

Reviews

A Review of the Clinical Evidence for Complementary and Alternative Medicine in Huntington's Disease

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Abstract

Background: There is a lack of published guidelines related to the use of complementary and alternative medicine (CAM) for Huntington's disease (HD). We conducted a review of the literature to summarize the available evidence for various mind–body practices and nutraceuticals.

Methods: PubMed and Cochrane Library electronic databases were searched independently from inception to February 2019 by two independent raters. Studies were classified for the level of evidence (Class I, II, III, or IV) according to the American Academy of Neurology (AAN) classification scale.

Results: Randomized controlled trials in HD were reviewed for mind–body interventions (dance therapy, music therapy, and exercise), alternative systems (traditional Chinese medicine [TCM]), and nutraceuticals/diet (aminooxyacetic acid [AOAA], coenzyme q10, creatine, cannabinoids, alpha-tocopherol, eicosapentaenoic acid, idebenone, levocarnitine, and triheptanoin). Few studies met AAN Class I or II level of evidence for benefits, and these are highlighted.

Discussion: There is a relative paucity of clinical trials examining CAM modalities in HD when compared to other neurodegenerative disorders. Currently, there is no evidence supporting disease modification or symptom improvement with any specific dietary or nutraceutical supplement for HD. Supervised exercise and contemporary dance are safe for people with HD, but more robust studies are warranted to guide specific recommendations for these and other mind–body interventions.

Keywords: Huntington's disease, CAM, nutraceuticals, mind–body

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Introduction

Huntington's disease (HD) is a neurodegenerative disorder caused by an unstable expansion of the CAG trinucleotide repeat in the *Huntingtin (HTT)* gene for which there is presently no approved disease-modifying therapy.¹ Patients with HD hope for effective treatments to help delay disease onset; slow down the clinical progression; and help with problematic motor, cognitive, and psychiatric symptoms. While there is abundant research into disease modifying strategies for HD, no currently available treatments have been convincingly demonstrated to impact disease progression.² Thus, many patients dealing with neurological disease are known to turn to complementary and alternative medicine (CAM) as a way of fulfilling the perceived void in effective conventional therapies. CAM includes products that are not considered conventional medicine and is broadly classified into four

categories: (1) alternative medical systems, (2) manipulation/bodywork therapies, (3) biologically based therapies, and (4) mind–body therapies.³ The use of CAM in HD has never been comprehensively reviewed, and the safety and efficacy of many specific CAM modalities are unclear.

The American Academy of Neurology (AAN) has published guidelines on the pharmacological management of HD. In a 2012 AAN publication, the CAM modalities of creatine, coenzyme Q10 (CoQ10), and ethyl-EPA are reviewed, but no specific guidelines for the use of other modalities are provided.⁴ Regardless of available evidence, 44.1% of US adults with neurological conditions reported having used some form of CAM therapy in the past 12 months.⁵ Specific frequencies of use in HD are not reported, but many CAM modalities appeal to a biological basis worthy of further investigation.

Neurodegeneration is thought to be in part related to inflammation, oxidant stress, and mitochondrial dysfunction, which trigger complex pathologic downstream cellular effects.⁶ Aspects of the inflammatory pathway are targets of industry-sponsored pharmaceutical investigations. Many natural supplements are proposed to have helpful antioxidative, anti-inflammatory, and neuroprotective effects which may be worthy of investigation as well.⁷ Alternative systems and mind–body focused interventions are appealing in HD from a symptomatic standpoint. HD is characterized clinically by a triad of motor, cognitive, and psychiatric-behavioral problems.² Many CAM modalities are suited to influence both the physical as well as the emotional, behavioral, and cognitive aspects of disease that impact the quality of life.

In order to fulfill a knowledge gap with regard to evidence-based recommendations for CAM use in HD, we conducted a review of the literature to summarize the data related to various CAM practices in HD, with specific attention focused on (1) mind–body interventions and (2) natural products (nutraceuticals and dietary changes) given the relative paucity of evidence for other modalities.

Table 1. Breakdown of RCTs by CAM Modality

Modality/Intervention	No. of RCTs	Total No. of Participants	Ref.	No. of Publications with Level I/II Evidence (AAN)
Alternative Medical System				
Traditional Chinese medicine	1	4	34	0
Mind–Body Interventions				
Dance therapy	2	43	18,19	1
Music therapy	3	85	15–17	2
Exercise/physical therapy based	7	303	24–30	6
Nutraceuticals/Dietary Supplementation				
Aminooxyacetic acid	1	7	44	1
Cannabinoids	3	88	47–49	3
CoQ10	2	783	42,43	2
Creatine	4	632	51–54	2
d-alpha-tocopherol	1	73	41	1
Eicosapentaenoic acid (EPA)	4	748	56–59	4
Idebenone	1	100	41	1
Levocarnitine	2	33	60,61	1
Triheptanoin	1	23	59	0
Dietary changes	5	288	65–69	0

Note: All CAM RCTs identified through the literature search are identified in this table. All studies were classified as different levels of evidence by AAN guidelines.⁸ The number of publications with levels I/II evidence are denoted in the last column. There are multiple CAM modalities that did not have any RCTs for their efficacy in HD. The following were specifically searched for without any currently published human RCTs: (1) Alternative Medical System (Ayurvedic medicine, aromatherapy, traditional healers, biofeedback, chelation therapy); (2) Mind–body interventions (acupuncture, reiki, tai chi, qi gong, guided imagery), and (3) Nutraceuticals/dietary supplementation (epigallo and glutamate).

