.

Neuroleptics and tetrabenazine may possibly have a beneficial effect on dexterity as a result of reducing chorea (Grade C) (46, 47, 53) but may also have a detrimental effect on dexterity by aggravating other symptoms such as bradykinesia.

Management with physiotherapy and occupational therapy may be useful to reduce the functional impact of fine motor skill deterioration (Grade B) (41). Adaptive aids may help to compensate for the deterioration of manual dexterity.

Global Motor Capacities

Early referral to a physiotherapist is recommended in order to facilitate the development of a therapeutic relationship, promote sustainable exercise behaviors and ensure long-term functional independence.

Physiotherapy and/or personalized exercise programs (Grade B) (40) are beneficial for the overall functional ability, motor function, and independence in HD, in combination with pharmacological treatments (Grade B) (39, 40, 42).

Cognitive Disorders

Cognitive deficits appear frequently before motor symptoms (8). They are, in addition to behavioral symptoms, the major cause of family disruption and social withdrawal (54). Cognitive symptoms cause intense psychological discomfort and a sense of powerlessness that can lead to behavioral symptoms.

Based on present knowledge, no pharmacological treatment is recommended for the treatment of cognitive symptoms.

Multiple rehabilitation strategies (speech therapy, occupational therapy, cognitive and psychomotricity) might improve or stabilize transitorily cognitive functions at some point of time in the course of the disease (Grade B) (55).

Executive Functions

Executive functions refer to the functions that allow the realization of complex task in daily living. They consist in a set of functions mostly dedicated to cognitive and behavior control and adaptation, which may be impaired in HD, even at the premanifest stages and thus impose adaptation from the environment, organization support including proactivity in planning appointments, behavior or daily life activities like cooking.

For the patients to maintain their independence for as long as possible, it is better to help the patients organize themselves and initiate activities rather than substitute for them, as long as they do not endanger themselves.

Treatment for anxiety and depression may help to improve executive function and cognitive stimulation through rehabilitation may improve planning and initiation more specifically (Grade C) (56). Sedative drugs and neuroleptics should be closely monitored as they impair executive functions and attention.

Bradyphrenia

Bradyphrenia is defined by slowing of cognitive information processing and a prolongation of reaction time depending on the complexity of the cognitive task (57). It becomes more apparent with HD disease progression.

Management is based on giving the patient enough time to process information and perform a task and avoiding time-pressured situations. Cognitive stimulation as part of rehabilitation may be beneficial.

Language and Communication Disorders

Language and communication disorders can be divided in speech and language disorders *per se*. Speech disorders consist of slurred and slowed speech causing dysarthria, inappropriate pauses or bursts of speech, and progressive reduction in verbal fluency (58). Language (e.g., syntax) impairments appears early in the disease course, with progressive difficulties in understanding and producing complex sentences. Reduction of lexical capacities appears later. This often goes unnoticed and may cause misunderstanding and impaired communication.

The changing communication needs of the person with HD should be reassessed throughout the course of the disease to plan effective management strategies (Grade C) (59). As communication disorder in HD is variable, its monitoring requires comprehensive assessment of language and of other factors such as mood, motivation, and behavior.

Early referral to Speech and Language Therapists is recommended (Grade C) (59) as they can play a major role in assessing and managing communication problems in HD at all stages of the disease. Communication strategies and techniques may include: management options (e.g., voice therapy techniques), advice on facilitation of communication (e.g., allowing time for communication, reduction of environmental distractions and noise) and the use of simple technics (e.g., gestures and rephrasing) or tools (e.g., pen and phones).

Family members and other communication partners should be educated to support patients to attempt verbal communication as long as possible. Augmentative and alternative communication (talking mats) can compensate

for communication difficulties and increase the individual's chance of participation in daily life. These strategies need to be implemented whilst there is still motivation and a capacity to learn (Grade C) (60).

Social Cognition Impairments

Social cognition impairments refer to a set of symptoms that affect relationships and social behavior. The most studied are the inability to recognize emotion others (61) but also to express emotions, both through facial expression or through the voice. Executive function impairments can make difficult for the patients to express their feelings. The capacity to infer other thoughts or feeling, are also reported to be impaired in patients (61). Furthermore, motor impairments can create a “facial mask,” often misunderstood as indifference.

Improvement of behavioral disorders may help with social and family integration. However, impact of SSRI or neuroleptics on social interaction *per se* has not yet been properly assessed to allow any recommendation specific to this domain.

Explaining the patients' disorders to their family, health care professionals or to their colleagues may facilitate the patient's social relationships. Moreover, third party intervention (e.g., caregiver, nurse, and social worker) may stimulate patients' social interaction.

Memory Disorders

Memory disorders are frequently reported in HD and may be confounded with or exacerbated by attention disorders. They are mostly characterized by difficulties in learning new information and retrieving information acquired (62).

Strategies such as establishing and keeping a regular daily routine may compensate memory loss. Rehabilitative approaches (speech therapy or neuropsychology) may help memory as part of an overall intervention plan. Specifically, domain-specific transcoding (verbal and visual) may help in recalling items.

Sedative drugs, neuroleptics and tetrabenazine may impact negatively on memory.

Disorientation

Disorientation, both in time and space, appear during the progression of HD but temporal orientation is altered earlier (63–66).

Investigations should be carried out to detect any potential intercurrent cause for a confusional state. Establishing a regular routine, in tune with the patient's environment as much as possible, and milestones enables the patient to manage their time better.

Visuospatial and Visual Perceptual Disorders

Visuospatial and visual perceptual disorders appear late in the course of the disease through interference with the integration and understanding of visual information (66).

It may be useful to make the patient's environment safe (padding furniture) to minimize falls and shocks linked to visual spatial difficulties and aggravated by motor disorders.

Psychiatric Disorders

Behavioral symptoms may appear before the motor diagnosis of the disease. They are, in addition to and in conjunction with cognitive symptoms, the major cause of family disruption, social isolation, and withdrawal.

Their management should be based on the identification of the underlying triggers causing changes in mood or behavior. Patients should be given the opportunity to express their worries and frustrations.

Using methods to calm and reassure patients is a major component of care of psychiatric disorders. Based on data from other neurodegenerative conditions, mindfulness-based cognitive therapy and Acceptance and Commitment Therapy may be useful in HD.

Depression

Depression is one of the most common psychiatric symptoms seen in HD (67, 68) with a significant negative impact on quality of life. It may affect patients at any stage of the disease, even before motor manifestation (69). Thus, vigilance to detect and treat depression is required at all stages of the disease.

Psychotherapy and cognitive behavioral therapy may enable early detection of mood changes. An antidepressant may be suggested if depression occurs in HD (Grade B) (70). It is recommended to use a selective SSRI or a serotonin noradrenaline reuptake inhibitor (SNRI), or alternatively Mianserin or Mirtazapine, in case of sleep disruption. In case of recurrent depression, long-term mood-stabilizer treatment may be introduced in complement to the treatment of the current episode to prevent relapses. If depression is thought to be an adverse effect of other medication, the dosage of the responsible drug should be reduced gradually. In the case of resistant depression, or depression associated with psychotic symptoms, a psychiatrist should be consulted. In case of severe depression and resistant to oral medications, electroconvulsive therapy (ECT) may be suggested under the guidance of a psychiatrist (Grade C) (71–73).

Suicidal Ideation or Attempts

Suicidal ideation or attempts are common in HD (74) and correlate with family history of suicide, a history of previous suicide attempts and the presence of depression, especially in prodromal stages (75).

Suicide risk should be assessed in HD irrespective of the stage, being particularly vigilant at the time of diagnosis and when the disease starts to impact on day-to-day life. Prevention of suicide includes treating risk factors such as underlying depression, social isolation and impulsivity.

Irritability

Irritability is a very common symptom in HD (67, 68, 76). This disorder is of fluctuating nature, characterized by impatience and a tendency to become angry in response to minimal provocation. Overflow and loss of control are favored by impulsivity, and can lead to aggressive behavior toward self or others, and rarely, to criminal behavior. This symptom can be caused by the frustrations felt by the patient because of the great loss of his capacities, and by troubles in expressing himself, as well as by neurological/psychological fatigue brought by the latter.

Before initiating pharmacological treatment, possible environmental causes for the patient's frustration and irritability should be explored. In order to reduce irritability, behavioral strategies should be considered. A structured plan with a regular routine in a calming environment is desirable. In addition, psycho-education for the patient's family regarding diversion strategies should be attempted to avoid confrontation as much as possible.

Whilst SSRIs are first lines for irritability (Grade C) (77, 78), it may be necessary to use them at or near the maximum recommended dose in order to be effective. Irritable patients who do not benefit from an SSRI alone may benefit from combination therapy with Mianserine or Mirtazapine, especially when sleep disorders are present. In patients with aggressive behavior, the recommended first-line treatment is a neuroleptic (Grade C) (79–81). In case

of overt aggression associated with depression, neuroleptic treatment should be associated with sedative antidepressants. If irritability does not respond to antidepressant therapies and/or neuroleptics, a mood stabilizer (Grade C) (82, 83) can be added.

Apathy

Apathy has been defined by Levy and Czernecki (84) as "a quantifiable reduction in goal-directed behavior," manifesting clinically as a reduction in interest, spontaneity, motivation, and drive. In patients with HD it is compounded by emotional blunting, resulting in social withdrawal, and lack of concern for others. It is the most frequent psychological and behavioral symptom in HD, especially in the middle and later stages, causing a severe reduction in the activities of daily living and often being a source of conflict in the family. With regard to cognitive and psychological symptoms, apathy and irritability are the two faces of the same coin (85). A patient can be apathic the morning and irritable the afternoon, depending on the situation. As for irritability, apathy can be caused by environmental and psychological issues. Apathy may also be an adaptive response when the patient feels overwhelmed by too much stimulation (HD patients are more sensitive to noise and environmental interferences), or with the feeling that his/her disease is progressing.

It is important to explain the various aspects and causes of the apathy to the family circle.

Personalized cognitive stimulation, establishing routines and a structured programme of activities is recommended when possible. A professional intervention at home can improve compliance and reduce the patient's opposition and irritability.

Depression may increase apathy. If depression is suspected, an SSRI should be tried.

Sedative medication may increase apathy, thus avoiding unnecessary prescription or reduce dosage is recommended.

Anxiety

Anxiety as defined by the uncomfortable feeling of nervousness or worry about something that is happening or might happen in the future, is common in HD. Anxiety is linked to the other symptoms (motor and cognitive), as the patient is anxious because of the loss of essential functions, and correlated to family, social and economic issues, and to the burden of his pathology (and the one of his proxies). However, anxiety does not increase with disease progression. It is associated with depression, suicide, irritability, quality of life, pain, illness beliefs, and coping.

SSRI or SNRI are first line treatments of anxiety, especially when associated with depression. On-demand prescription of an anxiolytic might be beneficial, but caution is required because of the associated risk of worsening or causing falls. Neuroleptics (Grade C) (86, 87) are valuable therapeutic alternatives in the treatment of anxiety when other treatments fail.

Obsessions

Obsessions are defined by recurrent and persistent thoughts, ideas or images that do not let the mind rest, causing anxiety. True obsessions, according to this definition, are not very common in patients with HD, but perseveration is very common, particularly in the middle and later stages (76). Perseveration may be defined as the repetition of a thought, behavior or emotion beyond the psychological context in which it arose, and in patients with HD these repetitive thoughts and behaviors can persist for hours, months, or even years after the original trigger. Patients have little or no insight into the problem (in contrast to obsessional thoughts, which are distressing and recognized as abnormal); however, it has been shown that perseveration is the one

behavioral symptom in HD which has a significant negative impact on the quality of life of family members and caregivers (88).

Over the course of HD, symptoms may change and repetitive thoughts may replace obsessive–compulsive disorder. The distinction between obsessive–compulsive phenomena and perseverations is important for the care strategy, both requiring differential approaches.

If pharmacological treatment is necessary for perseverative symptoms, an SSRI could be prescribed (Grade C) (89), in particular when symptoms are associated with anxiety. Olanzapine and risperidone (Grade C) (81, 86) are two valuable therapeutics for ideational perseverations, in particular when they are associated with irritability.

True obsessive–compulsive phenomena are sensitive to psychological intervention, such as Cognitive Behavioral Therapy, in non-cognitively impaired patients. If pharmacological treatment is necessary for obsessive-compulsive phenomena, a SSRI should be prescribed as first-line treatment (Grade C) (89).

Impulsivity

Impulsivity consists of acting without prior planning, which can lead to unpredictable behavior. When impulsivity is associated with depression or irritability, there is a significant increased risk of self-harm or suicide or aggressiveness. Impulsivity may be the result of cognitive impairments, which lead to an intense frustration toward patience, the patient being in the incapacity to wait or to deal cognitively with planning. Impulsivity may then be an adaptive response to language difficulties of patients who cannot explain what stresses them.

When impulsivity is associated with depression or personality disorders, there is a risk of auto- or hetero-aggressiveness, which justifies the prescription of a

neuroleptic in combination with a SSRI. Long-term mood-stabilizer treatment may be introduced in the case of mood lability and impulsivity.

Sexual Disorders

Sexual disorders are very common in HD. Decreased libido is the most common symptom while hypersexuality or disinhibited behavior are rarer, but can cause significant problems in relationships. Repetitive hypersexual behaviors are often a result of perseveration.

Identifying the existence of sexual disorders and determining their triggers and their impact on relationships is important. Psychological support and/or referral to a specialist in psychosexual disorders might be useful. In the case of decreased libido, an iatrogenic cause should be investigated (e.g., the use of an SSRI) and reducing the dose or substituting the treatment responsible may be suggested. In the case of erectile dysfunction, treatment for impotence may be suggested and seeking the opinion of an endocrinologist and/or a specialist in psycho-sexual disorders may be useful. In case of impotence, prescription of phophoesterase 5 inhibitors should be considered in the clinic when asked for by the patient and his sexual partner. A behavioral and psychological approach is useful in the case of hypersexuality, by re-establishing appropriate standards of behavior in the patient's social setting. If hypersexuality involves social discomfort or violence, the proposed first-line treatment is a neuroleptic (Grade C) (90) and/or a SSRI. If the treatment for hypersexuality with neuroleptics and/or SSRI is not successful, the addition of or substitution for an anti-androgen may be proposed (Grade C) (91–93) under the guidance of a specialist in sexual disorders or an endocrinologist. Where hypersexuality poses a risk to others, specific measures should immediately be put in place (e.g., referral to a psychiatrist).

Hallucinations

Hallucinations are defined as a perception without an object, at which the subject adheres to and reacts as if the perception came from outside. Delusions are false beliefs based on incorrect inferences about external reality, the cultural and social context to which the patient belongs.

The use by the patient of psychotropic agents should be searched for and interrupted in case of hallucinations and delusions. Second generation neuroleptics are the first line treatment for hallucinations and delusions (Grade C) (80, 81, 86, 94–106). Clozapine should be proposed as the first-line treatment in the case of akinetic forms of HD with debilitating Parkinsonian symptoms. Perseverative ideation can sometimes mimic psychotic symptoms, and in such circumstances the patient may benefit from treatment with serotoninergic antidepressants in combination with an atypical neuroleptic. Psychiatric intervention and support are particularly useful in the case of psychotic disorders occurring in HD, for treatment adjustments. If pharmacological treatments fail, the option of ECT can be discussed with psychiatrists (Grade C) (71, 73, 107).

In case of agitation, priority should be given to identifying environmental or somatic triggers (bladder distension, fecal impaction, pain, etc.) in order to treat the underlying cause, especially in the advanced stages of the disease when communication difficulties exist. When agitation is associated with an anxiety disorder, a benzodiazepine should be prescribed as needed to reduce the risk of dependence and falls (Professional agreement). Some benzodiazepines (e.g., midazolam) may be useful in emergency situations. Long-term treatment with benzodiazepines should be avoided as much as possible but remains necessary in some patients. In the case of extreme agitation, and if there are associated behavioral and personality disorders, it is advised to prescribe a neuroleptic (Grade C) (82, 90, 91, 102, 108, 109).

Other Disorders

Other symptoms than motor, cognitive and psychiatric disorders are often present. Among those, weight loss, dysphagia, and sleep disturbance are not unfrequently the most prominent symptoms. As they may cause discomfort, they should be looked for in order to limit them when present.

Sleep Disorders

Sleep disorders are common in HD. Around two-thirds of HD patients suffer from sleep disorders, with diverse causes such as depression, anxiety, intrinsic alteration in the circadian sleep-wake rhythm, and involuntary movements during sleep inducing awakenings (110, 111). They may present as difficulties in falling asleep and/or early awakenings in the middle of the night followed by insomnia. They may be associated with aimless wandering, and lead to difficulties in coping by the proxies. However, disturbances of diurnal rhythm (day-night reversal, etc.) are probably more common than simple insomnia in HD patients.

Potential underlying cause of sleep-related difficulties (e.g., depressive syndrome, anxiety, and severe involuntary movements) should be investigated. Simple lifestyle and dietary strategies (e.g., avoiding long nap, having no stimulants after 4 pm) are the first-line treatment of insomnia. When lifestyle strategies are ineffective to treat insomnia, prescribing a hypnotic may be suggested for a short duration to avoid the risk of drug dependence. Some agents may be proposed in place of a hypnotic and for a long duration (e.g., mianserin, mirtazapine, and antihistaminic drugs) as they have a reduced tendency for causing dependency. Melatonin may be suggested in case of sleep phase inversion. A neuroleptic should be prescribed in the evening when sleep disorders are associated with behavioral disorders or chorea.

Urinary Incontinence

Urinary incontinence may either be multifunctional or linked to a deterioration of the frontal lobe control centers, causing an overactive bladder with urge incontinence and/or unannounced urination (112).

Where there is urinary incontinence, a precipitating factor should always be investigated (urinary infection, prostate disease). It is useful to investigate the presence of diurnal unexpected complete urination (complete and sudden bladder emptying, without urge) for which carbamazepine may be of benefit (Grade C) (112). In the case of an overactive bladder with leakage and urge incontinence, therapy with selective antimuscarinic may be tried, whilst watching out for the appearance of potential side effects, in particular confusional state. If, after few weeks, the incontinence therapy has not been effective, it should be stopped. If simple therapeutic measures have failed, it is advised to undergo urodynamic testing to help guide the choice of drug therapy and to consult a urologist if necessary.

In all cases, it is recommended to implement simple lifestyle strategies: urination before every outing and at regular times.

Pain

Pain assessment is sometimes difficult because of communication disorders. Moreover, because of communication's disorders and a tendency for these patients not to complain, pain is often related to non-verbal language and behavioral disorders such as irritability and restfulness.

Behavioral change or worsening of involuntary movements should trigger the search for an underlying source of discomfort, and in particular pain.

Dental Pain

Patients suffer from poor oral health for a variety of reasons, including impaired motor ability (e.g., difficulties brushing teeth) or reduced motivation

to maintain oral health, the use of drugs affecting salivary secretion and frequent dental trauma due to falls and injuries, bruxism.

Multidisciplinary teamwork, especially with dietitians to avoid highly cariogenic foods, is recommended (Grade C) (113, 114). Verbal and written instructions on how to provide good oral hygiene at home should be given to patients and carers (Grade C) (114, 115). Dental care including descaling by a dentist or dental hygienist should be carried out at least once a year but should be more frequent in the later stages of the disease.

At later stages of the disease, treatment options should be discussed carefully and in advance. Treatment intervention, especially in late stage disease may require conscious sedation (midazolam, Diazepam) or general anesthesia in a hospital setting (Grade C) (115–117).

In view of the frequency of digestive disorders in HD (e.g., constipation, diarrhea, and vomiting) and their impact on the quality of life of patients, routine assessment for these symptoms is recommended in order to ensure their management.

Their diagnostic workup should be conducted by the relevant specialists (general and digestive examination, biological and radiological tests, scan, fibroscopy, colonoscopy, etc.). Fecal impaction should be routinely investigated where there is constipation/ diarrhea (“false” diarrhea) and/or vomiting. Vomiting is sometimes intractable. If no specific etiology is identified, the following should be considered: staggering meals, reviewing the patients' posture during and after the meal, and possibly reducing antichoreic agents, in particular neuroleptics.

Excessive Perspiration

Excessive perspiration can occur at all stages of HD. It can be associated with other autonomic disorders and reflects discomfort or emotional burst when sudden.

In the case of excessive perspiration, care must be taken to ensure patients are well-hydrated, monitored and that their fluid and electrolyte balance is adjusted. Thyroid function and the possibility of infection should be assessed in case of excessive perspiration.

Weight Loss

Weight loss is often present in HD, sometimes prior to the appearance of other symptoms. It might occur despite normal, or even high calorie intake, due to a significant energy expenditure in HD patients. It can also be caused by swallowing disorders, depressive syndrome with reduced appetite or gastrointestinal disturbance and gut abnormalities due to enteric neuron dysfunction (118).

Good nutritional care is a fundamental element of the management of HD (Grade C) (119, 120). Early assessment by a dietitian or nutritionist, and regular timely reviews of nutritional needs are recommended. Factors such as swallowing ability, cognitive changes, behavior, mood, and general functional ability should be considered to determine possible other causes of weight loss (Grade C) (23, 120–123). A multi-disciplinary approach is recommended and may include a Speech Language Therapist and an Occupational Therapist to assist with swallowing, positioning and feeding aids. Screening tools for malnutrition [e.g., malnutrition Universal Screening Tool (MUST)] are recommended.

A high Body Mass Index (BMI) within normal values should be maintained if possible and medical and/or social intervention is recommended when unintended weight loss is higher than 10% within last 3–6 months or when BMI is <20 kg/m^2 and unintentional weight loss of 5% is observed within last

3–6 months. When weight loss is observed, high-calorie and high-protein food supplements should be prescribed under instruction and monitored by a dietician/nutritionist (Grade C) (124, 125).

A Mediterranean diet may improve Quality of Life and nutritional composition (Grade C) (126).

In case of the initiation of antidepressant and/or neuroleptic treatments, treatments inducing weight gain should be preferred in patients with significant weight loss, whilst treatments inducing weight loss should be avoided (these effects can vary from one patient to another) (Grade C) (127).

Advanced care planning is essential and alternative feeding methods (PEG, see swallowing disorders) should be anticipated and discussed with relatives and patients still able to understand the benefits and risks of the intervention.

Hypersalivation

Hypersalivation can be troublesome in HD patients when associated with a salivary incontinence (caused by poor oral occlusion and or fault swallowing).

In the absence of a specific treatment for HD, drugs used in other chronic diseases may be considered to reduce salivary secretion: scopolamine given percutaneously, atropine given orally or other drugs that have an anticholinergic effect (amitriptyline), whilst watching out for iatrogenic risks, in particular confusional state, constipation, ocular hypertension and urinary retention. Injections of botulinum toxin into the salivary glands may be considered in a specialized setting if oral or oral mucosa treatment options have not induced benefit or were not well-tolerated.

Reduced Lung Function and Respiratory Muscle Strength

Reduced lung function and respiratory muscle strength are not only associated with end stage disease but occur much earlier, with evidence of some upper

airway changes in pre-symptomatic individuals and reduction of cough effectiveness, reduced lung volume, and impaired respiratory strength by mid-disease. Along with changes in posture reduced exercise capacity, these impairments negatively impact respiratory function, leaving patients vulnerable to respiratory infections.

Home-based respiratory muscle training program appeared to improve pulmonary function in manifest HD patients but had only a small effect on swallowing function, dyspnea, and exercise capacity (Grade B) (128).

Conclusion

The EHDN guidelines task force provides here scientific and consensual guidelines from experts from 15 European experts from the national and steering committees and 73 worldwide additional experts from 25 countries. Whereas, the literature extraction and scoring extent from 1965 to 2015, experts' input extended until October 2018. To ensure the validity of the guidelines in the light of the latest scientific results, two authors reviewed the literature from 2015 to 2019. They extracted 573 abstracts and selected the 17 relevant studies to HD management, which were then added to the grids. Two authors analyzed them separately and assigned each of them a level of scientific evidence. Because these recent relevant studies were not used to formulate recommendations reviewed by the International Multidisciplinary HD Health Professionals group, they are mentioned in the conclusion. Except for deutetrabenazine (Grade A) (129, 130), none of the studies justified to modify the recommendations. Deutetrabenazine may indeed be proposed as an alternative to tetrabenazine for the treatment of chorea in countries where the marketing authorization is already obtained, like in the USA. In addition, a number Grade B and C studies were in agreement with the current recommendations and reinforce the interest of rehabilitation (131–135). Therefore, as they stand, with this precision, these guidelines are likely to serve as international for care in HD. They are likely to support both general

practitioners and specialists' decisions. Patients associations and patients themselves may use them and also disseminate them to inform their doctors.

It becomes increasingly clear that the cost of health is one of the major issues of public policy. In countries where there is a medical insurance system, the question of the choice of therapeutic care or medication and rehabilitation in the insured basket constitutes a central issue. The difficulty is even greater in rare diseases such as HD because the number of patients is too small to carry out double-blind placebo-controlled studies on large cohorts (Grade A) as required for the selection of health policies according to evidence-based medicine. In this work, based on therapeutic trials conducted between 1965 and 2015, only one grade A study was found among 376 studies analyzed, which is insufficient to eliminate or recommend enough products to meet the patients' needs. In parallel, thanks to specific international networks dedicated to HD (EHDN, HSG, and ERN) experts' know-how has increased with a knowledge-learning culture over time. In this context, the French Ministry of Health has labeled Rare Diseases Reference Centers in 2004, imposing on them various duties, one of which is producing National Protocols for Diagnostics and Care (NPDC). These protocols are designed as a combination of comprehensive literature reviews and expert consensus combining the work of an expert panel, and then its validation by outside experts to compensate for the information that is lacking. The recommendations from these NPDCs made it possible to provide decision-makers with comprehensive information based on an adapted version of evidence-based medicine to rare diseases. In addition, they allowed the health professional to refer to a document to answer their questions of day-to-day care. EHDN, with more than 2,000 members in 50 countries, is concerned by the relevance of prescriptions, medical procedures, hospital stays, care pathways, and care arrangements. It thus commissioned an international adaptation of the French NPDC. To give it an international value, we replaced face-to-face meetings with electronic votes and added international

committees and patient associations to national committees. Thus, beyond offering international guidelines to practitioners for the management of HD, this document proposes a method that is likely usable in all rare diseases.

Author Contributions

A-CB-L supervised the elaboration of the guidelines. OA, KY, CS-G, and RM selected the studies to be analyzed. A-CB-L, KY, CP, CS-G, and DR analyzed each study and assigned a level of scientific evidence. Members of the National Committees (A-CB-L, CV, KY, CP, CS-G, OA, DR, and DC) formulated initial recommendations for each HD symptom. Members of the Steering Committee (A-CB-L, JF, KY, AR, MB, DC, RR, GD, DR, FS, KS, and J-MB) reviewed the initial recommendations and supervised the writing of the final recommendations. RM supervised the online surveys, analyzed the results, and assisted the Steering Committee in the writing of the recommendations. Members of the Steering Committee and RM wrote the manuscript (original draft preparation, review, and editing).

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Section G ix

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Is cannabis an effective treatment for anxiety disorders?

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Is cannabis really an effective treatment for anxiety? Research and evidence shows mixed results so learn the facts here and consult a professional.

Facts v. Fiction: What the research says

- What is cannabis (marijuana)?
- What are common misconceptions?
- Yes - cannabis can be an effective anxiety treatment - but the opposite is also true
- Participate in a clinical trial about cannabis
- Proceed “with caution” and keep these considerations in mind

With the growing legalization of medical cannabis throughout the United States, researchers are often tasked with answering the question of whether cannabis can be useful in alleviating conditions like anxiety-related disorders. Typically, cannabis use will likely worsen anxiety symptoms and interfere with evidence-based treatments, such as exposure therapy. However, preliminary research may suggest some positive benefits. For novice users looking to medical cannabis as an alternative method for anxiety reduction, using CBD is often a recommended starting point, so long as it is managed under the care of both a medical provider and mental health professional.

The rise of medical cannabis in the United States has left many wondering whether jumping on the cannabis bandwagon is right for them. Often portrayed as a user-friendly substance that can help “mellow out” our responses to everyday life stressors, using medical cannabis for anxiety symptoms and disorders has been of interest to those seeking alternative treatment methods. Considering its controversial history, inconsistent research findings, and the current federal regulations around cannabis in the United States, answering the question, “will medical cannabis treat my anxiety?” is not so simple. Let’s explore the science behind cannabis, cannabis use, and the legal ramifications to getting a bit closer to answering the question “should I start using cannabis?

What is cannabis?

Cannabis, sometimes referred to as "marijuana," is made up *cannabinoids*, which are naturally occurring compounds found in the *Cannabis sativa* plant. Cannabinoids act on cannabinoid receptors in the brain that make up the endocannabinoid system, which plays an important role in a host of bodily processes, including memory, perception of pain, mood, and appetite[1]. The two most commonly known and studied cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD), with the former being the principal psychoactive component of cannabis and the latter being a non-intoxicating compound[2,3].

As a plant, cannabis can be manipulated to exhibit certain characteristics in the form of varying "strains", including the two most polarized: *sativa* and *indica. Sativa* strains of cannabis have higher levels of psychoactive THC and lower levels of non-intoxicating CBD, while *indica* strains are the more "mellow" of the two with lower levels of THC and higher levels of CBD. However, strains are often blended to allow for more varied cannabis effects, while ingestion types and dosage also vary, making the consumption of cannabis a multifaceted practice[4].

Cannabis – Fact v. Fiction

Given its tumultuous history and inaccurate and exaggerated portrayals in films and media, particularly as a result of the ongoing "War on Drugs" implemented by former president Richard Nixon in the 1970s, many misunderstandings, misinterpretations, and misrepresentations exist around cannabis and its effects. Some of the more common being:

- Cannabis is a harmful drug that can lead to significant memory loss, lung disease, psychosis and/or death
- Cannabis is a "gateway" drug and leads to more severe substance use
- Cannabis is a highly addictive drug that is abused by many

In contrast, it is not uncommon for the benefits of cannabis use to be overstated by supporters, which can be misleading to those looking for alternative methods to alleviate difficulties with mood and anxiety. Recent surveys of the general population show that anxiety management is the second most endorsed reason for medical cannabis use[5]. Reports such as these suggest that those struggling with anxiety may be reaching for cannabis to treat their symptoms, which underscores the importance of reviewing the objective findings available on this topic. Common misconceptions among those in favor of cannabis use include:

- There is conclusive evidence that cannabis can treat anxiety
- There are minimal negative side effects of cannabis
- Cannabis is safe for long-term use

What does the research say?

- THC in cannabis has been shown to be more anxiety-inducing, while CBD has shown to be more anxiety-reducing

- For chronic recreational users, cannabis use can lead to significant health risks, as well as increased anxiety particularly during withdrawal
- Individuals suffering from PTSD or chronic pain have reported a reduction of anxiety-related symptoms when using cannabis medically
- Small sample sizes and significant limitations in the research make it difficult to conclusively state the benefits of cannabis use in treating anxiety

Debunking some common myths, research on the risks of cannabis use has not shown a direct causal link between cannabis use and psychosis or death. Additionally, while cannabis is the most widely-used illicit drug and accompanies the use of other substances, determining its capacity as a "gateway" drug to more harmful psychoactive drugs has mixed findings[6]. However, a systematic review of research suggests that high doses of cannabis use can lead to addiction, psychosis-related health disorders in predisposed individuals, impaired cognition, and overall adverse effects on health outcomes and quality of life in long-term recreational users [2]. Such patterns of use have also been linked to cannabis use disorder (CUD) and cannabis withdrawal syndrome, which are characterized by a host of symptoms including irritability and anxiety[7,8]. In contrast, a meta-analysis of 23 randomized control trials found no evidence of higher adverse outcomes when patients were prescribed medical cannabis[9]. In fact, a study of 244 medical cannabis patients with chronic pain found that patients experienced a 64% decrease in opiate use, decreased amount and intensity of side effects of adjunct medications, and improved quality of life[10].

Do you have Cannabis Use Disorder?

Although some positive outcomes have been shown in those using cannabis for medical purposes, an analysis of the therapeutic utility of cannabis for treating anxiety symptoms has proven much more challenging. For example, we know that cannabis can have both anxiety-inducing and anxiety-reducing properties:

- **THC shows a greater tendency toward anxiety-induction.**
- **CBD shows slight anxiety-reduction properties.**

Specifically, THC has been shown to increase anxiety in animal studies[11,12] while CBD has demonstrated decreased anxiety in similar studies as well as in the treatment of anxiety caused by high levels of THC[13,14]. Similar opposing effects of CBD and THC were found in a neural activation study of 15 healthy men[15]. Despite these findings, sweeping conclusions remain unclear, making it difficult to parse out how different strains of cannabis use effect and interact with anxiety.

Although research has linked increased risk of panic attacks and panic disorder to cannabis use in some[16,17], encouraging findings point to cannabis use as possibly alleviating anxiety in others, particularly through the use of CBD. For example, a double-blind randomized design study of 24 people with social anxiety disorder found that one 600 mg dose of CBD reduced performance anxiety and cognitive impairment in a speech performance[18]. A promising 2015 literature review showed that there is evidence that CBD is not only useful in social anxiety disorder, but in generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, and posttraumatic

stress disorder[19]. A 2019 study found anxiety scores decreased with CBD over a month in 72 patients with anxiety and sleep concerns[20]. Another study from 2019 found perceived symptom improvement in 888 Canadian users of medical cannabis[21] In Washington, over 11,000 sessions recorded using the app StrainprintTM (which provides users of medical cannabis a way to track changes in symptoms) demonstrated a 50% reduction in depression and a 58% reduction in anxiety and stress following cannabis use with high CBD/low THC levels[22]. However, other studies have shown that individuals with social anxiety are more likely to abuse marijuana and that these individuals are more likely to experiences problems related to their cannabis use[19]. Additionally, a 2017 meta-analysis found no relevant association between cannabis use and anxiety symptoms in a general population sample[23].

Results from studies investigating the administration of a synthetic form of cannabis (Nabilone) found a reduction of treatment-resistant nightmares in 72% of 47 patients with PTSD[24]. Nabilone has been demonstrated to have similar anxiety reduction in other anxiety disorders as well[25]. Furthermore, a systematic review of cannabis use in individuals diagnosed with PTSD found evidence of reduced restlessness, irritability, and sleep difficulties as well as reports of greater emotion regulation, reduced feelings of anxiety, and improved functioning overall[26].

Legal regulations for medical cannabis

Once a well-established and widespread treatment modality, the federal government began placing sanctions on the sale and cultivation of cannabis in 1937, with concerns about its psychoactive effects leading to its prohibition and classification as a Schedule I controlled substance in 1970 [2]. Today, cannabis containing THC continues to be considered a prohibited substance under federal law, however, state legislators have found loopholes in the governing of cannabis use for both medical and recreational use. Beginning with California's "Compassionate Use Act" (Prop 215) in 1996, today only four states - Idaho, Kansas, Nebraska, and South Dakota - have opted to not follow on the lingering smoke trail that is the legalization of cannabis in some capacity. Thirty-two states, along with Washington D.C., Guam, Puerto Rico, and the U.S. Virgin Islands, have departed from the federal government to impose their own individual laws and restrictions around the sale and use of medical cannabis, but the conditions for which medical treatment is approved varies from state to state[27].

Most commonly used as an analgesic, appetite stimulant, and for controlling nausea and vomiting, medical cannabis is primarily recommended for individuals battling chronic conditions. The most common across states being cancer, HIV/AIDS, chronic pain, anorexia and wasting syndrome, seizure disorders (e.g., epilepsy), skeletal muscle spasms (e.g., multiple sclerosis), and post-traumatic stress disorder. Anxiety, in particular, is only explicitly named by New Jersey and West Virginia as a symptom or disorder to be treated by medical cannabis; however, many states have an "other" option for which physicians could determine anxiety as a qualifying condition[27].

Given the disagreement in regulations between federal and state governments around the sale and use of medical cannabis, particularly THC-laden cannabis, there exists technicalities around

what is and is not prohibited. For example, it is illegal for physicians to "prescribe" medical cannabis to patients under federal law and are only allowed to certify or recommend medical cannabis treatment for patients with state-approved medical conditions. In addition, reimbursement is not permitted by either federal or private health insurance companies for alternative methods, like medical cannabis, therefore those recommended for such therapies are required to pay in full for their treatment[27].

Clinical Trials

Below are current trials investigating the effects of cannabis use on anxiety. See the link for more information.

- Title: Cannabidiol for the Treatment of Anxiety Disorders: An 8-Week Pilot Study
  Sponsor: McMaster University
  Link: https://clinicaltrials.gov/ct2/show/NCT03549819

- Title: Anxiety, Inflammation, and Stress
  Sponsor: University of Colorado, Boulder
  Link: https://clinicaltrials.gov/ct2/show/NCT03491384

- Title: Sublingual Cannabidiol for Anxiety
  Sponsor: Mclean Hospital
  Link: https://clinicaltrials.gov/ct2/show/NCT02548559

- Title: Cannabinoid Medication for Adults with OCD (recently completed)
  Sponsor: New York State Psychiatric Institute
  Link: https://clinicaltrials.gov/ct2/show/NCT02911324

Conclusion & Recommendations

Given federal regulations of cannabis in the United States, along with the recent boom of the medical cannabis industry, research on its effects are considered to still be in its infancy and unable to keep up with the demands of those seeking alternative therapeutic treatments. With the complexity of both symptomatology of anxiety and the effects of cannabis use, answering the question of whether medical cannabis is a safe and effective method of treating anxiety is a difficult task. More rigorous and controlled research is needed to provide more conclusive answers, so for now, the response to those exploring the options of medical cannabis treatment for anxiety symptom is to "proceed with caution!"

If you are experiencing anxiety that is impairing your daily life, we strongly urge you to reach out to a mental health professional specializing in the treatment of anxiety-related disorders so they may accurately diagnosis your anxiety difficulties and discuss evidenced-based treatments best suited for you. Currently, cognitive behavioral therapy is the most effective and first-line treatment for most anxiety-related problems, and it comes without the possible cost of side effects. Using cannabis or other substances to manage anxiety without the care of a doctor or experienced professional will typically interfere with therapeutic interventions and likely worsen your symptoms in the long run. However, if you are considering using cannabis to alleviate your

anxiety, the picture is complex and its usefulness may depend on the chronicity and severity of your anxiety, as well as your history with cannabis use, other substance use, and psychiatric illnesses.

All things considered, the following recommendations should be kept in mind for those interested in pursuing medical cannabis treatment:

- Do not rely on cannabis as either a sole or long-term treatment modality
- If you have not done so already, seek counseling from a mental health professional to support you in your treatment journey
- Speak with your medical provider about both past and present psychological and physiological symptoms for a more comprehensive understanding of whether medical cannabis is appropriate for you
- Know that it is not a one-size-fits-all treatment and be mindful that this treatment is not right for everyone

Section G vii
Adi Jaffe Ph.D.

All About Addiction

THC for Huntington's Disease? CB1 receptors important for more than drug use

Smoking marijuana doesn't have to be a bad thing - Especially if you have HD

Posted Feb 25, 2011 Psychology Today

Here at A3, we believe in equal opportunity. We recognize that saying we have an addiction problem is not the same as saying we have a drug use problem and that just because some people abuse substances (or belief systems) doesn't means that these have no actual value when not abused. Enter this recent paper on CB1 receptors, THC, and Huntington's Disease.

Those of you who haven't been reading A3 for too long (shame on you!) may not be familiar with my comparison of the cognitive (or mental) impulsivity associated with substance use disordersand the physical "impulsivity" common to Huntington Disease(HD) patients. To make a long story short - both of these dysfunctions have to do with the striatum, a brain area responsible for inhibiting and controlling unwanted brain output (as in thoughts or actions). When this area starts malfunctioning, everything goes awry. When it comes to HD, "goes awry" doesn't really do the disorder justice. Patients with a progressive form of the condition end up flailing their limbs in a manner that's been coined the "Huntington Dance," a euphemism if I ever heard one. This motor flailing is closely followed by severe cognitive impairments and a premature death. Not a pretty story.