Abbreviations: AAN, American Academy of Neurology; CAM, Complementary and Alternative Medicine; EPA, Eicosapentaenoic Acid; RCTs, Randomized controlled trial.

Methods

PubMed and Cochrane Library electronic databases were searched independently from inception to February 2019. The search was conducted separately by two independent reviewers MY and DB. The search terms are provided in Appendix A. These particular CAM modalities were queried in the literature review because they have been studied in other neurodegenerative diseases like Alzheimer’s disease (AD) and Parkinson’s disease (PD). In addition, they are the more commonly used modalities with some basis from basic science data.⁵ Articles were restricted to English language publications. Only those articles that reported a randomized controlled trial (RCT) design in human subjects with HD were included in this review. In total, 37 articles were identified. All studies were classified for the level of evidence (Class I, II, III, or IV) according to the AAN classification of level of evidence.⁸ Both reviewers agreed on the levels of classification for all studies.

Results

Table 1 shows the breakdown of RCTs available for review by CAM modality, along with the number of trials meeting level I/II evidence.

Mind–body interventions

Mind–body therapies access the relationships between the brain, mind, body, and behavior to influence health and disease. Many mind–body interventions involve some form of relaxation or meditation, which may have relevance for psychological and psychosocial stress related to HD.⁹ Basic science work and research in other disease states have shown interactions between the endocrine system, immune system, autonomic system, and the central nervous system, which could be the basis of health benefits proposed with some CAM modalities.¹⁰ Mind–body activities that have been evaluated in HD include music therapy (MT) and dance therapy (DT). As specific exercise interventions have not been established as a conventional part of HD management (unlike in other disorders like PD), we include a summary of the evidence for exercise in this review as well.

Music therapy

MT is the use of music or any of its elements such as rhythm, melody, or harmony with the goal of meeting physical, emotional, mental, social, or cognitive needs.¹¹ MT has been used and studied in many neurodegenerative diseases including AD and PD. In AD, MT has been associated with improvement in multiple cognitive domains.¹² In PD, it has been used for social and quality-of-life benefits as well as gait training.¹³ Physiological studies have demonstrated increased limbic activity in the orbitofrontal cortex and alterations in mesolimbic dopamine release on functional MRI (fMRI) in response to music.¹⁴ In HD, music may have the potential to address abnormal movements as well as quality-of-life issues that arise from the loss of expressive and communicative skills, especially in advanced disease.

The effects of MT compared with a recreational therapy control intervention in 63 HD patients were studied over 16 weeks.¹⁵ No differences in communication or behavior between the two groups were found.¹⁵ Rhythm therapy for HD was also investigated.¹⁶ The researchers implemented a behavioral intervention involving drumming and rhythm exercises to target early dysexecutive problems in 10 people (1 preclinical and 9 with early to advanced stages of HD). The study aimed to assess both clinical executive function improvement and changes in the white matter microstructure on MRI. There was some evidence for cognitive benefits as well as some changes in the callosal white matter microstructure with rhythm therapy, but the sample size and the study design limit conclusions.¹⁶ Multisensory stimulation (MSE) was also studied for HD.¹⁷ MSE utilizes a selection of sensory equipment arranged to stimulate a participant's primary senses, without the need for intellectual or structured responses. The investigators randomized mid-late staged HD participants to 4 weeks of MSE or relaxation activities and found no significant difference between the two groups in measures of behavior, mood, dyskinesia, or physiological measures. The MSE group may have had some positive responses during this session on secondary outcomes (the immediate effect of MSE on participant's mood) but the significance of this was unclear.¹⁷

Conclusion: There is insufficient evidence to support the use of MT for HD cognitive or motor symptoms. Case reports have described

benefits on the quality of life, but this was not clearly replicated in trials. There was one Class II study of MT and one Class III study of MSE that did not demonstrate significant benefits in HD. A small Class III study of rhythm therapy did have positive outcomes on cognitive and microstructural changes, but the sample size and the study design limit conclusions. Considerations such as group versus individual sessions, early versus late-disease participants, and sensitivity of specific measures evaluated may need to be accounted for if future studies are designed.

Dance therapy

DT uses movements (often in combination with music) therapeutically to support the intellectual, emotional, and motor functions of the body. Balance and gait deficits impact most patients with manifest HD, and DT may target these deficits while providing an enjoyable outlet for physical and emotional activities.