Cannabinoids, motor control, and Huntington's Disease

In the striatum, CB1 receptors (the most common cannabinoid receptors and the main target for THC) are very important in this mechanism of inhibiting output. In fact, there's some evidence that their activation is important in savings cells

from dying in cases of over excitation, an idea we'll return to shortly. It's important to note that Huntington's patients and animal models of the disease have been shown to have reduced levels of CB1 receptors in this area.

A group of researchers in Madrid wanted to examine what exactly the role of this reduced cannabinoid receptors was in the development of Huntington's Disease. The researchers created transgenic mice that expressed both the human version of the HD gene (called Huntingtin) and reduced levels of CB1 receptors (we'll call these the combined-type mice). Using a battery of tests that are supposed to assess motor coordination, exploration, and strength, the researchers compared these mice with mice expressing only the Huntingtin gene.

The results were pretty clear: Having reduced CB1 receptors made HD symptoms appear four weeks earlier in the combined-type mice when compared with the HD mice and the disease symptoms also progressed much more quickly. The CB1 deficit was also associated with a greater level of neuron loss in the striatum and a whole mess of other problems with neuron structure. It was clear that these mice were suffering due to the increased absence of cannabinoid receptors.

As a theraputic experiment, the researchers then tried to give THC to the Huntingtin mice (not the combined-type this time, that wouldn't do much since they don't have CB1 receptors though it would have been interesting to test other receptor effects like CB2). The reasoning went that if losing CB1 receptors made things worse then maybe activating those receptors more strongly in HD mice would make their symptoms better - and it worked! Giving HD mice THC improved their motor function, slowed the disease symptom progression, and improved the volume of their striatum.

A deeper look into the mechanism of this revealed that as mentioned earlier, the activation of CB1 receptors by THC apparently served a protective role and helped the HD mice delay, or reduce, the extent of neuron loss in their straitum that was the cause for all their Huntington's Disease symptoms.

Conclusion, limitations, and thoughts on weed for Huntington's disease

The idea that THC can be used to relieve disease symptoms isn't a new thing - Glaucoma, HIV, and cancer patients have all benefited from the use of CB1

agonists whether in the form of marijuana leaves or a pharmacologically similar product (like dronabinol). Nevertheless, the idea of using THC or other CB1 agonists for the treatment of HD is pretty new. There have been a small handful of studies but only one well-constructed experiment that used a placebo-controlled crosover design, which yielded some positive results. The results of this study suggest that THC and other CB1 compounds may not only be able to improve symptoms in already symptomatic HD patients, but also slow down the progression of such a devestating disease. Good news all around and a great use of THC as far as I'm concerned (medical use and removal from schedule-1 anyone?!).

Some of you may be asking yourself why I decided to write about a study so focused on Huntington's Disease for a site called All About Addiction. As far as I'm concerned, discussions of commonly abused drugs generally fit with the concept I have for this site: An information hub having to do with addictions and all related matters. Moreover, the close connection that I see between HD and addictions, in terms of loss of control brought about specifically by compromised brain structures and function, makes this study one that is crucially important for understanding control in general. Add to that the evidence for THC's use in a medical setting and I think we have a winner, if a slightly unusual one, for A3.

Citation:
Peggy C. Nopoulos, Elizabeth H. Aylward, Christopher A. Ross, James A. Mills, Douglas R. Langbehn, Hans J. Johnson, Vincent A. Magnotta, Ronald K. Pierson, Leigh J. Beglinger, Martha A. Nance, Roger A. Barker, Jane S. Paulsen, and the PREDICT-HD Investigators and Coordinators of the Huntington Study Group (2011) Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease. Brain 2011 134: 119-136.

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Section G viii

How Does Medical Cannabis Stimulate Appetite?

For many patients, finding the desire to eat is difficult. Patients battling cancer and those with HIV-related anorexia know this struggle particularly well. Other patients may find certain medications suppress their appetite. Conditions such as chronic pain can decrease the desire to consume food. Nausea and vomiting caused by some medications and conditions can also interfere with your appetite.

For patients living with these conditions, mealtime can be distressing. It's enough to leave you wondering, "what medication increases appetite?"

Medical cannabis is one of the most reliable medications for boosting appetite.

Medical Cannabis Can Cause "the Munchies"

If you look at popular culture, one of the side effects typically associated with recreational cannabis use is hunger, colloquially called "the munchies." Characters in TV shows and movies will often use cannabis, then seek out junk food.

There's truth to this, and it's that THC, one of the active cannabinoids in cannabis, can boost appetite. Medical researchers have been studying this effect for some time, especially as they sought to determine how medical marijuana could be used to help cancer patients during treatment.

Medical cannabis strains with a high THC content usually boost appetite. How exactly does it work?

The Science Behind Hunger

Hunger is regulated by certain processes in the body. After you eat, the body produces a substance called leptin, which can suppress the appetite. As leptin decreases, you'll become hungrier. If another medication or a physical condition causes an increase in leptin or leptin levels to drop more slowly, you won't feel hunger. For those with HIV-related anorexia, for example, the neurons slow down or fail to send the message of hunger altogether.

Neurons in the brain also send signals to tell you that you are full after having eaten. When THC is introduced to the system, these neurons slow down and fail to send the message. THC also appears to inhibit the production of the appetite-suppressing leptin.

In essence, medical cannabis tricks your brain into telling you that you're hungry. For patients who are suffering from a lack of appetite, this can help them maintain nutrition during their illness.

Refining the Palate

Medical cannabis also seems to assist by increasing your appreciation of food. Not only do you feel hungrier, but food tastes better and is more satisfying when you're using medical marijuana. This is likely because THC enhances the sensory system, making the taste buds more engaged.

The mechanism behind this is less understood, although it appears THC also signals the brain to fuel this increase in food desirability. This is helpful for patients who are suffering from a suppressed appetite, since it encourages them to eat. Not only do they feel hungrier, but meals are more enjoyable as well.

Assisting with Nausea and Vomiting

Another area medical cannabis can help with is nausea and vomiting. These symptoms can be associated with a wide range of medical conditions, and they may be side effects of certain medications as well.

Nausea and vomiting after eating can create incredibly strong food aversions. This biological mechanism is designed to protect people from eating poisonous or spoiled foods. If you eat something and you don't feel well afterwards, you're likely to avoid that food in the future.

This is particularly problematic for cancer patients, who may be very ill after therapy. Food aversions may be particularly strong and may extend to a wide range of foods.

Some evidence suggests manipulations to the endocannabinoid system regulate vomiting and nausea. Medical marijuana can help alleviate these symptoms by activating CB1 receptor sites of the endocannabinoid system, which in turn can prevent food aversions from developing.

Is It Right for You?

There are several different conditions that cause appetite suppression, and medical marijuana is being investigated as a potential aid for these patients. There's some hope it may assist those who have eating disorders, as well as people whose medications suppress their appetite.

The best-known use is as an aid for cancer patients. If you're in treatment for cancer, you may want to ask your doctor about medical cannabis as part of your treatment plan.

By Dr. Michael Verbora| November 5th, 2018

Section G x

Does Cannabis Help Insomnia?

by Dr. Michael Breus | Feb 4, 2020 | Health, How to Sleep Better

In the United States and around the world, cannabis is more popular than ever. Attitudes about cannabis are changing fast—and so are laws that govern its use for medical and recreational purposes. As has been the case for thousands of years, people use cannabis for a variety of reasons, many therapeutic, including to alleviate anxiety and relieve pain. One of this ancient medicinal plant's most popular uses through the ages? To help with sleep.

What does science tell us about cannabis' effectiveness in treating the most common sleep disorder, insomnia? That's what I'll be discussing today, with a look at the latest science on the effects of cannabis on insomnia.

What is insomnia, exactly?

First, let's tackle a quick refresher on what insomnia is, because it's a term that carries a lot of meaning and detail. At its essence, insomnia is a difficulty falling sleep and/or staying sleep, when you have the time and circumstances to get the sleep you need. Insomnia exists both as a set of symptoms and a clinical disorder. That's to say, people can experience symptoms of insomnia without necessarily having insomnia disorder. (That's no reason not to address the symptoms; even insomnia symptoms that don't meet the criteria for a clinical sleep disorder can be disruptive and undermining to sleep, health, well-being and performance.)

What distinguishes insomnia symptoms from insomnia disorder? To a great degree, the severity and frequency of symptoms, and—*this is important*—the impact of those symptoms on daily functioning. The more frequent, severe, and disruptive, the more likely insomnia symptoms constitute a sleep disorder.

The duration of symptoms can matter to—but keep in mind, insomnia disorder can flare up quickly and cause significant disruption before resolving, all within a short time span. Acute insomnia comes on suddenly and typically lasts for as little as a single night, up to a few weeks. Insomnia is considered chronic when it is present at least three nights a week for three months.

Scientific estimates suggest that somewhere between 35-50% of the adult population experience insomnia symptoms every year, with somewhere between 10-30% of the population suffering from insomnia disorder. Among that 10-30%, an estimated 40-70% have insomnia disorder that is chronic.

What are the symptoms of insomnia?

- Trouble falling asleep
- Difficulty staying asleep, with frequent and/or prolonged awakenings at night
- Waking very early
- Waking feeling unrefreshed

People with insomnia disorder also typically experience some form of daytime impairment, including:

- Fatigue, daytime sleepiness
- Irritability and mood disturbances
- Problems with memory, concentration, attention
- Decrease in energy, motivation, initiative
- Lack of interest and/or capacity for social interactions
- Physical pain and discomfort, including muscle tension, headache, gastrointestinal distress
- Anxiety or worry about one's ability to sleep

A person need not have all the sleep symptoms and daytime impairment in order to have insomnia disorder. Even one symptom and one form of daytime impairment is enough. Often, however, symptoms occur together, and daytime impairment is spread across multiple issues.

How does cannabis help insomnia?

Studies show cannabis is already widely used by people in treating their insomnia and sleep issues. That's not new. With its long history as a medicinal herb, cannabis has been employed for centuries to help with trouble falling asleep and staying asleep, to make sleep more refreshing, and to extend sleep's duration.

In recent years, scientific studies have found that insomnia is a top reason for using cannabis, along with issues including pain, anxiety and depression, which often co-occur with insomnia. One study

published in 2019 found that among cannabis users who said they were using cannabis to improve sleep, 84% said it was “very” or “extremely” helpful. And 83% of people who reported having used over-the-counter sleep medications in the past were able to either reduce or eliminate those drugs from their routines, when they began using cannabis for sleep. That’s important because many of the OTC sleep aids have been linked to Alzheimer’s disease.

So, what does the science tell us about how effective cannabis is at improving insomnia?

Research into the effect of cannabis on insomnia and its symptoms stretches back decades. Studies from the 1970s, 80s, and 90s show cannabis can have a broad impact on sleep, including shortening the time it takes to fall asleep. Difficulty falling asleep is a hallmark symptom of insomnia.

Cannabis can be sedating

What’s behind the ability of cannabis to make falling asleep easier and faster? Most often, that’s been attributed to the sedative effects of the cannabinoid THC. (For a refresher on THC and other cannabinoids, read some of my previous articles here and here.) Indeed, most of the early studies of cannabis and sleep focused on THC-heavy strains of the plant.

Research on cannabis’ influence over sleep problems has been hampered historically, by laws making cannabis illegal even medicinally, and by long-embedded negative attitudes about cannabis. Now that those laws and attitudes are changes—and cannabis is showing up in so many products related to health and wellness—scientific interest and inquiry are on the rise. That’s important: we need plenty of rigorous research to show us precisely how cannabis affects different aspects of sleep, and how it may best be used therapeutically to help alleviate insomnia and other sleep issues.

Terpenes have sleep-boosting abilities

One promising element of more recent research is that scientists are looking more closely at the other active compounds of cannabis, and how they affect sleep. (The more we understand about how different cannabinoids and other components of this complex plant influence sleep, the better medical professionals and patients and consumers

themselves will be able to identify the type of cannabis that's right for their individual needs.)

For example, several different terpenes found in cannabis have been shown to have sedative effects. Terpenes are tiny molecules found across the plant world. They give taste and aroma to plants and fruit. They also have therapeutic abilities, from pain and inflammation relief to anxiety reduction. Cannabis contains hundreds of different terpenes; several have been identified as having sedative properties and at reducing specific insomnia symptoms.

- Myrcene, Limonene, Terpineol, and **Terpinolene** all have been shown in research to function as sedatives
- Pinene **and** Phytol have been shown specifically to shorten the time it takes to fall asleep, and phytol has also been shown to increase overall sleep amounts

We're really just at the beginning of the investigation into how individual terpenes may address sleep problems, including insomnia. For a more in-depth look at terpenes—what they are, how they work, where to find them—you can read this recent article.

CBD is emerging as a sleep promoter

The cannabinoid CBD (cannabidiol) has shown up everywhere in recent years, and it's being used for things like stress and anxiety relief, pain management, enhanced concentration/focus, and even sexual enhancement. We've still got a lot to learn about CBD's impact on insomnia, and on sleep more broadly. Some recent research indicates that this cannabinoid may have a role to play in improving insomnia symptoms. I've talked before about CBD and its potential therapeutic benefits for sleep, both directly and indirectly through addressing anxiety, physical pain, and other sleep-disrupting conditions.

In particular, one 2018 study caught my eye recently. It's perhaps the first study to analyze the effects of medical cannabis (in dried form) on insomnia, as measured under naturalistic, real-world conditions (i.e., not in a lab). Researchers found cannabis significantly improved insomnia symptoms overall. In particular, they found CBD was associated with more significant relief from symptoms of insomnia than THC. The study also discovered a pretty staggering range of

cannabis strains being used to treat insomnia—more than 460 different strains among a group of slightly more than 400 individuals. That shows just how much choice is out there, and how much potential for specialization and targeting may be possible, in matching strains to sleep and specific sleep problems like insomnia.

To be clear, we need to see more laboratory-based, rigorously controlled studies. But this kind of real-world investigation also delivers valuable information and insight, and can point to future directions for scientific inquiry.

How cannabis may address *comorbid* insomnia

Another way to think about the influence of cannabis on insomnia is in terms of the type of insomnia. There isn't just one kind. We've talked about acute and chronic, and I've discussed how cannabis appears to be particularly effective in addressing onset insomnia—trouble falling initially to sleep.

Comorbid insomnia (until relatively recently this was often referred to as "secondary" insomnia), is insomnia that arises alongside another medical condition. Not all insomnia disorders are comorbid, but many are. Insomnia frequently arises with other health conditions, and as a side effect of medication and other treatments for health problems. There's a growing body of research indicating that cannabis can be useful in treating comorbid insomnia. For example:

Physical pain is a major source of insomnia. A robust body of research demonstrates thatcannabis can alleviate physical pain. Pain management is another prime reason why people use cannabis in the first place. Recent research shows cannabis can improve pain and insomnia symptoms. This 2014 study found a group of people using cannabis therapeutically had an average of 64% reduction in their pain severity, and about half of them experienced signification relief to their insomnia.

Anxiety is another condition that causes significant problems for sleep, and a big driver of insomnia and its symptoms. (It's also another major reason why people use cannabis and cannabis-derived products such as CBD oil.) This 2019 study found people using cannabis for insomnia and comorbid conditions, including anxiety, depression and physical pain, reported significant improvements to all their co-occurring conditions. It's worth pointing out that three-quarters

of participants in this study had 2 or more conditions simultaneously. It's common for insomnia to exist in a cluster of other health conditions, both physical and psychological, and to have these factors all interact with one another in complex, escalating ways.

It's not only anxiety and depression with insomnia that cannabis may effectively treat. Studies are starting to show that cannabis may help alleviate insomnia symptoms that occur with PTSD, or post-traumatic stress disorder. Sleep disorders, including insomnia and REM sleep behavior disorder, as well as intense nightmares, are frequently present with PTSD. With its ability to help improve sleep onset (i.e., to make falling asleep easier), and to reduce nightmares and suppress some amounts of REM sleep (when most active, intense dreaming occurs), cannabis appears to be promising as a therapy for PTSD-related insomnia. This is an exciting and important area of research that deserves critical attention.

One of the best-known uses of therapeutic *cannabis is for relief from cancer symptoms* ***and the side effects of cancer treatment***. Cannabis has a well-documented ability to relieve pain, reduce nausea, and alleviate anxiety. That makes this complex plant well suited to address symptoms faced by people living with cancer and undergoing treatment. Insomnia often occurs with cancer and as a result of therapies such as radiation and treatment. Research, including this 2019review of studies, shows cannabis may improve insomnia that is comorbid with cancer.

These are just a few of the comorbid insomnia conditions that cannabis has shown promise in treating. In future discussions, we'll look at some of these conditions and their relationship to sleep and cannabis therapy in greater depth—and we'll also continue to go where the research takes us, as cannabis is investigated in relation to other comorbid insomnia conditions.

Coming soon in this series, a look at how the effects of cannabis on sleep compare to another common real-world sleep aid: alcohol.

Sweet Dreams,

Michael J. Breus, PhD, DABSM

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Medical Marijuana In Huntington's Disease: Report of Two Cases

Karl Meisel, MD and Joseph H. Friedman, MD

Chart 1. Results of medical marijuana on mood, cognitive, and motor symptoms in subjects with Huntington Disease

	Subject 1 60 year old man College education One year since HD diagnosis			Subject 2 52 year old man High school education Three years since HD diagnosis		
	On	Off	Change	On	Off	Change
STAI	57	62	-5	49	58	-9
MOCA	27	27	0	25	26	-1
MADRS	34	28	+6	20	30	-10
UHDRS	24	29	-5	19	18	+1

STAI (State-Trait Anxiety Inventory), MOCA (Montreal Cognitive Assessment), MADRS (Montgomery-Åsberg Depression Rating Scale), UHDRS (Unifie Huntington's Disease Rating Scale).

Huntington's disease (HD) is an autosomal dominant inherited disorder characterized by chorea or other movement abnormalities, dementia, and a wide spectrum of psychiatric disorders. The treatment of HD is symptomatic and limited.[1] Some HD patients in the Movement Disorders clinic at Butler Hospital revealed that they were using marijuana on a regular basis. We hypothesized that marijuana provided psychological or physical relief of the patient's HD symptoms. Prior studies have used isolated compounds from marijuana and focused on motor symptoms.[2, 3] The results of this study will hopefully direct further research into how marijuana might benefit patients with HD or other neurodegenerative disorders perhaps adding another therapeutic option to a devastating disease.

Patients with HD taking **medical marijuana** (MM) were invited to participate in the study, which was approved by the Butler Hospital IRB. The patients provided written informed consent. The patient was evaluated while taking MM as usual and then was asked to refrain from using marijuana for 48 hours. Subjects were tested when taking the MM and when off the drug. We performed the State-Trait Anxiety Inventory, Montgomery-Åsberg Depression Rating Scale, and Montreal Cognitive Assessment. The Unified Huntington's Disease Rating Scale was used to assess motor function. The subjects' scores on these tests were compared to themselves on and off the drug.

Our study showed that subjects had less anxiety on marijuana (improved five and nine points respectively). Subject two had less depression (ten point improvement) whereas subject one had slightly worse depression, deemed not clinically significant. Subject one had minor improvement in his motor exam (five points) and subject two had insignificant worsening (one point). There was no change in cognitive performance (Table 1) for either subject. There were no adverse events while on or off marijuana.

Pathologic studies of HD show selective loss of CB1 (cannabinoid receptor).[4] CB1 is found in the basal ganglia, cerebellum, dorsal primary afferent spinal-cord region and hippocampus. Marijuana is from the cannabis plant and it may contain over 60 cannabinoid compounds. The role of each of these compounds in the behavioral response to the drug is unknown. However, THC (tetrahydrocannabinol) is the main psychoactive compound, while cannabidiol and cannabinol are the main non-psychoactive components. In a rat model it was found that stimulation of CB1 slows experimental HD.[4] In humans, two studies evaluated the ability of cannabidiol to reduce chorea in HD. One study showed mild improvement using the tongue protrusion test and chorea severity evaluation scale.[2] The second study evaluated 15 patients in a placebo-controlled, double-blind, randomized, cross-over design and found no significant effect on chorea severity.[3] Neither study found adverse reactions to the medication. In our study both subjects reported that marijuana helped them with anxiety and depression, allowing them to sleep as well as to gain motivation.

Overall our study supports the hypothesis that marijuana improved anxiety in these two subjects; however this conclusion is limited because of a small sample size, open label testing and the possibility of a withdrawal effect in patients who had been taking the drug on a chronic basis.

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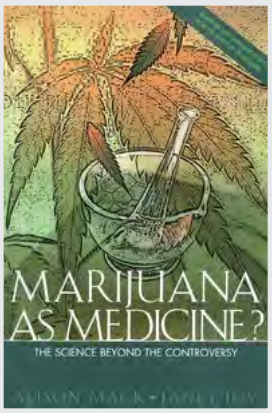

Marijuana As Medicine?: The Science Beyond the Controversy (2001)

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8

Marijuana and Neurological Disorders

While frequently touted as a folk remedy for spasticity, marijuana is only occasionally mentioned with regard to other neurological disorders. Perhaps people with movement disorders, epilepsy, or Alzheimer's disease derive little benefit from marijuana, but it may also be the case that relatively few patients with these conditions have tried it.

Only a handful of clinical trials have explored the effects of marijuana or cannabinoids on the symptoms of neurological disorders other than multiple sclerosis. For the most part these studies are too small to be considered conclusive, and their results are far from promising. Nevertheless, they are worth considering in light of the abundance of cannabinoid receptors in the brain, especially in areas associated with Parkinson's and Huntington's diseases. And since conventional treatments for movement disorders, epilepsy, and Alzheimer's disease leave much to be desired, no source of potential remedies should be overlooked.

Movement Disorders

This group of neurological diseases is caused by defects in the basal ganglia, clusters of nerve cells in the brain that control muscular activity. Injury to these regions ultimately affects the

motion of muscles in the face, limbs, and trunk. The movement disorders most often discussed as candidates for marijuana-based therapies are dystonias, Huntington's disease, Parkinson's disease and Tourette's syndrome. As a general consideration, it is important to note that stress and anxiety tend to worsen the symptoms of movement disorders. Thus, marijuana's calming effect could be a primary reason why some patients claim that it brings them relief.

Dystonias are a subgroup of movement disorders that share similar symptoms: slow, sustained, involuntary muscle contractions that often cause sufferers to hold their limbs, trunks, or necks in odd positions. They may be confined to one part of the body; for example, spasmodic torticollis affects only the neck, while Meige's syndrome distorts the face. These chronic, slowly progressive disorders are often painful and can cause mild to severe disability. Some dystonias are inherited, while others occur as side effects of certain drugs. Scientists have yet to discover the specific neurological malfunctions that cause dystonias.

Several different drugs are used to treat various forms of dystonia. The most commonly prescribed drugs—benzodiazepines, baclofen, Botulinum toxin, anticholinergic agents, and tetrabenazine—merely relieve the symptoms of dystonia rather than resolving the condition itself. In many cases the relief they provide is incomplete. Baclofen (Lioresal) and benzodiazepines, including diazepam (Valium) and clonazepam (Klonopin, Rivotril), act by reducing the nervous system's ability to stimulate muscle contractions. Both drugs usually make patients drowsy and may also cause a range of additional side effects, including muscle weakness and behavioral problems. Botulinum toxin—a bacterial compound that also causes food poisoning—also blocks muscle stimulation; it produces few side effects but must be injected directly into the affected muscles. Anticholinergic drugs such as trihexyphenidyl (Artane) and diphenhydramine (Benadryl) deactivate muscle contractions; they, too, cause drowsiness and other side effects that can become severe at high doses. Tetrabenazine, although not available in the United States, is a dopamine-depleting compound available in Canada and Europe that is often prescribed for the relief certain types of dystonia.

No controlled study of marijuana in patients with dystonia

has yet been published. Cannabidiol, a chemical component of marijuana (see Chapter 2), was tested in a preliminary open trial in which patients knew they were receiving the experimental drug. The five participants showed only modest improvements, which increased with the amount of drug they received.[1] Better results occurred in a study of an animal model for dystonia—a mutant strain of hamsters—in which researchers tested a synthetic cannabinoid that activates the same cellular receptors as THC. The hamsters exhibited a type of dystonia that produces either sudden spasms of rapid, jerky motions or slow, repetitive writhing movements, both of which decreased under the influence of the cannabinoid.[2]

Besides being a diagnosis in its own right, dystonia is also a symptom of other major movement disorders, including *Huntington's disease*. This inherited disorder usually manifests itself in middle age, continues to worsen, and ultimately leads to death within 15 years of its appearance. Symptoms include rapid, uncontrolled muscle movements (called "chorea," from the Greek word for dance), emotional disturbance and eventually dementia. Patients may take drugs, including reserpine or haloperidol, mainly to control their psychological symptoms. All of these medicines produce adverse side effects, so physicians often wait to prescribe them until a patient's symptoms become severe.

Since anxiety and stress appear to worsen involuntary movements in many patients with Huntington's disease and since marijuana reduces those feelings in most users, some have proposed it as an alternative to existing medications. Animal studies suggest that cannabinoids might suppress choreic movements, presumably by stimulating receptors in the basal ganglia (see Chapter 2). In a preliminary study of four people with Huntington's disease, one patient showed improvement under the influence of cannabidiol.[3] Based on this limited success, researchers attempted a double-blind crossover study (see Introduction to Part II for a discussion of clinical study design) on 15 patients who were not taking medications to inhibit chorea but found that participants' symptoms neither improved nor worsened after treatment with cannabidiol.[4] These results are perhaps to be expected, though, since cannabidiol does *not* bind to the predominant type of cannabinoid receptor (CB_1) on neurons affected by Huntington's dis-

ease. THC or other cannabinoids that readily bind CB_1 receptors seem likelier candidates as medications for Huntington's disease, but their effects on patients with the disorder remain unknown.

One of the most devastating movement disorders, *Parkinson's disease*, affects approximately 1 million Americans age 50 and older. Symptoms include tremor, muscular rigidity, instability, and impeded motion (both slowed movement and abrupt stopping in midmovement). The single most effective drug to treat Parkinson's disease, levodopa (L-Dopa, Larodopa, Dopar), has many drawbacks, so physicians tend to reserve it for functionally impaired patients. After several years of use, levodopa tends to wear off quickly after each dose, so patients constantly cycle through phases of mobility and disability. Additional side effects include nausea, hallucination, and confusion. Researchers also suspect that, while levodopa dramatically improves all of the signs and symptoms of Parkinson's disease, its use may accelerate the disease's progress; no clinical evidence confirms this concern.

Because they act on the same neurological pathways that Parkinson's disease disrupts, cannabinoids could in theory be useful in treating the disorder (see Chapter 2). The IOM team found only one published account of a clinical trial of marijuana for Parkinson's disease. The study was prompted by a patient's report that smoking marijuana reduced tremor, but when researchers tested the drug on five additional patients with tremor, they found no evidence of improvement. On the other hand, conventional medications, including levodopa, successfully reduced tremor in all five patients.[5]

Unlike Huntington's and Parkinson's diseases, *Tourette's syndrome* typically appears during childhood. Patients exhibit a variety of rapid, involuntary, repetitive movements and vocalizations, collectively called tics. The causes of Tourette's syndrome are largely unknown but are thought to impair brain areas that convert a person's intent to move into actual movements. Damage to these same areas produces involuntary movement in Huntington's disease and restricts voluntary movement in Parkinson's disease.

Two widely used medications for Tourette's syndrome, pimozide (Orap) and haloperidol (Haldol) inhibit the effects of

the neurotransmitter dopamine. Cannabinoids, by contrast, increase dopamine release, so one might predict that cannabinoids would actually exacerbate the symptoms of Tourette's syndrome. Yet four clinical case histories indicate that marijuana use can reduce tics in Tourette's patients. In three of the four cases, however, the investigators suggest that marijuana's anxiety-reducing properties—rather than any specific effect on the neural pathway that produces tics—caused the patients' symptoms to improve.[6]

In summary, while persuasive basic evidence exists for the role of cannabinoids in movement, clinical evidence for their usefulness in relieving the symptoms of movement disorders is lacking. The few existing studies were performed on small numbers of patients and without consideration that marijuana's antianxiety effects might reduce the symptoms in question. Moreover, while there are a few isolated anecdotal reports that marijuana helps patients with these disorders, there are no surveys to suggest that these patients' experiences are at all representative.

Thus, with the possible exception of spasticity in multiple sclerosis, there is little reason to recommend additional clinical trials of marijuana or cannabinoids for movement disorders, the IOM study team concluded. That is not to say that more extensive animal studies will never provide stronger evidence in favor of human trials. But until reliable animal models exist for most movement disorders, such evidence is unlikely to be forthcoming. In the meantime the IOM team recommends conducting double-blind, placebo-controlled clinical trials of individual cannabinoids such as THC—but not smoked marijuana—for the treatment of movement disorders.

The IOM team further specified that these trials should test the effects of cannabinoids on movement alone—that is, the experiments should distinguish cannabinoids' effects on movement from their effects on anxiety or mood. For if cannabinoids merely provide a psychological boost to people with multiple sclerosis, their use would probably not warrant the risk of short-term memory loss, cognitive impairment, and other known side effects. But if cannabinoids directly improve spasticity and other movement-related symptoms, as well as mood, they would offer a uniquely useful treatment. Cannabinoids therefore represent an

interesting possibility for treating movement disorders but one that has yet to be proven.

Epilepsy

A chronic seizure disorder, epilepsy affects about 2 million Americans and an estimated 30 million people worldwide. Symptoms include recurrent sudden attacks of altered consciousness, convulsions, and other uncontrolled movement, apparently brought on by the simultaneous stimulation of numerous nerve cells. People may become vulnerable to epileptic seizures through a wide variety of possible causes, including physical injury and exposure to chemical toxins.

Some people with epilepsy have partial seizures, which are also known as focal seizures. These disturbances arise in the cerebral cortex, a part of the brain that governs consciousness, movement, and sensation—functions that become temporarily disordered when partial seizures occur. Other people with epilepsy, who develop the condition after sustaining damage to centrally important regions in the brain, experience seizures that affect many aspects of behavior. These generalized seizures may occur as either relatively mild petit mal or violent grand mal events.

A variety of conventional anticonvulsant medications may be used in attempts to control epileptic seizures. Because different drugs work better for different types of seizures, patients must often try several medications before finding the most effective treatment. In general, antiepilepsy drugs suppress seizures completely in about 60 percent of patients and reduce their severity in another 15 percent or so. Many of the remaining 25 percent suffer from a serious underlying brain disease that cannot be relieved through anticonvulsant therapy; others continue to have seizures because they refuse prescribed medication, they use it incorrectly, or their bodies do not reliably absorb the drugs.

Anticonvulsants commonly make people feel drowsy and mentally slow; the drugs may also cause tremor, hair loss, headache, dermatitis, and several other side effects. Nevertheless, most people with epilepsy endure these drawbacks in order to prevent seizures, which can be both physically dangerous and emotionally devastating.

Although some anecdotal accounts—as well as a few reports from small clinical and individual case studies—suggest that marijuana helps control epileptic seizures, no solid evidence supports this assertion.[7] The only relevant controlled study that has been published to date was designed to evaluate whether illicit drug use affected the age at which people with epilepsy had their first seizures. In this study of 600 patients, researchers found that men, but not women, who used marijuana were less prone to develop seizures than men who did not use the drug, suggesting that marijuana provided some sort of protection for men.[8] However, it is also possible that the marijuana-using men in this study tended to be healthier than those who had not used the drug; in other words, their health status influenced their drug use rather than the other way around.

Researchers have also investigated the antiepileptic properties of cannabidiol, which shows little promise. In three controlled trials conducted with patients with both focal and generalized epilepsy, oral doses of cannabidiol failed to lessen the frequency of either type of seizure.[9] Even if cannabidiol had appeared to suppress seizures, however, these trials would have been far too small to prove its effectiveness. Studies of drugs for epilepsy generally require large numbers of patients who must be followed for months, since symptoms are highly variable and tend to occur unpredictably.

Currently, the only biological reason to believe that cannabinoids could suppress epileptic seizures is the abundance of CB_1 receptors in some of the regions of the brain (the hippocampus and amygdala) where partial seizures originate. While basic research could reveal stronger links between cannabinoids and seizure initiation, this does not seem as promising as other potential uses for marijuana-based medicines.

ALZHEIMER'S DISEASE

An estimated 4 million Americans currently have Alzheimer's dementia, a number that is likely to grow as the country's population ages. Alzheimer's is an incurable progressive disease of the nervous system that typically begins with memory loss and behavioral changes. At present, therapies for

Alzheimer's are limited to relieving its various symptoms. Even the two drugs, donepezil (Aricept) and tacrine (Cognex), that improve mental functions in some patients do not stop the progression of the disease.

There are two possible applications for cannabinoid treatments in Alzheimer's disease: to stimulate patients' appetites and to improve their behavior. Food refusal, which may be symptomatic of depression, is a common problem among people with Alzheimer's dementia; sometimes, but not always, antidepressant medications improve patients' appetites. Treatments would also be welcome that reduced agitation or antisocial behavior in Alzheimer's patients—behaviors that are not only unsafe but that also reduce caregivers' ability to help patients.

In one study, 11 Alzheimer's patients were treated with oral THC (dronabinol, Marinol) for six weeks, followed by six weeks of a placebo. Researchers found that the drug produced significant weight gain and reduced disturbed behavior without causing serious side effects.[10] Most of the patients were severely demented, and their memories were also seriously impaired. Although short-term memory loss is a common side effect of THC in healthy people, it was not measured in this study. In the future it would be useful to study how THC and other cannabinoids affect people with Alzheimer's whose memories remain largely intact. Such patients would be ill served by a medication that accelerated memory loss.

At the time of writing, additional clinical trials of Marinol in Alzheimer's patients and others with dementia appear likely to begin soon. In late 1998, Unimed Pharmaceuticals, which makes Marinol, received a U.S. patent for use of the drug in improving disturbed behavior in people with dementia, including the dementia of Alzheimer's and Parkinson's diseases.

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Review Article

Health-related quality of life across cancer cachexia stages

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Abstract: Cancer cachexia (CC) is common in advanced cancer and is accompanied by negative effects on health-related quality of life (HRQOL). However, methods to identify the impact of CC on HRQOL are limited. Single questionnaire items may provide insight on the effect of CC on HRQOL. Specifically, the use of "feeling of wellbeing" (FWB) on the Edmonton Symptom Assessment System (ESAS) questionnaire and the Distress Thermometer (DT) have been explored. Assessing how these two surrogate measures of HRQOL are impacted among CC stages and what drives these negative effects may allow for focused treatments. Five-hundred and twelve patients referred to a Cancer Rehabilitation Program completed the ESAS, with the question on FWB and the DT at baseline. Patients were separated into CC stages: non-cachexia (NC), pre-cachexia (PC), cachexia (C), refractory cachexia (RC). A mixed model ANOVA with *post hoc* Tukey adjustment was used to compare means of FWB and distress among the CC stages. To understand what was driving the differences between CC stages, a robust regression model was created with either distress or FWB as the outcome measure, dependent on the other measures in ESAS, age and sex. Finally, the use of cannabinoids in treating appetite loss was examined, as it has a detrimental effect on FWB; 54 patients underwent cannabinoid treatment for appetite loss within a community-based, physician-lead, medical cannabis clinic. A *t*-test to assess changes in ESAS appetite score after 3 months of cannabinoid treatment was examined. RC patients had a significantly poorer sense of wellbeing than the other cachexia stages (RC: 6.07±0.33). Significant differences in distress were identified between RC patients and those with NC and C, but not with PC (RC: 4.87±0.38, NC: 3.35±0.26, PC: 4.11±0.30, C: 3.60±0.28). FWB was negatively affected by worsening appetite in all CC stages except NC (PC: 0.19±0.08, P=0.022; C: 0.26±0.06, P<0.001; RC: 0.23±0.08, P=0.007). ESAS score for lack of appetite significantly improved between baseline (5.07±3.21) and follow-up (3.56±3.15, P=0.003) after cannabinoid treatment, with no significant difference in weight (baseline: 70.7±14.6 kg, 3-month follow-up: 71.0±14.8 kg). Future research should validate both multidimensional and single-item tools to measure HRQOL in patients at different stages of CC. Improvement of HRQOL via appetite stimulation, may be achieved through a multidisciplinary approach, which includes cannabinoid therapy.

Keywords: Cachexia; quality of life; appetite; cannabinoids

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Introduction

Up to 80% of advanced cancer patients will experience cachexia in their disease trajectory (1,2). It is known that cancer cachexia (CC) has a negative effect on function, treatment tolerance and overall mortality, with cachexia being the cause of death in 30% of cancer patients (3). As such, understanding the effect of CC on health-related quality of life (HRQOL) is important. HRQOL is a multidimensional concept including, but not limited to, symptoms of disease, side effects of treatment, perception of wellbeing and life satisfaction and measures of physical, mental and social function (4). Significant associations have been identified between weight loss, malnutrition, CC and poor HRQOL outcomes (5-7). This paper will review the current definition and methods to classify CC. Tools used to measure HRQOL in cachexia will be identified. Additionally, results from our laboratory assessing HRQOL along the CC continuum and the factors driving poor HRQOL in CC will be presented. Finally, preliminary evidence for the use of cannabinoids to relieve symptoms that impair HRQOL will be put forth.

CC: definition and classification

In 2011, Fearon *et al.* published the following international consensus statement defining CC, "*A multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism*" (8). Furthermore, criteria for diagnosis were put forth, which included: (I) weight loss >5% in 6 months (in absence of starvation) or, (II) BMI <20 and any degree of weight loss >2% or, (III) appendicular skeletal muscle index <7.26 kg/m^2 in males or <5.45 kg/m^2 in females with weight loss of >2% (8). Once cachexia is diagnosed, Fearon *et al.* proposed a classification system dividing cachexia into three stages: pre-cachexia (PC), cachexia (C) and refractory cachexia (RC). PC is defined as a ≤5% weight loss with anorexia and metabolic change. C patients present with weight loss of >5%, or BMI <20 and weight loss of >2%, or sarcopenia and weight loss of >2%. They also often have reduced food intake and systemic inflammation. In RC, the cancer is pro-catabolic and not responsive to treatment. Additionally, patients will have low performance scores.

Following this very important work, Vigano *et al.* established a CC classification system that uses clinically available tools (*Figure 1*) (9). Classification is based on five criterion that can be determined using the results of a simple blood test and the abridged Patient-generated Subjective Global Assessment (aPG-SGA) questionnaire. Using these criteria, PC is classified as a combination of abnormal biochemistry with decreased food intake or moderate weight loss, or decreased food intake with moderate weight loss. C is identified by a severe weight loss with either abnormal biochemistry or decreased food intake. RC is classified as C with decreased activities and function, or albumin <20 g/L with decreased activities and function.

Methods to assess HRQOL in CC patients

Tools for assessing HRQOL in CC are limited. In a 2013 review, Wheelwright *et al.* identified the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) as the only cachexia-specific instrument available at the time (10). The FAACT tool assesses five domains: physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing and CC specific symptoms. However, weaknesses in the methodology used to validate the tool, the absence of additional psychosocial domains affecting patients with CC and doubt in the ability to use the tool internationally led the authors to conclude that a robust instrument to assess HRQOL in CC is lacking (10).

Since then, the European Organization for Research and Treatment of Cancer (EORTC)-CAX24 scale has been developed to fill this void (11). To be used with the more generic HRQOL assessment tool, the EORTC-QLQ-C30 (12), it proposes five domains and four individual items capturing relevant issues affecting CC patients. These include: food aversions (5 questions), eating and weight loss worry (3 questions), eating difficulties (3 questions), loss of control (6 questions), physical decline (3 questions) and dry mouth, indigestion/heartburn, forcing self to eat and inadequate information. This tool is currently in the process of being fully validated on an international scale (11).

A recent study by Zhou *et al.* used the Chinese version of the MD Anderson Symptom Inventory (13), with the addition of 8 cachexia-specific symptoms (feeling dizzy, early satiety, lack of energy, changes in taste and smell, diarrhea, constipation, anxiety, and depression), to assess symptom burden among the CC stages (14). Results suggested that lack of appetite was the most frequent and severe symptom among the four CC groups, followed by fatigue, disturbed sleep, lack of energy and distress. The

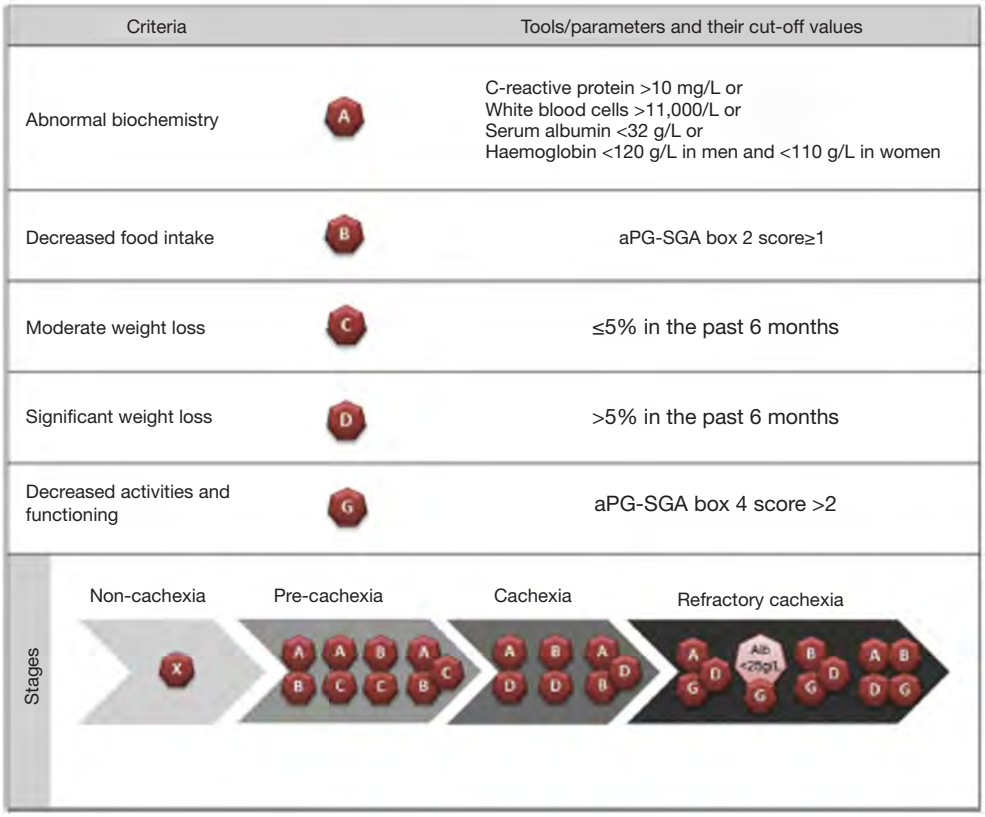


Figure 1 Criteria and cut-offs for the clinical application of the cachexia stages. aPG-SGA, abridged Patient-Generated Subjective Global Assessment (box 2, food intake; box 4, activities and functioning); X, insufficient number of criteria or criteria that do not correspond to any combinations mentioned for the cachexia stages.

authors cite limitations of this study, which include (I) the lack of validation of the new tool developed; and (II) the CC staging method used, based on the work of Blum *et al.* (7), which the authors criticize as not using sarcopenia as part of their classification system, and only weight loss as the definition for RC (14).

Non-cachexia specific tools to assess HRQOL in CC

Due to the paucity of CC specific instruments to assess HRQOL, surrogates must be identified. Ideally, tools would be simple to use and not burdensome to patients. There has been some work pursuing correlations between "feeling of wellbeing" (FWB) as a single item on a questionnaire, and total scores on multi-item HRQOL assessment instruments. Stiel *et al.* (15) analyzed the relationship between the "How do you feel today?" question on the German Minimal Documentation System (MIDOS) (16) and total scores of the EORTC-QLQ-C30 and the Functional Assessment of Cancer Therapy-General (FACT-G) (17). In both instances, social domains were not captured by the single question. However, it was significantly associated with the physical ($r=0.38$, $P<0.01$), cognitive ($r=0.34$, $P<0.01$), emotional ($r=0.33$, $P<0.01$) and role functioning ($r=0.26$, $P<0.05$) domains of the EORTC-QLQ-C30 and the physical ($r=0.58$, $P<0.01$), functional ($r=0.42$, $P<0.01$) and emotional ($r=0.38$, $P<0.01$) domains of the FACT-G (15). Similarly, Bush *et al.* found a moderate association between the FWB question on the Edmonton Symptom Assessment System (ESAS) (18) and total FACT-G score ($r=0.48$, $P<0.0001$) (19). In a smaller study, Paiva *et al.* compared ESAS FWB and the EORTC-QLQ-C30, with a moderate association with the overall symptom scales ($r=0.61$, $P<0.0001$) (20).

Another single item that may prove useful in identifying poor HRQOL is the Distress Thermometer (DT) (21). The DT is a vertical scale ranging from 0 to 10 asking patients to rate their feeling of distress in the past week,

Table 1 Participant characteristics

Characteristics	Data
Age (year), mean ± SD	62.1±13.5
Cancer cachexia stage, n (%)	
Non-cachexia	172 (33.6)
Pre-cachexia	115 (22.5)
Cachexia	154 (30.1)
Refractory cachexia	71 (13.9)
Diagnosis, n (%)	
Lung	123 (24.0)
GI	81 (15.8)
Pancreatic	60 (11.7)
Other	248 (48.4)
Metastatic disease, n (%)	
Yes	295 (57.6)
No	217 (42.4)
On treatment, n (%)	
Yes	263 (51.4)
No	249 (48.6)

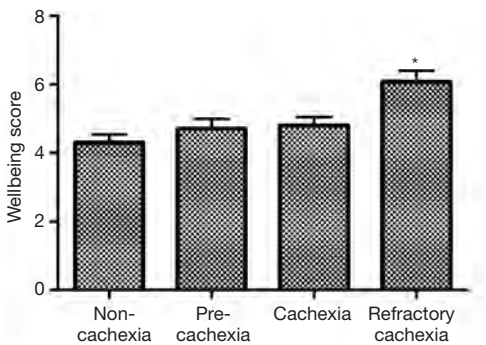


Figure 2 Wellbeing among cancer cachexia stages. Mixed model ANOVA controlled for age, sex, diagnosis, current treatment, metastatic disease. Data reported as mean ± standard deviation. * denotes significance P>0.05.

with zero denoting "no distress" and ten indicating "extreme distress." The National Comprehensive Cancer Network defined distress as, "a multifactorial, unpleasant, emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis" (22). High levels of distress are associated with poor effect on quality of life (23). The DT is comparable to longer screening tools in its ability to correctly identify distress among cancer patients; a cutoff of four has been associated with the best sensitivity and specificity (24). To the knowledge of the authors, there is no specific tool identifying distress among CC patients.

Assessing HRQOL in CC using single-item measures: original research

Given the current lack of a validated CC-specific HRQOL assessment tool, we decided to retrospectively examine how the single-item of FWB from the ESAS questionnaire and the DT would differ between the CC stages. Five hundred and twelve patients who were referred to the Cancer Rehabilitation Program of the McGill University Health Centre (Montreal, Canada), completed these two questionnaires and were separated into CC stages, as per the classification system of Vigano *et al.* (9). Participant characteristics are reported in *Table 1*. Mixed model ANOVA with *post hoc* Tukey adjustment was used to identify differences in wellbeing and distress between CC groups. The models controlled for age, sex, diagnosis, current treatment and the presence of metastatic disease. Significance was determined at P<0.05. *Figures 2* and *3* illustrate the results. RC patients had a significantly greater poor sense of wellbeing than the other cachexia stages (RC: 6.07±0.33) (*Figure 2*). Significant differences in distress were identified between RC patients and those with NC and C, but not with PC (RC: 4.87±0.38, NC: 3.35±0.26, PC: 4.11±0.30, C: 3.60±0.28) (*Figure 3*).

With the data suggesting differences between CC stages and the HRQOL-surrogate measurements of FWB and distress, we then wanted to understand what is driving these differences. To achieve this, a robust regression model was created with either distress or FWB as the outcome measure, which was dependent on the other measures in ESAS, namely pain, tiredness, nausea, depression, anxiety, drowsiness, appetite and shortness of breath (SOB). Additionally, age and sex were considered in the model. Results for each are shown in *Tables 2* and *3*. FWB is negatively affected by worsening appetite in all CC stages

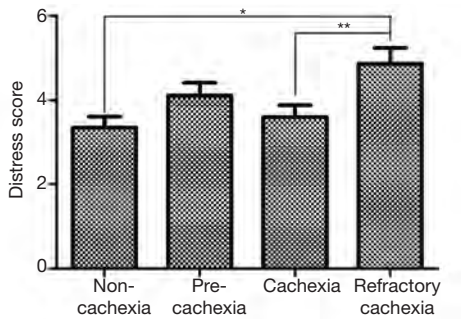


Figure 3 Distress among cancer cachexia stages. Mixed model ANOVA controlled for age, sex, diagnosis, current treatment, metastatic disease. Data reported as mean ± standard deviation. * denotes significance P>0.05.

except NC. This mirrors results from Zhou *et al.* (14). Additionally, anxiety had a poor effect on FWB in all CC stages. Fatigue was also predictive of poor wellbeing in the C and RC stages. Feelings of distress increased in all CC stages, except RC, as anxiety increased. The relationship between distress and anxiety has previously been demonstrated in ambulatory cancer patients (21). None of the ESAS symptoms were significantly related to feelings of distress in RC patients.

Symptom of interest: anorexia

The presence of anorexia leads to decreased food intake, which is a characteristic of cachexia; in our laboratory's previous work creating a CC staging system, 63% of patients reported decreased intake, reflecting a lack of appetite (9). While the cluster of other CC symptoms such as anxiety, fatigue, pain and depression have effective pharmacological and nonpharmacological interventions available, the ability to treat anorexia remains difficult. Orexigenic agents used to reverse anorexia include corticosteroids, megestrol acetate, serotonin antagonists, anamorelin (ghrelin-mimetic) and cannabinoids.

Corticosteroids

Corticosteroids have been used effectively in the treatment of many symptoms in advanced disease. Improvements have been demonstrated in anorexia, but also in relieving symptoms of pain, fatigue, chemotherapy-induced nausea and vomiting and overall quality of life (25). Unfortunately, the reversal of anorexia using corticosteroids is short lived, generally lasting less than 4 weeks (26). Additionally, long-term use of corticosteroids is associated with myopathy, gluconeogenesis leading to insulin resistance, immunosuppression, bone loss and mood disturbances (25).

Megestrol acetate

A recent updated Cochrane Review on the effectiveness of megestrol acetate for the reversal anorexia in cancer

Table 2 Relationship between wellbeing and ESAS symptoms by CC stage

CC stage	Category	B	SE	P	R^2
Non-cachexia (n=167)	Pain	0.24	0.07	<0.001	0.33
	Anxiety	0.19	0.08	0.022	
Pre-cachexia (n=111)	Pain	0.22	0.09	0.012	0.44
	Anxiety	0.23	0.10	0.017	
	Appetite	0.19	0.08	0.022	
	SOB	0.15	0.07	0.042	
Cachexia (n=152)	Fatigue	0.32	0.10	0.002	0.37
	Anxiety	0.20	0.09	0.026	
	Appetite	0.26	0.06	<0.001	
Refractory (n=67)	Fatigue	0.60	0.13	<0.001	0.53
	Anxiety	0.33	0.15	0.029	
	Appetite	0.23	0.08	0.007	

ESAS, Edmonton Symptom Assessment System; CC, cancer cachexia; SE, standard error; SOB, shortness of breath.

Table 3 Relationship between distress and ESAS symptoms by CC stage

CC stage	Category	B	SE	P	R^2
Non-cachexia (n=156)	Pain	0.13	0.06	0.026	0.55
	Depressed	0.21	0.07	0.004	
	Anxiety	0.58	0.07	<0.001	
Pre-cachexia (n=105)	Fatigue	0.29	0.11	0.01	0.43
	Anxiety	0.28	0.11	0.014	
Cachexia (n=136)	Depressed	0.28	0.10	0.003	0.47
	Anxiety	0.53	0.09	<0.001	
	Age	−0.03	0.01	0.041	
Refractory (n=61)					0.35

ESAS, Edmonton Symptom Assessment System; CC, cancer cachexia; SE, standard error.

patients demonstrated favorable results (27). Megestrol acetate was effective in significantly improving both appetite when compared to placebo [RR 2.19 (1.4–3.4)] (27). Modest weight gain was also observed: 1.96 kg (95% CI: 1.11–2.81 kg) (27). Despite this, the quality of evidence for the improvement of anorexia versus placebo was graded as "very low" due to possible bias introduced from unclear blinding methods, sequence generation and allocation concealment. Additionally, side-effects such as edema, dyspnea, thromboembolic events and death were associated with the use of megestrol acetate versus placebo in both low and high doses (±800 mg/day) (27).

Serotonin antagonist: cyproheptadine

The use of cyproheptadine as an orexigenic agent for advanced cancer patients has yielded few benefits. Kardinal *et al.* only demonstrated a moderate improvement in appetite over placebo, with weight loss in both groups (4.5±0.72 versus 4.95±1.01 lb, P=0.72) (28).

Ghrelin mimetic: anamorelin

Recent phase III trials have demonstrated a positive effect of anamorelin on both appetite and weight vs placebo in stage III/IV non-small cell lung cancer patients. In the ROMANA 1 and ROMANA 2 studies, participants were given 100 mg anamorelin/day or placebo for 12 weeks (29). Pooled analysis of the studies demonstrated the anamorelin group had modest increases in mean total body weight (ROMANA 1 anamorelin: 2.2±0.33 kg, placebo: 0.14±0.36 kg; ROMANA 2 anamorelin: 0.95±0.39 kg, placebo: −0.57±0.44 kg) and median lean body mass (ROMANA 1 anamorelin: 0.99 kg (95% CI: 0.61 to 1.36 kg), placebo: −0.47 kg (95% CI: −1.00 to 0.21 kg); ROMANA 2 anamorelin: 0.65 kg (95% CI: 0.38 to 0.91 kg), placebo: −0.98 (95% CI: −1.49 to −0.41 kg) (29). Strength, as measured by handgrip dynamometry, was not significantly improved. Overall mean anorexia-cachexia scale score, as measured by FAACT, was significantly greater in the anamorelin group (29). There were no differences in treatment-related adverse events between study groups; the most common were hyperglycemia, nausea and edema (29). While its effect in treating anorexia seems promising, anamorelin is not yet commercially available.

Cannabinoids

The potential effect of cannabinoids on appetite and weight has been repeatedly reviewed in patients with cancer and HIV/AIDS (30-33). Two studies looked at natural extracts, six studies looked at dronabinol, a synthetic cannabinoid, as orexigenic agents and one study assessed nabilone. In 2006, the Cannabis-In-Cachexia-Study-Group compared the effects of cannabis extract, delta-9-tetrahydrocannabinol (THC), and placebo on appetite and quality of life in patients with cancer-related anorexia-cachexia syndrome (34). The cannabis extract, administered at a dose of 2.5 mg of THC and 1 mg of cannabidiol (CBD), was well tolerated by patients with anorexia. However, no significant differences in appetite and HRQOL were found for cannabis extract as compared to placebo (34). In another study, higher

Table 4 Demographic and clinical characteristics

Characteristics	Data
Age (years)	47.3±16.1[†]
Gender	
Males	34 (63.0)[‡]
Females	20 (37.0)
Diagnosis	
Cancer	23 (42.6)
Non-cancer	31 (57.4)
Cannabinoid therapy	
THC/CBD (1:1 ratio)	With SC[§]: 2; no SC: 4; total: 6 (11.1)
THC-rich	With SC[§]: 8; no SC: 9; total: 17 (31.5)
CBD-rich	With SC[§]: no SC: 0; total: 0
Combined therapies	
THC/CBD and THC-rich	With SC[§]: 7; no SC: 10; total: 17 (31.5)
THC/CBD and CDB-rich	With SC[§]: 3; no SC: 4; total: 7 (13.0)
THC-rich and CBD-rich	With SC[§]: 8; no SC: 9; total: 17 (31.5)
THC/CBD, THC-rich, CBD-rich	With SC[§]: 0; no SC: 1; total: 1 (1.9)
Route of administration	
Oral	11 (20.4)
Inhaled	14 (25.9)
Combined oral and inhaled	29 (53.7)
Adverse effects	
Mild	11 (20.4)
None	41 (75.9)
Not recorded	2 (3.7)

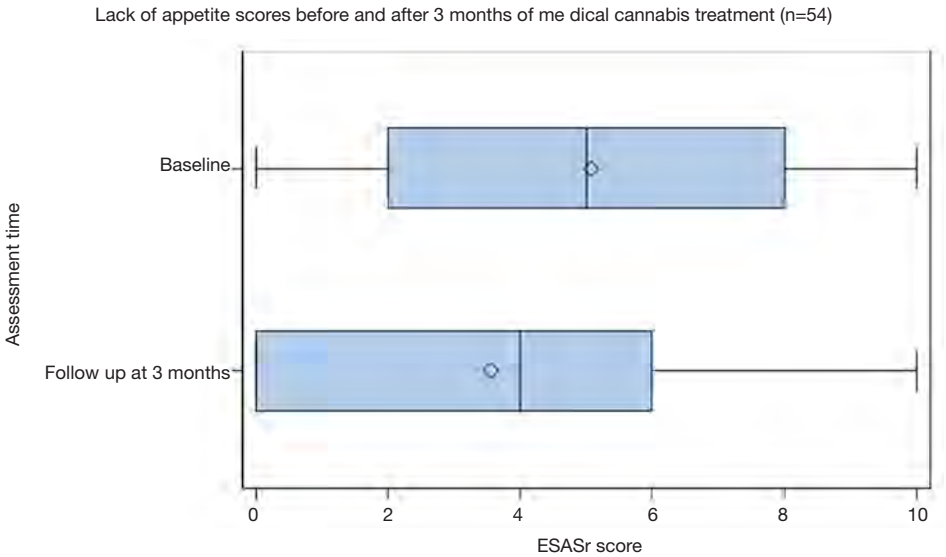
[†], values expressed as mean ± standard deviation; [‡], all values expressed as number of patients; [§], nabilone—synthetic cannabinoid product. Round bracket indicates percentage. SC, synthetic cannabinoid co-treatment. THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol.

doses of natural cannabinoids (up to 22.5 mg/day of THC) provided more consistent and favorable results for appetite stimulation and decreased weight loss associated with cancer (total weight gain of 1.25 lb; on placebo: total weight loss of 21.25 lb) (30). Equally, the combination of both oral and inhaled methods of administration provided favorable results for an increase and stabilization of weight in HIV patients (30). Studies that examined dronabinol also found limited and low-quality evidence supporting cannabinoids for appetite stimulation and weight gain in cancer patients. More recently, a randomized, double-blind, placebo-controlled study evaluated the effect of nabilone (0.5 mg/day/2 weeks followed by 1.0 mg/day/6 weeks) in patients with advanced non-small cell lung cancer. Patients on nabilone (n=9) showed an increase in their average caloric intake (342 kcal/day) and significant improvements in their quality of life particularly for role functioning, emotional functioning, social functioning, pain, and insomnia, which were not seen in the patients on placebo (n=13) (35).

Assessing cannabinoids for increasing appetite and stabilizing weight in chronic cancer and non-cancer diseases: original research

In order to gather more specific data on the effect of different types of cannabinoids on appetite and weight in chronic cancer and non-cancer diseases, a retrospective chart review was conducted at Santé Cannabis, the only community-based, physician-lead, medical cannabis clinic in Quebec, Canada. At baseline, 54 patients with "increase appetite" as a treatment goal completed the ESAS question on appetite, with 51 subjects also having their weight measured. These assessments were repeated at 3-month follow-up. The mean age of patients was 47.3±16.1 years; 63% were male and 43% of our sample was represented by patients with a cancer diagnosis (*Table 4*).

Of the 54 patients analyzed, the ESAS score for lack of appetite significantly improved between baseline (5.07±3.21) and follow-up (3.56±3.15, paired *t*-test P=0.0026) (*Figure 4*). Bivariate regression reveals a significant improvement with the use of nabilone (–2.73, 95% CI: –4.19 to –1.27, P=0.0358). Route of administration also had an effect on appetite: (I) favoring only inhaled *vs.* only oral (–2.36, 95% CI: –4.17 to –0.54, P=0.024) and (II) favoring combined oral and inhaled *vs.* only oral (–2.00, 95% CI: –3.26 to –0.74, P=0.023). With regression models adjusted for age and gender (multivariate), only a marginal improvement was detected for the use of nabilone (–2.84, 95% CI: –4.34 to –1.34, P=0.0521). A more pronounced



ESASr: Edmonton system assessment system revised (0 =no lack of appetite; 10 =worst lack of appetite). The bars provide minimun, Q1(25%), median, mean (diamond), Q3 (75%) and maximum of the variables. The p-value for the difference test is 0.0026.

Figure 4 Box-plot demonstrating appetite at baseline and follow-up.

improvement was demonstrated among the methods of administration: (I) favoring only inhaled *vs.* only oral (–2.01 to 95% CI: –4.85 to –1.17, P=0.006) and (II) favoring combined oral and inhaled *vs.* only oral (–2.34 to 95% CI: –3.61 to –1.07, P=0.009).

Among the 51 subjects who were examined for weight change over time, there was no significant difference found and weight remained stable between baseline (70.7±14.6 kg) and 3-month follow-up (71.0±14.8 kg). Regression models, with and without adjustment for age and gender, did not show any difference in weight associated with nabilone use or with different routes of administration.

The majority of study patients did not report any side effects to cannabinoids (*Table 4*). Eleven patients reported mild side effects, including anxiety, fatigue, dizziness and dry mouth.

Conclusions

Despite the incidence and prevalence of CC, there is still a paucity of data regarding its impact on HRQOL. Latest research in this area has focused on developing and/or applying routinely available criteria to identify CC stages in clinical practice, specific multidimensional tools (such as FAACT or EORTC-CAX24) or non-specific single-item scales (such as DT and FWB scale from ESAS) to assess HRQOL across CC stages and orexigenic agents such as anamorelin and cannabinoids. Original research from our group suggests wellbeing is negatively affected by anorexia and anxiety in all CC stages, with fatigue also being predictive of poor wellbeing in the cachexia and RC stages. Cannabinoids, when prescribed through an interdisciplinary, physician-lead, care model appear to be promising orexigenic agents in chronic cancer and non-cancer diseases, particularly if used concomitantly through the oral and the inhalation route of administration. Future research should further validate both multidimensional and single-item tools to measure HRQOL in patients at different stages of CC, for whom the above pharmacological interventions are trialed to improve appetite and stabilize weight.

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Footnote

Conflicts of Interest: A Vigano is the Research Director of Santé Cannabis—a medical cannabis clinic specializing in clinical research; the principal investigator for a phase II and a phase III clinical trial sponsored by Tetra Bio-Pharma, Inc. The other authors have no conflicts of interest to declare.

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Review
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A Systematic Review of the Effectiveness of Medical Cannabis for Psychiatric, Movement and Neurodegenerative Disorders

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The discovery of endocannabinoid's role within the central nervous system and its potential therapeutic benefits have brought forth rising interest in the use of cannabis for medical purposes. The present review aimed to synthesize and evaluate the available evidences on the efficacy of cannabis and its derivatives for psychiatric, neurodegenerative and movement disorders. A systematic search of randomized controlled trials of cannabis and its derivatives were conducted via databases (PubMed, Embase and the Cochrane Central Register of Controlled Trials). A total of 24 reports that evaluated the use of medical cannabis for Alzheimer's disease, anorexia nervosa, anxiety, dementia, dystonia, Huntington's disease, Parkinson's disease, post-traumatic stress disorder (PTSD), psychosis and Tourette syndrome were included in this review. Trial quality was assessed with the Cochrane risk of bias tool. There is a lack of evidence on the therapeutic effects of cannabinoids for amyotrophic lateral sclerosis and dystonia. Although trials with positive findings were identified for anorexia nervosa, anxiety, PTSD, psychotic symptoms, agitation in Alzheimer's disease and dementia, Huntington's disease, and Tourette syndrome, and dyskinesia in Parkinson's disease, definitive conclusion on its efficacy could not be drawn. Evaluation of these low-quality trials, as rated on the Cochrane risk of bias tools, was challenged by methodological issues such as inadequate description of allocation concealment, blinding and underpowered sample size. More adequately powered controlled trials that examine the long and short term efficacy, safety and tolerability of cannabis for medical use, and the mechanisms underpinning the therapeutic potential are warranted.

KEY WORDS: Cannabis; Cannabinoids; Randomized controlled trial; Mental disorders; Movement disorders; Neurodegenerative diseases.

INTRODUCTION

Cannabis (marijuana) has long been used for medical and recreational purposes. The *Cannabis sativa* and *Cannabis indica* are two common species used for consumption. Between the two species, *C. sativa* has comparatively higher delta-9-tetrahydrocannabinol (THC) concentration while *C. indica* has comparatively higher cannabidiol concentration. Cannabinoids can be classified into three subtypes, endocannabinoids (naturally present in human body), phytocannabinoids (present in cannabis plant) and synthetic cannabinoids (produced chemically). Presently, over 60 different types of pharmacologically active cannabinoids have been identified and isolated from the cannabis plant.[1)] These include the exogenous cannabinoids such as the psychoactive THC and non-psychoactive cannabidiol, as well as the endogenous cannabinoids such as anandamide, which affects most systems in the human body, especially the central nervous system. The cannabinoid binds to two types of G protein-coupled receptors: CB_1, which are most abundant in the brain, and CB_2, which are expressed on cells in the immune system where inflammation is modulated.[1)] Hence, cannabinoids are involved in psychomotor coordination, memory, mood, and pain.[2)] Given the expression of these receptors in the human body, and the interactions between cannabinoids with neurotransmitters and neuromodulators, such as dopamine, glutamate, serotonin, gamma-aminobutyric acid (GABA), it has been thought that cannabis may potentially confer some degree of medical benefit.

Medical cannabis refers to the use of cannabis and its derivatives to treat disease and relieve symptoms.[3)] Common commercially available cannabinoids for medical use are presented in Table 1.[4-6)] Testing of other synthetic cannabinoid compounds such as Epidiolex (GW

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Table 1. Summary of cannabinoids

Generic name	Trade name	Administration method	Formulation	Dosage	Pharmacokinetics
Dronabinol	Marinol	Oral capsule	Synthetic THC	2.5 mg, 5 mg, 10 mg	t_{max}=2-4 hr. Completely absorbed (90-95%) after a single dose Alpha (plasma) half-life: 4 hr Beta (tissue) half-life: 25-36 hr*
Nabilone	Cesamet	Oral capsule	Synthetic structural analogue of THC Methylgroup at C9 and pentyl side chain in THC substituted with a ketone group and a dimethyl heptyl side chain respectively.	1 mg	t_{max}=2 hr Alpha (plasma) half-life: 2 hr Beta (tissue) half-life: 35 hr*
Nabiximols	Sativex	Oromucosal spray	Whole plant cannabis extract	2.7 mg THC and 2.5 mg CBD, per spray (100 μl)	t_{max}=98-253 min Variable plasma half-life of 85-130 min Clearance within 12-24 hr after dose*
CBD	None	Oral capsule	Cannabis plant extract	Variable	No available information in humans[4]
THC	Namisol	Oral capsule	Cannabis plant extract	Variable	t_{max}=1-2 hr Half-life: 72-80 min[5,6]

THC, tetrahydrocannabinol; CBD, cannabidiol.
*Marinol (Abbott Products, 2010), Cesamet (Valeant Canada, 2009), and Sativex (GW Pharmaceutical, 2010).

Pharmaceuticals, Cambridge, UK), Namisol (Echo Pharmaceuticals, Weesp, the Netherlands) and Cannador (Society for Clinical Research, Berlin, Germany) are currently underway. These cannabinoid formulations of varying THC or cannabidiol concentration and/or ratio have been widely studied for a variety of illnesses, most notably somatic conditions like pain and spasticity.[3] More recently, there has been a growing interest in the neuroprotective potential of cannabinoids for neurological conditions, and the antipsychotic properties of cannabidiol. Preclinical evidences suggest that cannabinoids may attenuate neurodegeneration by reducing excitotoxicity and oxidative damage via CB_1 and CB_2 receptors and receptor-independent mechanisms.[7,8] In the case of cannabidiol, there are indications that cannabidiol modulates the endocannabinoids system by enhancing anandamine levels, thereby reducing psychotic symptoms.[9] Although reviews of preclinical and clinical studies have been conducted on movement disorders[8] and psychosis,[10,11] the aim of the present review is to provide a more in-depth evaluation of the efficacy of medical cannabinoids by appraising the quality of evidences from clinical studies across a broader range of neurodegenerative disorders and psychiatric conditions.

METHODS

Types of Studies

Randomized controlled trials that compared and examined the pharmacological intervention of cannabis (in any preparation form, and any route of administration) with placebo or other active treatments were included. Other quantitative study designs such as cohort studies, retrospective chart review studies, and case studies were excluded. Opinion and discussion papers were also excluded. This review only considered studies on human participants that were published in English-language.

Types of Participants

People of any age and sex with any of the following conditions, and/or clinically diagnosed with movement disorders (e.g., dystonia, Huntington's disease, Parkinson's disease, Tourette syndrome), neurological conditions (e.g., Alzheimer's disease, dementia, amyotrophic lateral sclerosis [ALS]) and psychiatric condition (e.g., psychosis, schizophrenia, anxiety).

Types of Interventions

Any form of cannabis for medical use irrespective of the route of administration, duration of intervention or dosage: Smoked cannabis, natural or synthetic cannabinoid including, THC, cannabinol (CBN), cannabidiol, or combinations of abovementioned agents. The comparators included placebo, usual care, other types of active treatments, or derivatives of cannabis.

Search Strategy

An electronic search of human studies published in English-language was conducted in PubMed, Embase, and the Cochrane Central Register of Controlled Trials

(CENTRAL) from its inception to present (April 2017), using the following keywords: "randomized controlled trial (RCT), cannabinoids, cannabis, tetrahydrocannabinol, THC, cannabidiol, movement disorder, neurodegenerative, psychiatric, dystonia, Huntington's disease, Parkinson's disease, Tourette syndrome, Alzheimer's disease, dementia, ALS, psychosis, schizophrenia, anxiety". The reference lists of retrieved papers were also reviewed for additional papers. The full texts retrieved were assessed for relevance based on the objectives and inclusion criteria of this review. Studies in which full text were unavailable were excluded.

Data Extraction and Quality Assessment

The data extracted from each report included the study type, sample characteristics, type and dosage of intervention, primary outcome measures, side effect and adverse events. Studies were evaluated for methodological quality using the Cochrane risk of bias tool,[12] on sequence generation, allocation concealment, blinding, incomplete data and selective outcome reporting. The ratings were high, low or unclear risk of bias (Table 2[13-36]). The assessment of methodological quality was performed by two independent raters. Discrepancies were resolved by mutual discussion.

Table 2. Cochrane risk of bias tool ratings of included studies

Study	Cochrane risk of bias tool						
	Random sequence generation	Allocation concealment	Blinding of participant/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall
Psychiatric condition							
Anorexia Nervosa							
Gross *et al.* (1983)[13]	?	?	?	?	?	–	–
Andries *et al.* (2014)[14]	+	+	+	+	+	+	+
Anxiety							
Fabre *et al.* (1981)[15]	?	–	–	–	–	?	–
Glass *et al.* (1981)[16]	?	?	–	–	?	?	–
Zuardi *et al.* (1982)[17]	?	?	?	?	+	+	?
Bergamaschi *et al.* (2011)[18]	–	–	+	?	+	+	–
Crippa *et al.* (2011)[19]	?	?	?	?	+	+	?
Post-traumatic stress disorder							
Jetly *et al.* (2015)[20]	?	?	+	+	+	+	?
Psychotic symptoms							
Leweke *et al.* (2012)[21]	+	?	?	?	+	–	–
Neurodegenerative disorders							
Alzheimer's disease							
Volicer *et al.* (1997)[22]	?	?	?	?	?	+	?
Dementia							
Walther *et al.* (2011)[23]	?	?	?	?	+	?	?
van den Elsen *et al.* (2015)[24]	+	?	+	+	?	+	?
van den Elsen *et al.* (2015)[25]	+	?	+	+	?	+	?
Amyotrophic lateral sclerosis							
Weber *et al.* (2010)[26]	+	?	+	+	+	+	?
Movement disorders							
Dystonia							
Fox *et al.* (2002)[27]	+	+	?	?	?	?	?
Zadikoff *et al.* (2011)[28]	+	?	?	?	–	+	–
Huntington's disease							
Consroe *et al.* (1991)[29]	?	?	+	+	?	+	?
Curtis *et al.* (2009)[30]	?	+	?	?	+	+	?
López-Sendón Moreno *et al.* (2016)[31]	+	?	+	+	+	+	?
Parkinson's disease							
Sieradzan *et al.* (2001)[32]	?	?	?	?	?	+	?
Carroll *et al.* (2004)[33]	+	?	+	+	+	+	?
Chagas *et al.* (2014)[34]	?	?	+	+	+	+	?
Tourette syndrome							
Müller-Vahl *et al.* (2002)[35]	?	?	+	+	+	+	?
Müller-Vahl *et al.* (2003)[36]	?	?	+	+	–	+	–

+, low risk of bias; –, high risk of bias; ?, unclear risk of bias.

RESULTS

The search yielded 931 records (hits), of which 916 records remained after removing duplicates. Eighty-six records were then considered as potentially relevant after evaluation of title and abstract. The reference lists of these records were also reviewed. The full texts of these records were retrieved and reviewed based on the inclusion criteria and objectives of this review. A total of 62 records were excluded and 24 records were included in this review (Fig. 1).[37] Of the 24 reports (480 participants), 18 were crossover trials, 6 were parallel trials. All of the studies were conducted in Western societies.

Psychiatric Disorders

Anorexia nervosa

Two studies (36 participants), rated as having an low and high risk of bias, evaluated cannabinoids for the treatment of anorexia nervosa.[13,14] In an early crossover trial involving 11 females with anorexia nervosa, titrated THC 7.5 mg (2.5 mg, three times a day) to a maximum of 30 mg (10 mg, three times a day) showed similar weight gain to titrated diazepam 3.0 mg (1 mg, three times a day) to 15.0 mg (5 mg, three times a day). Three patients in the THC treated group were withdrawn due to severe dysphoric reactions. More recently, in two 4-week treatments separated by a 4-week washout period, dronabinol (2.5 mg, twice a day) produced significant weight gain of 0.73 kg ($p < 0.01$), compared to placebo.[14]

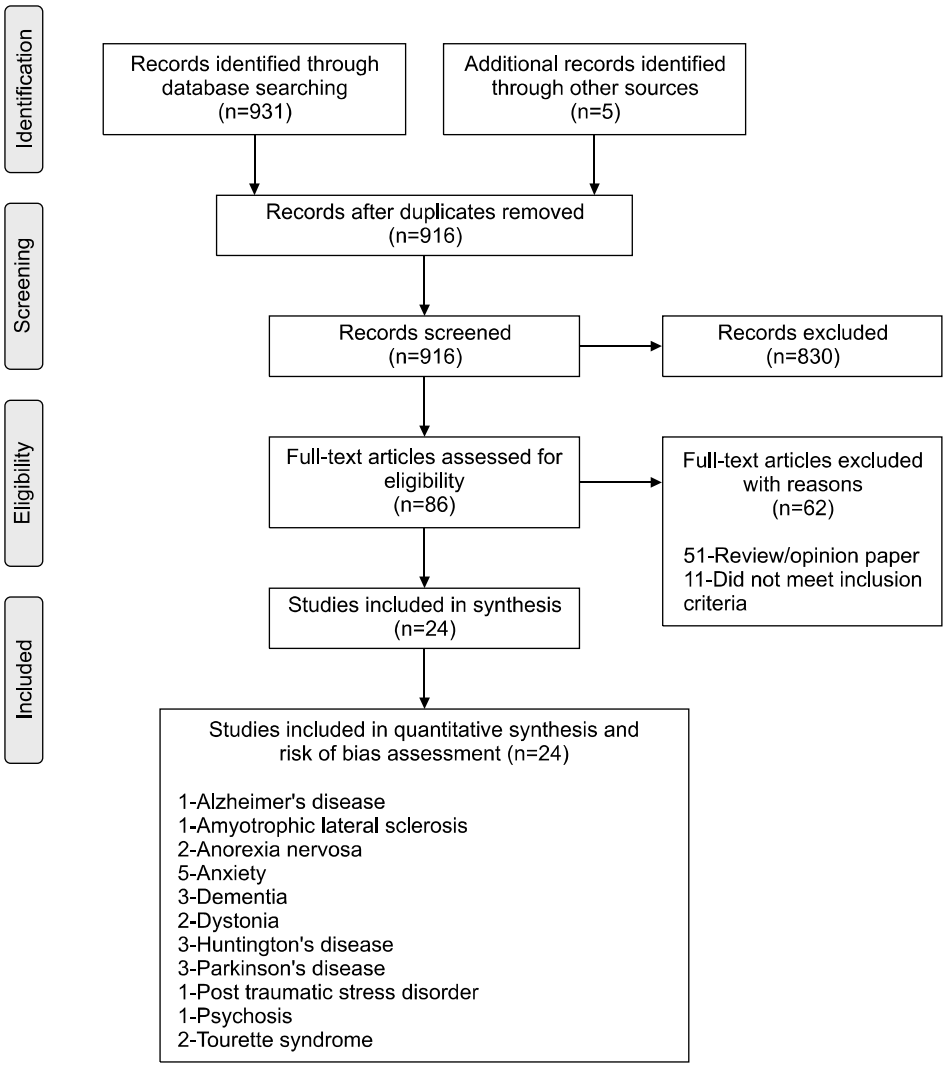

Fig. 1. Flow diagram of study review process – PRISMA flow chart.[37]

Table 3. Clinical trials of cannabis and its derivatives for psychiatric conditions

Study	Design/ duration	Condition	Sample characteristics*	Intervention (No. of patients)	Outcome	Side effects / adverse events	Results	Cochrane risk of bias
Anorexia nervosa								
Gross *et al.* (1983)[13]	Double blind Crossover	Anorexia nervosa	• n=11 • All females • Mean age, 23.6 yr	• THC 2.5-10 mg×3 • Diazepam 1-5 mg×3	Primary: • Weight gain	3 withdrawn due to severe dysphoria	• No significant difference between groups on weight gain	High
Andries *et al.* (2014)[14]	Double blind Crossover	Anorexia nervosa	• n=25 • All females	• Dronabinol 2.5 mg×2 • Placebo	Primary: • Weight gain Secondary: • EDI-2	No severe adverse event	• Significant weight gain of 0.73 kg with dronabinol ($p<0.01$) • No difference in EDI-2	Low
Anxiety								
Fabre *et al.* (1981)[15]	Double blind Parallel (28 days)	Anxiety	• n=20 • 15:5 • 9-41 yr (mean age, 29 yr)	• Nabilone 1 mg×3 • Placebo	• Hamilton rating scale for anxiety	Dry mouth Dry eyes Drowsiness	• Improvement in anxiety in nabilone group compared to placebo group ($p<0.001$)	High
Glass *et al.* (1981)[16]	Single blind Crossover	Generalized anxiety disorder	• n=8 • 3:5 • 22-30 yr	• Nabilone 2 mg • Placebo	• Heart rate, blood pressure • POMS	Light-headedness Headache Nausea	• Lack of antianxiety effects	High
Zuardi *et al.* (1982)[17]	Double blind Crossover	Anxiety induced by THC in healthy volunteers	• n=8 • 6:2 • 20-38 yr • Mean age, 27 yr	• THC 0.5 mg/kg • CBD 1 mg/kg • Mixture (THC 0.5 mg/kg+CBD 1 mg/kg) • Diazepam 10 mg • Placebo	• Anxiety-interviews and spontaneous reports • STAI • ARCI-Ma	Sleepiness	• CBD attenuated but did not completely block the anxiety induced by THC	Unclear
Bergamaschi *et al.* (2011)[18]	Double blind Parallel	Anxiety induced by simulated public speaking in social phobia patients	• n=36 (24, generalized social anxiety disorder; 12, healthy control) • 18:18 • Mean age, 22.9-24.6 yr	• CBD 600 mg • Placebo	• VAMS • SSPS-N • Physiological measures (blood pressure, heart rate, and skin conductance)	No information	• BD treatment significantlyreduced anxiety, cognitive impairment and discomfort in their speech performance, and significantly decreased alert in their anticipatory speech; placebo group scored higher on these measures compared to healthy controls • Significant increase in SSPS-N for placebo group; no difference between CBD treated and healthy control	High
Crippa *et al.* (2011)[19]	Double blind Crossover	Generalized social anxiety disorder	• n=10 • ll males • 20-33 yr (mean, 24.2 yr)	• CBD 400 mg • Placebo	• VAMS • Regional cerebral blood flow using SPECT technique	No information	• Significant decrease in subjective anxiety ($p<0.001$) • Reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus ($p<0.001$, uncorrected), and increased ECD uptake in the right posterior cingulate gyrus ($p<0.001$, uncorrected)	Unclear

Table 3. Continued

Study	Design/ duration	Condition	Sample characteristics*	Intervention (No. of patients)	Outcome	Side effects / adverse events	Results	Cochrane risk of bias
Post-traumatic stress disorder (PTSD)								
Jetly *et al.* (2015)[20]	Double blind Crossover	PTSD associated nightmares	• n=10 • All males • Mean age, 43.6 yr	• Nabilone 0.5-3.0 mg • Placebo	• CAPS • CGI-C • PTSD dream rating scale • WBQ	Dry mouth Headache	Significant improvement in: • CAPS recurring and Distressing Dream scores (p=0.03) • CGI-C (p=0.05) • WBQ (p=0.04)	Unclear
Psychotic symptoms								
Leweke *et al.* (2012)[21]	Double blind Parallel	Schizophrenia patients	• n=42 • Mean age, 29.7 yr	• CBD 800 mg/day • Amisulpride 800 mg/day	• PANSS • BPRS	No information	• Decreased BRPS and PANSS scores with no difference between both treatment groups • Lesser side effects with CBD	High

THC, tetrahydrocannabinol; EDI-2, Eating Disorder Inventory-2; POMS, Profile of Mood States; CBD, cannabidiol; STAI, State-Trait Anxiety Inventory; ARCI-Ma, Addiction Research Center Inventory for marihuana effects; VAMS, visual analogue mood scale; SSPS-N, Negative Self-statement scale; SPECT, single-photon emission computed tomography; ECD, ethylene cysteine dimer; CAPS, Clinicians Administered PTSD scale; CGI-C, Clinical Global Impression of change; WBQ, General Well-Being Questionnaire; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale.
*• Total (completed)/• male:female/• age.

Anxiety

The anti-anxiety efficacy of cannabinoids was assessed in 5 studies[15-19] involving a total of 38 patients and 44 healthy volunteers (Table 3). Three studies were rated as high risk of bias and 2 as unclear risk of bias. Two early studies indicated equivocal anti-anxiety effects of nabilone.[15,16] Specifically, in a double-blind study involving 20 patients, compared to placebo, 1 mg nabilone administered twice daily for 28 days significantly improved anxiety measured by the Hamiliton Rating Scale for Anxiety.[15] However, this was not observed in another study involving 8 symptomatic volunteers.[16] In another crossover trial involving 8 healthy volunteers with a history of cannabis use, cannabidiol attenuated anxiety induced by THC.[17] More recently, in a parallel study, 24 generalized social anxiety disorder patients were randomized to receive either a single dose of 600 mg cannabidiol or placebo, and were also subjected to a simulated public speaking test.[18] Pre-treatment of cannabidiol significantly reduced anxiety measured by the visual analogue mood scale. In a another crossover trial involving 10 male patients with generalized social anxiety disorder, a single dose of 400 mg cannabidiol was associated with a significant decrease in subjective anxiety measured by the visual analogue mood scale ($p < 0.001$).[19]

Post-traumatic stress disorder (PTSD)

In a first randomized controlled crossover trial on PTSD, 10 males with PTSD associated nightmares were administered with titrated 0.5 to 3.0 mg nabilone or placebo, in two 7-week treatment periods, separated by a 2-week washout period.[20] Compared to placebo, nabilone significantly (p=0.03) reduced nightmares as measured by the Clinicians-administered PSTD scale. Furthermore, the Clinical Global Impression of Change (CGI-C) indicated a greater global improvement in nabilone (1.9±1.1, i.e. much improved) than placebo group (3.2±1.2, i.e. minimally improved). This study was rated as having an unclear risk of bias.

Psychotic symptoms

To date, only one published trial investigated the antipsychotic properties of cannabidiol in patients with schizophrenia.[21] This study was rated as high risk of bias. In this 4-week parallel, active-controlled trial, 42 patients with schizophrenia were randomized to receive either cannabidiol or amisulpride (up titration of 200 mg per day each, to a daily dose of 200 mg four times daily).[21] While significant clinical improvements were observed in both

Table 4. Clinical trials of cannabis and its derivatives for neurodegenerative conditions

Study	Design/ duration	Condition	Sample characteristics	Intervention (No. of patients)	Outcome	Side effects/ adverse events	Results	Cochrane risk of bias
Alzheimer's disease								
Volicer *et al.* (1997)[22]	Double-blind Crossover	Disturbed behavior in Alzheimer's disease	• n=12 • 11:1 • 65-82 yr • Mean age, 72.7 yr	• Dronabinol 2.5 mg • Placebo	• CMAI • Lawton observed affect scale	Common side effects: • Anxiety • Emotional lability • Tiredness • Somnolence	• Decreased severity of disturbed behavior (CMAI, p=0.05) • Decreased negative affect (p=0.045), but not positive affect	Unclear
Dementia								
Walther *et al.* (2011)[23]	Crossover	Nighttime agitation in Alzheimer's disease	• n=2	• Dronabinol 2.5 mg • Placebo	• Nonparametric circadian rhythm analysis • NPI	No adverse event	• Reduced nighttime agitation and strengthened circadian rhythms	Unclear
van den Elsen *et al.* (2015)[24]	Double-blind Crossover	Dementia	• n=54 • Mean age, 78.4 yr	• THC (Namisol) 1.5 mg×3 • Placebo	• NPI • CMAI • Barthel index • QoL-AD • CCGIC	Common side effects: • Dizziness • Somnolence	• No significant difference on all measures	Unclear
van den Elsen *et al.* (2015)[25]	Double-blind Crossover	Dementia	• n=22 • Mean age, 76.4 yr	• THC (Namisol) 0.75-1.5 mg×2 • Placebo	• NPI • CMAI • ZBI	Lack of information on common adverse event	• No significant difference on all measures	Unclear
Amyotrophic lateral sclerosis (ALS)								
Weber *et al.* (2010)[26]	Double-blind Crossover	ALS	• n=27 • 20:7 • 34-48 yr (mean, 57 yr)	• THC 5 mg×2 • Placebo	Primary: • Daily cramp severity (VAS) Secondary: • ALSFRS-R • ALSAQ-40 • SDQ24	2 serious adverse events	• No significant difference on all measures	Unclear

CMAI, Cohen-Mansfield Agitation Inventory; NPI, Neuropsychiatric Inventory; THC, tetrahydrocannabinol; QoL-AD, Quality of Life in Alzheimer's Disease scale; CCGIC, Caregiver Clinical Global Impression of Change; ZBI, Zarit Burden Interview; VAS, visual analogue scale; ALSFRS-R, ALS functional rating scale revised; ALSAQ-40, ALS assessment questionnaire; SDQ24, Sleep Disorder Questionnaire.
*• Total (completed)/• male:female/• age.

treatments as indexed by the Brief Psychiatric Rating Scale and the Positive and Negative Syndrome Scale, no statistical significant difference was reported between groups. However, cannabidiol treatment displayed a superior side-effect profile, compared to amisulpride treatment. Specifically, cannabidiol was associated with significantly smaller weight gain, lower prolactin levels and lesser extrapyramidal symptoms.

Neurodegenerative Disorders

Alzheimer's disease

One trial on Alzheimer's disease, rated as unclear risk of bias, examined the use of dronabinol for managing Alzheimer's disease (Table 4).[22] In a 6-week crossover trial, 2.5 mg dronabinol appeared to reduce disturbed behaviors in 12 patients, as measured by the Cohen-Mansfield Agitation Inventory (p=0.05).[22]

Dementia

Three trials on dementia (78 participants), rated as having an unclear risk of bias, showed equivocal results. In a 4-week trial, 2.5 mg dronabinol reduced night-time agitation and strengthened circadian rhythms in the 2 patient enrolled in the study.[23] However, two recent trials on showed that THC capsules (0.75-1.5 mg) did not improve neuropsychiatric symptoms in patients with dementia.[24,25]

Amyotrophic lateral sclerosis

The only RCT was conducted in 27 patients with ALS.[26] In this crossover trial, patients were randomized to receive 2 weeks of 5 mg THC twice daily or placebo, separated by a 2-week washout period. There is a lack of treatment effect on cramp intensity and number of cramps. This study was rated as having an unclear risk of bias.

Movement Disorders

Dystonia

Two trials[27,28] (24 participants) indicated lack of evidence on the use of cannabinoid for dystonia (Table 5). The studies were rated as having an unclear risk of bias and high risk of bias. In a crossover trial, 15 patients with primary dystonia received a single dose of 0.03 mg/kg nabilone or placebo.[27] Although four patients reported a subjective improvement in dystonia severity, there was no significant difference between groups on the primary endpoint at 60, 120 or 180 minutes post-treatment, as indexed by the Burke-Fahn-Marsden dystonia scale. In another 8-week crossover trial, 9 female patients with cervical dystonia were randomized to receive titrated 2.5 mg dronabinol, up to 3 tabs twice a daily (15 mg/day) or placebo.[28] There was no significant treatment effect of dronabinol on cervical dystonia as indexed by the Toronto Western Hospital Spasmodic Torticollis Rating Scale, or any of the secondary measures.

Huntington's disease

The efficacy of cannabinoids for Huntington's disease was assessed in 3 trials (84 participants).[29-31] All studies were rated as having an unclear risk of bias. A 6-week crossover trial evaluated cannabidiol (a total of 10 mg/kg over two doses daily) for chorea in 15 patients with Huntington's disease. There was no significant difference between placebo and cannabidiol on chorea severity measured by the Marsden and Quinn's Chorea Severity Scale. Conversely, in another 10-week placebo-controlled crossover trial, nabilone (1 or 2 mg) showed significant treatment effect as measured by the total motor and chorea score on the Unified Huntington's Disease Rating Scale (UHDRS).[30] More recently, no significant treatment effect was reported on the UHDRS, in a sample of 25 patients who receive nabiximols (up to 12 sprays/day) in a crossover trial.[31]

Parkinson's disease

Three studies (49 participants) examined the use of cannabinoids for Parkinson's disease.[32-34] All studies were rated as having an unclear risk of bias. In an early crossover trial involving 9 Parkinson's disease patients with dyskinesia, 0.03 mg/kg nabilone significantly improved dyskinesia as indexed by the Rush dyskinesia disability scale. Conversely, in a 4-week dose escalation crossover trial, 19 Parkinson's disease patients with levodopa-induced dyskinesia were administered with titrated cannador up to 0.25 mg/kg THC or placebo.[33] Cannador failed to show any significant treatment effect on the primary outcome, the Unified Parkinson's Disease Rating Scale (UPDRS) dyskinesia items, as well as the secondary measures such as motor symptoms and quality of life (39-item Parkinson's disease questionnaire, PDQ-39). More recently, in a placebo-controlled trial, 21 patients with Parkinson's disease were randomized to receive cannabidiol (75 mg/day or 300 mg/day) or placebo for 6 weeks. There was no statistical significant difference between the groups on the UPDRS. However, a significant improvement was reported for PDQ-39, particularly the activities of daily living and stigma subscale for the 300 mg/day cannabidiol group.[34]

Table 5. Clinical trials of cannabis and its derivatives for movement disorders

Study	Design/ duration	Condition	Sample characteristics	Intervention (No. of patients)	Outcome	Side effects / adverse events	Results	Cochrane risk of bias
Dystonia								
Fox *et al.* (2002)[27]	Double-blind Crossover	Primary dystonia	• n=15 • 6:9 • 28-63 yr (mean, 47 yr)	• Nabilone 0.03 mg/kg • Placebo	• Dystonia-movement scale scores	2 patients withdrawn due to postural hypotension and marked sedation	• No significant reduction in dystonia movement scale scores	Unclear
Zadikoff *et al.* (2011)[28]	Double-blind Crossover	Cervical dystonia	• n=9 • All females • Mean age, 60 yr	• Dronabinol up to 15 mg/day • Placebo	• TWSTRS-motor severity, daily activities, pain	• Lightheaded-ness • Sleepiness • Dry mouth • Blurred vision • Bitter-taste • Vertigo	• No significant difference on all subscales of TWSTRS	High
Huntington's disease								
Consroe *et al.* (1991)[29]	Double blind Crossover	Chorea severity in Huntington's disease	• n=15 • 8:7 • 17-66 yr (median, 52 yr)	• CBD 10 mg/kg • Placebo	• Marsden and Quinn's Chorea Severity Scale	No information	• No significant difference on chorea severity	Unclear
Curtis *et al.* (2009)[30]	Double-blind Crossover	Huntington's disease	• n=44 • 22:22 • 34-72 yr (mean, 52 yr)	• Nabilone 1 or 2 mg • Placebo	• UHDRS	Common side effects: • Drowsiness • Forgetfulness	• Significant treatment effect of nabilone on motor and chorea subscale of UHDRS, compared to placebo, but no difference between 1 and 2 mg nabilone	Unclear
López-Sendón Moreno *et al.* (2016)[31]	Double-blind Crossover	Huntington's disease	• n=25 • 14:11 • Mean age, 47.6 yr	• Nabiximols up to 12 sprays/day • Placebo	• UHDRS	Common side effects: • Dizziness • Disturbance in attention	• No significant difference on all measures	Unclear
Parkinson's disease								
Sieradzan *et al.* (2001)[32]	Double-blind Crossover	Dyskinesia in Parkinson's disease	• n=9 • 4:5	• 0.03 mg/kg nabilone • Placebo	• RDS	Common side effects: • Floating sensation • Dizziness • Disorientation	• Significant 22% reduction on RDS for treatment group	Unclear
Carroll *et al.* (2004)[33]	Double-blind Crossover (4 weeks)	Dyskinesia in Parkinson's disease	• n=19 • 12:9 • Mean age, 67 yr	• 2.5 mg THC:1.25 mg CBD-cannador • Placebo	• UPDRS	• Drowsiness • Dry mouth	• Lack of treatment effect of THC:CBD for dyskinesia assessed by UPDRS	Unclear
Chagas *et al.* (2014)[34]	Double-blind Parallel (6 weeks)	Parkinson's disease	• n=21 • 15:6	• CBD 75 or 300 mg/day	• UPDRS • PDQ-39	No reported side effects	• No significant difference on UPDRS • Significant difference between placebo and 300 mg CBD for PDQ-39 (p=0.05)	Unclear

Table 5. Continued

Study	Design/ duration	Condition	Sample characteristics	Intervention (No. of patients)	Outcome	Side effects / adverse events	Results	Cochrane risk of bias
Tourette syndrome								
Müller-Vahl *et al.* (2002)[35]	Double-blind Crossover	Tic in Tourette syndrome	• n=12 • 11:1 • 18-66 yr (mean age, 34 yr)	• Delta-9-THC 5-10 mg • Placebo	• TSSL • STSSS • YGTSS • TS-CGI	Common side effects: • Tiredness • Dizziness	• Significant improvement of tic, TSSL (p=0.015) and obsessive compulsive behavior (p=0.041)	Unclear
Müller-Vahl *et al.* (2003)[36]	Double-blind Parallel	Tourette syndrome	• n=24 • 19:5 • 8-68 yr (mean age, 33 yr)	• THC up to 10 mg • Placebo	• TS-CGI • STSSS • YGTSS • TSSL	Common side effects: • Tiredness • Dizziness • Dry mouth	• Significant improvement in TS-CGI, STSSS, YGTSS, TSSL	High

TWSTRS, Toronto Western Hospital Spasmodic Torticollis Rating Scale; CBD, cannabidiol; UHDRS, Unified Huntington's Disease Rating Scale; RDS, Rush dyskinesia disability scale; THC, tetrahydrocannabinol; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, 39-item Parkinson's disease questionnaire; TSSL, Tourette's Syndrome Symptoms List; STSSS, Shapiro Tourette syndrome severity scale; YGTSS, Yale Global Tic Severity Scale; TS-CGI, Tourette Syndrome-Clinical Global Impression Scale.
*• Total (completed)/• male:female/• age.

Tourette syndrome

Only two controlled trials (36 participants) evaluated the efficacy of cannabinoid for Tourette syndrome.[35,36] The studies were rated as having a high and unclear risk of bias. In a placebo-controlled crossover trial, 12 patients with Tourette syndrome received a single dose of THC 5 to 10 mg (dose based on body weight). Using the Tourette Syndrome Symptom List, there was a significant treatment effect of THC on the subscale of tics (p=0.015) and obsessive-compulsive behavior (p=0.041). Mild adverse reactions such as dizziness, headache and mood changes were reported in 5 patients. In another 6-week trial from the same research group, 24 patients with Tourette syndrome were given oral THC up to 10 mg per day.[36] Similarly, THC significantly reduced tic compared to placebo.

DISCUSSION

There is a lack of evidence on the therapeutic effects of cannabinoids for ALS and dystonia. Although results were inconsistent, there appears to be some low quality evidence of cannabinoids for anorexia nervosa, anxiety, PTSD, psychotic symptoms, agitation in Alzheimer's disease and dementia, Huntington's disease, and Tourette syndrome, and dyskinesia in Parkinson's disease. However, concrete conclusion of its efficacy could not be made due to the unclear risk of bias presented by these trials, as rated on the Cochrane risk of bias tool. Methodological issues such as inadequate description of allocation concealment and blinding, varying cannabinoid formulations and doses, and small sample sizes limit its potential clinical utility.

Consistent with previous case studies[38,39] and experimentally-controlled studies,[40] the only RCT on cannabidiol and psychosis showed promising results on the antipsychotic potential of cannabidiol.[21] Specifically, clinical symptoms negatively correlated with anandamide, an endogenous cannabinoid. It has been hypothesized that cannabidiol enhances anandamide signaling by indirectly blocking enzyme fatty acid amide hydrolase, resulting in an inhibition of anandamide degradation. Although the biological pathways of cannabidiol and anandamide is still unclear, and various potential mechanisms of action have been proposed,[10] the protective role of anandamine for psychotic symptoms could potentially be a new viable antipsychotic mechanism. Nonetheless, more adequately powered clinical trials evaluating the ef-

fect of varying doses, and long term safety and efficacy are needed to supplement current findings.

For trials involving movement and neurodegenerative disorder, the limited number of trials, lack of quantitative data and underpowered samples inhibits reliable conclusion from being made. Nonetheless, the expression of endocannabinoid receptors (CB_1 and CB_2) in the basal ganglia and the immune systems could indicate the protective role of cannabinoids for movement and neurodegenerative disorder. This warrants future studies, in vivo and animal models, to clarify the biological mechanisms underpinning the modulatory role of cannabinoids.

Cannabinoids appear to be well-tolerated in these trials. The common short-term effects included dry mouth, dizziness, tiredness, and headache. Indeed, reviews that discussed the adverse effect of cannabis administration have reported that cannabis or cannabinoid administration was associated with a greater risk of non-serious adverse events.[3,41] This illuminates the need to conduct trials that compare the effects and efficacy of cannabinoids with existing treatment. This would provide a clear cost-benefit evaluation of medical cannabis.

Overall, there are few RCTs that evaluated the efficacy of cannabis for psychiatric, neurodegenerative and movement disorders. While inconsistency in results may be attributed to different outcome measures used, varying doses and formulations, it raises the question on the mechanism underlying the therapeutic benefits of cannabinoids across indications with different pathophysiology (i.e., psychiatric, neurodegenerative and somatic conditions). Clarification of the cellular pathways and mechanisms of cannabinoids for various indications could reveal the cascading effect of cannabinoids and its interactions with pathways associated with these indications.

CONCLUSION

While there are trials that suggest potential benefit of cannabinoids for anorexia nervosa, anxiety, PTSD, psychotic symptoms agitation in Alzheimer's disease and dementia, Huntington's disease, and Tourette syndrome, and dyskinesia in Parkinson's disease, insufficient conclusion could be made due to the low quality of evidence as indexed by the Cochrane risk of bias, and underpowered samples. An improved knowledge of the precise mechanism of cannabinoids at the cellular level could provide insights on the therapeutic benefits of cannabinoids for movement, psychiatric and neurodegenerative disorder. This could facilitate development of cannabinoid formulations and the conduct of clinical trials on these indications.

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Medical Marijuana Program
Connecticut Department of Consumer Protection
Drug Control Division
450 Columbus Boulevard.
Hartford, CT 06103

July 16, 2021

RE: Testimony supporting including Huntington Disease as a qualifying condition

Please include the attached letter that includes my testimony supporting adding Huntington disease as a qualifying condition for prescribing medical marijuana.

My understanding is the State of CT Physicians Board will be meeting on July 23, 2021, at 8:30 via Zoom. While I will make every attempt to be online, I am schedule for a meeting that day in North Carolina and can not guarantee internet service. I am submitting this in writing if I am unable to attend.

Thank you for your consideration, please let me know if you have any questions or concerns.

Sincerely,

[redacted]

[redacted]

Medical Marijuana Program
Connecticut Department of Consumer Protection
Drug Control Division
450 Columbus Boulevard.
Hartford, CT 06103

July 16, 2021

RE: Testimony supporting including Huntington Disease as a qualifying condition

My name is [redacted] and I am an adult nurse practitioner, and I am certified to enroll patients in the CT Medical Marijuana program.

I am writing to you today in support of adding Huntington Disease as a qualifying condition. I have taken the liberty of attaching supporting research for your review.

My experience with my patients supports this research in relieving neurologic symptoms such as spasms, tremors, spasticity, chorea, and quality of sleep following treatment with medical marijuana. While there is no cure for this disease, I support adding it as a qualifying diagnosis for its relief of symptoms and increased quality of life for my patients.

I appreciate your consideration and look forward to the possibility of adding Huntington's Disease as a qualifying condition.

[redacted]

Attachements:

Medical Marijuana Effects in Movement Disorders, Focus on Huntington Disease; A Literature Review

[redacted]

Medical Marijuana Effects in Movement Disorders, Focus on Huntington Disease; A Literature Review

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ABSTRACT - Purpose: We aimed to comprehensively evaluate the effects of medical marijuana on symptoms that are relevant to movement disorders with a focus on Huntington disease (HD). **Methods**: A systematic review by literature search through PubMed and EBSCO electronic databases was conducted for relevant studies reported after 2002 on the effects of medical marijuana or cannabis use on tremor, spasm, spasticity, chorea, sleep quality and HD-specific rating scales. Study selection, quality assessment and data extraction was performed by three reviewers. Outcome measures were changes in psychomotor, and sleep related symptoms. The methodological quality of the included studies was evaluated. **Results**: A total of 22 studies were reviewed. There was strong evidence for significant improvement in the neurologic symptoms of spasms, tremors, spasticity, chorea, and quality of sleep following treatment with medical marijuana. Analysis of specific motor symptoms revealed significant improvement after treatment in tremors and rigidity. Furthermore, all pretreatment and post-treatment measures indicated a significant increase in average number of hours slept. **Conclusion**: Larger scale studies are warranted to test the benefits of medical marijuana in HD patients. In the meanwhile, clinicians may consider prescribing medical marijuana as part of their strategy for better symptomatic treatment of patients with HD.

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INTRODUCTION

Neurodegenerative diseases are characterized by a loss of neurons and neuropathological lesions distributed in particular regions of the central nervous system. Huntington disease (HD) is an autosomal dominant inherited neurodegenerative disease caused by an elongated CAG repeat (36 repeats or more) in the huntingtin gene on the short arm of chromosome 4p16.3 (1,2). In HD, there is neuronal loss in the neostriatum, most markedly in the caudate nucleus, and progressing through the putamen (1). Clinically, HD is characterized by worsening involuntary choreic movements, behavioral and psychiatric disturbances, and dementia (2). Psychomotor processes become severely retarded as patients experience psychiatric symptoms and cognitive decline (2). The prevalence of HD in the Caucasian population is estimated at 1/10,000-1/20,000 with mean age of onset at 30-50 years (2).

Cannabidiol (CBD) is regarded as a compound with therapeutic potential against neurodegenerative and hyperkinetic disorders in view of its neuroprotective effects (3). The endocannabinoid system has been implicated in a broad range of physiological functions such as cognition, mood, motor control, feeding behaviors, and pain (4). The clinical manifestation of movement disorders includes motor symptoms such as resting tremors, rigidity (cogwheel...), akinesia, bradykinesia, loss of righting reflex, chorea, gait disturbances (shuffling gait...), spasticity, and loss of automatic movement, retrocollis, impaired eye movement (downward gaze), pseudobulbar palsy; as well as autonomic dysfunction, cognitive impairment, and depression (1). Preclinical research suggests that cannabinoids

have symptomatic and neuroprotective potential for a variety of neurologic conditions- including movement disorders (3, 4). Marijuana contains around 60 pharmacologically active compounds known as "cannabinoids" (5).

Studies have shown that non-psychoactive cannabidiol is well tolerated and safe in humans even at high doses (6). Cannabis strains high in CBD content have been used for treatment of patients with intractable seizures, and to relieve symptoms in patients with chronic pain, arthritis, tremors, dementia, post-traumatic stress disorder, and in patients undergoing chemotherapy (6, 7). The medical properties of CBD that have been demonstrated in animal studies include antiemetic, anticonvulsant, antipsychotic, anti-inflammatory, antioxidant, anti-cancer, anxiolytic, and anti-depressant effects (7). As of July 2019, 33 states and the District of Columbia in the United States of America have enacted laws allowing marijuana use to treat certain medical conditions (8).

The most common cause of death in HD is pneumonia, followed by suicide (2). In this study, we focus on the effects of medical marijuana on the symptoms of HD including emotional turmoil (depression, apathy, irritability, anxiety, obsessive behavior), cognitive loss (inability to focus, plan, recall or make decisions; impaired insight), and physical deterioration (weight loss, involuntary movements, diminished coordination, difficulty walking, talking, and swallowing) (9).

METHODS

A systematic review was conducted by literature search through PubMed and EBSCO electronic databases. The text words "marijuana", "cannabis", "THC", "medical marijuana", "CBD", "cannabidol", "Nabilone", "Sativex®", with the use of the Boolean operator "AND" the terms "Huntington disease", "chorea", "rigidity", "psychomotor decline", "cognitive impairment", "tremor" "gait disturbance", "akinesia", "bradykinesia", "retrocollis" and "depression" were used to identify relevant studies discussing the effectiveness of medical marijuana in patients with HD.

The inclusion criteria were the following: 1) must be a scholarly or peer-reviewed source, 2) a relevant article published after 2002, and 3) articles published in the English language only. Exclusion criteria were the following: 1) publications potentially used for marketing purposes, 2) articles in foreign languages, 3) articles dated prior to 2002.

Outcome measures included any changes in symptoms such as choreic movements, chorea, rigidity, tremors, psychomotor decline, cognitive impairment, and depression. The quality of evidence was assessed by scoring the articles according to the following rating scheme: (1) properly conducted randomized clinical trial, (2) well-designed controlled trial without randomization or prospective comparative cohort study, (3) case-control study or retrospective cohort study, (4) cross-sectional study or case series, (5) case reports or opinion of respected authorities.

RESULTS

All together 50 relevant reports were identified, 43 through direct and 7 by indirect searches. After cutting the redundancies, 27 full-text articles were assessed, from which 22 were found eligible for inclusion.

The outcomes data were extracted from studies conducted on populations with several conditions including multiple sclerosis (MS), parkinson disease (PD), fibromyalgia, posttraumatic stress disorder (PTSD) and HD. Effects of cannabis use or medical marijuana treatments were tabulated by signs and symptoms of relevance to HD including spasm and spasticity (Table 1), tremor (Table 2), sleep quality (Tables 1 and 3), chorea, motor and dystonia subscales on the Unified Huntington's Disease Rating Scale (UHDRS) which assesses motor function, cognitive function, behavioral abnormalities, and functional capacity (Table 4), and biochemical markers in animal models (Tables 5 and 6).

Table 1: Effects of medical marijuana on spasticity

Study	Year	Findings	Formulations
Zajicek et al. *Randomized Controlled Trial* (10)	2003	630 MS patients were enrolled in a randomized, placebo-controlled clinical trial at 33 centers in the UK. There was evidence of a treatment effect on patient-reported spasticity and pain (p=0.003), with improvement in spasticity reported in 61% (n=121, 95% CI 54.6-68.2), 60% (n=108, 52.5-66.8), and 46% (n=91, 39.0-52.9) of participants on cannabis extract, Δ^9-THC, and placebo, respectively (10).	Oral cannabis extract capsules containing 2.5 mg Δ^9-THC equivalent and 1.25 mg CBD and < 5% other cannabinoid vs Δ^9-THC alone
Vaney et al. *Randomized Controlled Trial* (11)	2004	57 MS patients were enrolled in a prospective randomized, double-blind, placebo-controlled, crossover study in Switzerland. Treatment consisted of cannabis-extract capsules standardized to 2.5 mg tetrahydrocannabinol (THC) and 0.9 mg cannabidiol (CBD). In 37 patients who received 90% of their prescribed dose (THC and CBD), significant improvements in spasm frequency were observed (p=0.013) (11).	Cannabis-extract capsules standardized to 2.5 mg THC and 0.9 mg CBD
Brady et al. *Open-label pilot study* (12)	2004	21 MS patients were recruited for treatment with cannabis-based extracts and data from 15 were evaluated in the UK. Urinary urgency, incontinence, and nocturia decreased significantly (p <0.05) and patient self-assessment of pain, spasticity and quality of sleep improved significantly (p <0.05) (12).	Δ9-THC and CBD 2.5 mg of each per spray for eight weeks followed by 2.5 mg THC-only per spray for a further eight weeks
Novotna et al. *Randomized Controlled Trial* (13)	2011	572 MS patients were enrolled in a randomized, double-blind, placebo-controlled, parallel-group, enriched-design study. Results showed significant improvements in spasticity Numeric Rating Scale (NRS), Spasm Frequency Score and Sleep Disturbance following treatment with nabiximols (Sativex®) (p<0.001) (13).	Nabiximols (Sativex®) study medication was delivered using a pump action oromucosal spray. Each 100-µl actuation of active medication delivered 2.7 mg THC and 2.5 mg CBD to the oral mucosa. Subjects were restricted to a maximum of 12 sprays in any 24-h period.

Table 2: Effects of medical marijuana on tremor

Study	Year	Findings	Formulations
Venderova et al. *Cross-sectional study* (14)	2004	Of 339 PD patients surveyed, 25% reported *Cannabis* use and, of those, 31% reported improvement of resting tremor. Patients using cannabis for at least 3 months reported significant improvement in resting tremors (p<0.01) (14).	Determined patients' personal use of cannabis by survey questions and correlated change in symptoms with concentrations of 11-nor-δ-9-THCOOH in urine
Lotan et al. *Case-control study* (15)	2014	22 PD patients attending the motor disorder clinic of a tertiary medical center in Israel, who were evaluated on the motor Unified Parkinson Disease Rating Scale at baseline and 30 minutes after smoking cannabis, were found to have significant improvement in tremor (p<0.001), bradykinesia (p<0.001) and rigidity (p=0.004) (15).	Smoking cannabis 0.5 grams

Table 3: Effects of cannabis use on sleep quality

Study	Year	Findings	Formulations
Fiz et al. *Cross-sectional* (16)	2011	28 fibromyalgia patients surveyed in Spain reported no significant changes in overall sleep quality between cannabis-users and non-users on the Pittsburgh Sleep Quality Index (PSQI) (16).	Determined patients' personal use of cannabis by survey questions probing patterns of smoking and eating recreational cannabis (hashish or marijuana)
Tringale and Jensen *Cohort Study* (17)	2011	Amongst 166 subjects analyzed in a focused, retrospective cohort study from two cannabis clinics in Southern California (Ventura and San Clemente), there was a significant decrease in total time to fall asleep after the use of cannabis ($p=0.001$) (17).	Oral, pipe, bong, vaporizer, and joints route of administration of cannabis. Use per week up to 20 grams.
Cameron et al. *Cohort study* (18)	2014	101 subjects from a correctional population with PTSD in Ontario, Canada reported a significant increase in mean number of hours slept from 5.0 [SD 1.4] pretreatment, to 7.2 [SD 1.2] posttreatment ($p<0.001$) (18).	Synthetic Nabilone 4.0 mg given in powder form with water

Table 4: Effects of medical marijuana in Huntington disease patients

Study	Year	Findings	Formulations
Curtis and Rickards *Case report* (19)	2006	A 43-year-old female HD patient in the UK reported improvements in behavior and reduction of chorea maintained by daily dosage of Nabilone (19).	Nabilone, Synthetic 9-keto cannabinoid, 1 mg capsule per day
Curtis et al. *Randomized Controlled Trial* (20)	2009	44 HD patients were enrolled in a double-blind, placebo-controlled, cross-over study of nabilone (1 or 2 mg) versus placebo in the UK. Results demonstrated significant improvement in chorea ($p=0.009$) and neuropsychiatric index ($p=0.04$); and a trend for improvement in behavior score ($p=0.06$) (20).	Nabilone 1 or 2 mg capsule
Saft et al. *Case-control study* (21)	2018	7 HD patients in Europe were evaluated before and after the start of cannabinoids without any other changes in medication. Their Unified Huntington's Disease Rating Scale (UHDRS) motor score improved from 70.9 [SD 25.5] to 60.6 [SD 26.9] ($p=0.018$), and the dystonia subscore improved from 12.3 [SD 4.0] to 8.9 [3.6] ($p=0.0180$) (21).	Sativex® 12 sprays or Dronabinol 4-4-5 drops (9.1 mg) or Sativex ® 7 sprays or Dronabinol 2-2-1 drops (3.6 mg) or Dronabinol 2-0-2 drops (2.8 mg) or Nabilone 0.5 mg-0-1 mg or Dronabinol 1-1-1 drops (2.2 mg)
López-Sendón Moreno et al. *Randomized Controlled Trial* (21)	2016	26 patients were enrolled in a double-blind, randomized, placebo-controlled, cross-over pilot clinical trial with Sativex® in Spain. 24 completed the trial which showed no differences on the motor subscore of the Unified Huntington's Disease Rating Scale ($p = 0.286$) (22).	Both Sativex(®) and placebo were dispensed as an oral spray, to be administered up to 12 sprays/day for 12 weeks.

Table 5: Loss of striatal type 1 cannabinoid receptors in Huntington-like animal model

Study	Year	Findings	Formulations
Blazquez et al *Experimental Observational Study* (23)	2010	Pharmacological activation of CB1 cannabinoid receptors ameliorates Huntington's disease-like symptomatology, neuropathology and molecular pathology in R6/2 (Huntington-like) mice (23). Expression of the endocannabinoid-deactivating enzyme fatty acid amide hydrolase (FAAH) is higher in symptomatic (8- to 12-week-old) R6/2 mice than in their wild-type littermates (23).	THC 2 mg/kg body weight per day intraperitoneally

Table 6: Results reporting the recovery of N-acetyl-aspartate/Choline (NAA/Cho) in mice: Reduced NAA/Cho levels possibly reflect neuronal and mitochondrial dysfunction/damage

Study	Year	Findings	Formulations
Valdeolivas et al *Experimental Observational Study* (24)	2017	R6/2 and wild-type mice were housed in rooms with controlled photoperiod with free access to standard food and water. Sativex®-like combination of phytocannabinoids treatment completely reversed the reduction in NAA/Cho ($p<0.005$) (24).	Δ9-THC- and CBD-enriched botanical extracts combined in a Sativex®-like ratio 1:1 (4.5 mg/kg equivalent to 3 mg/kg of pure CBD + Δ9-THC)

Studies have demonstrated that Fatty acid amide hydrolase (FAAH), an anandamide-degrading enzyme that deactivates endocannabinoids, is upregulated in striatal brain tissue from symptomatic Huntington disease-like R6/2 mice, as well as in Huntington disease patients (23).

NAA/Cho (N-acetyl-aspartate/Choline) levels were shown to be reduced in Huntington disease-like mice, possibly reflecting neuronal and mitochondrial dysfunction/damage (24). Treatment with either a broad-spectrum cannabinoid, or combinations of cannabinoids with complementary profiles, have been found to delay progression in an experimental Huntington disease model, and to preserve the integrity of striatal neurons demonstrating that a Sativex®-like combination of phytocannabinoids treatment completely reversed the reduction in NAA/Cho ($p=<0.005$) (24).

DISCUSSION

A systematic review was conducted to evaluate the strength of evidence for the efficacy of medical marijuana in alleviating the symptoms that manifest in movement disorders that are particularly relevant in Huntington disease. The eligible studies included 5 randomized placebo-controlled clinical trials, 2 case-control studies, 2 cross-sectional studies, 2 cohort studies, 2 experimental observational studies, 1 open-label pilot study, and 1 case report. The studies of highest quality were the 5 randomized placebo/controlled trials which included a sum total of 1,329 human subjects. The human studies reviewed demonstrated therapeutic effects for medical marijuana in the management of movement disorder symptomatology including the use of Sativex®, which is an oral spray that contains a combination of tetrahydrocannabinol and cannabidiol, and Nabilone, which is a synthetic cannabinoid capsule that is a selective agonist for CB1 and CB2 receptors (4,25). It is assumed that the effects demonstrated by data extracted from the studies which utilized standardized pharmaceutical formulations would be more clinically reliable than those from survey studies which collected self-reported accounts of cannabis use. Furthermore, since pain is also prevalent in Huntington disease patients, the use of medical marijuana could be helpful for them in light of evidence that cannabinoid-based pharmacotherapies might be effective

for management of chronic pain (26). It would be expected that any benefits experienced by patients would have been longer lasting after ingestion as compared to inhalation.

Although the majority of studies showed statistically significant results favoring the use of medical marijuana, especially for improving motor symptoms and quality of sleep, the number of Huntington disease patients who were available to participate in these studies was a sum total of 78, and it was necessary to examine the effects seen in patients diagnosed with other diseases in which the same type of symptoms exist. As such, the findings of decreased spasticity were demonstrated primarily by measurements in patients with the autoimmune demyelinative disease multiple sclerosis (Table 1). The findings of reduced tremor were demonstrated primarily by assessements in patients with the nigrostriatal neurodegenerative parkinson disease (Table 2). The findings of improved sleep quality were derived from populations of respondents with either the chronic pain disorder fibromyalgia, or the anxiety disorder PTSD, or miscellaneous conditions for which they sought treatment at a cannabis clinic (Table 3). The findings that were shown in patients with the basal ganglial neurodegenerative Huntington disease were improvements in chorea, improvements in the neuropsychiatric index, and trends for improvements in the Unified Huntington's Disease Rating Scale motor score, the dystonia subscore and behavior score (Table 4).

The animal studies reviewed included experimental observations following activation of CB1 receptors by THC that demonstrate a protective role of the endocannabinoid system against the development and progression of symptoms in R6/2 murine models for Huntington-like disease (22,23).

CONCLUSION

The observed or reported improvements in the symptoms of movement disorders are consistent with the principal pharmacological effects of THC and CBD. Alleviation of spasticity, tremors, chorea and dystonia might be attributed to the muscle relaxant and analgesic effects of both THC and CBD. Improvements in sleep quality, behavioral and neuropsychiatric indices could be attributable to the anxiolytic, neuroprotective, anti-oxidant, anticonvulsant, and anti-psychotic activities of CBD. Large scale, randomized, clinical trials, perhaps international collaborative efforts, are warranted to test the use of medical marijuana more widely in HD patient populations, and who may be at various stages of disease progression. Acknowledging the need for determining that the therapeutic benefits shall outweigh any long term risks, we nevertheless recommend that physicians consider prescribing medical marijuana as adjunctive treatment for symptomatic relief to slow the progression or reverse spasms, tremor, spasticity, chorea, dystonia, behavioral, neuropsychiatric and sleep disturbances in patients with Huntington disease.

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