Two RCTs have examined the impact of dance-related interventions on HD symptoms and quality of life. A study on the effects of Dance Dance Revolution (DDR-Harmonix Music Systems Incorporated, Cambridge, MA) has been performed.¹⁸ In DDR, players move to targets in response to visual cues seen on a video screen that match a song rhythm. The participants enjoyed DDR and showed significant improvements in forward walking, backward walking, and reduced need for gait support compared to when playing a handheld game. Contemporary dance in HD for 2 hours per week was studied over 5 months. Patients enjoyed the classes and the compliance was high. However, while there was some improvement in motor impairment with DT compared with usual care, the neuropsychiatric variables and cognitive outcomes assessed were not improved in this study.¹⁹

Conclusion: Conventional and unconventional dance therapies have been studied in HD. Based on evidence from Class II and Class III studies, dance may be a safe and enjoyable activity in patients with HD. The beneficial effects of DT might be limited to motor symptoms and more suitable to people with less severe motor and cognitive impairments. Other forms of dance may need to be studied, and classes specifically tailored to the cognitive and motor needs of people with HD may need to be considered for future trials. In addition, the current data do not offer a good consensus for the most beneficial intensity, frequency, and duration of dance intervention in patients with HD. In DT studies in patients with PD, it appears that sessions of 60 minutes appear to be challenging but manageable while sessions of 90 minutes appear to induce some fatigue, causing participants to rest more often during the latter portion of a 90-minute session.²⁰ It is possible that there is a similar saturation effect in HD, but this is an area that needs further elucidation.

Exercise

Physical activity has the potential to impact not only cardiovascular health but also aspects of physical health such as postural control, gait, and quality of life across various neurodegenerative diseases. PD is an example of a disease where exercise was once considered a

complementary strategy and has since become a mainstay of conventional treatment, but practice guidelines have not emphasized exercise recommendations in HD to nearly the same extent. In HD mice, treadmill exercise has been shown to enhance spatial learning ability and slow down hippocampal cell loss.²¹ HD mice given playgrounds to maintain activity had delayed onset of general health decline compared to mice simply given access to food.²² A retrospective analysis of HD patients in Australia and New Zealand demonstrated that lifestyle passivity was an independent predictor of age of HD symptom onset, with an average of 4.6 years later onset in the least compared to the most passive subjects.²³

There are four RCTs involving exercise modalities in HD. Importantly, physical activity was not associated with major adverse events or injuries in these studies. When injuries occurred, they were minimal – mainly back pain and exacerbation of preexisting unrelated cardiac disease.²⁴

The exercise methods ranged from home visits conducted by exercise coaches over 16 weeks, 8 weeks of exercising at home with a DVD, 9 months of outpatient multidisciplinary rehabilitation therapy, and 12 weeks of an outpatient progressive exercise program.^{24–27} These studies demonstrate that participants tend to enjoy exercise programs regardless of modality, and improvements in measures of gait and mobility are demonstrated. On the other hand, measures of postural stability and quality of life did not consistently improve.

Whether patients with HD physiologically respond to exercise differently from healthy controls has been debated. One study showed that patients with HD had higher serum lactate levels after exercise compared to controls.²⁸ On the other hand, endurance training over 26 weeks demonstrated evidence of mitochondrial change and muscle fiber distribution in people with HD.²⁸ This demonstrated that the inherent physical benefit in HD is not necessarily hindered by the disease process itself. This finding was replicated in another RCT.²⁹

Conclusion: Regular exercise should be recommended to people with HD. The general health benefits of exercise likely extend to HD. Most studies investigated supervised exercise programs and showed that these were safe. Some benefits for gait measures were seen in Class II studies. Future studies should be designed to better understand how exercise affects people across all stages of the disease, and what frequency and methods of exercise are best suited to HD.³⁰

Alternative medical systems

Alternative medical systems include TCM, Ayurveda, and homeopathy, among others. Many are traditions that can be culturally appealing or familiar to patients who come from specific ethno-cultural backgrounds and fulfill a philosophical congruency.³¹ Others turn to alternative systems to deal with limitations in current treatment approaches for HD.

TCM is centuries old and is based on the concept of Yin and Yang (two complementary and opposite aspects of nature). Disease is thought to be related to disturbances in Yin (roughly can be translated as “cool”) and Yang (roughly can be translated as “heat”). Treatment of the disease often uses herbs to restore balance.³² Only one English-language trial of

TCM has been published for HD. The herb used in this study, Yi-Gan San (YGS), consists of seven herbs and the original Chinese description states that it has a restraining relationship with the liver.³³ In TCM, the liver is thought to be the organ that stabilizes mental activities and ameliorates involuntary muscle movements.³³ Improvement on UHDRS motor score from 106.3 ± 4.7 to 89.6 ± 5.8 (mean \pm SD) was seen in four HD patients with severe chorea after taking YGS for 8 weeks.³⁴

There were no RCTs conducted for other alternative medical systems like Ayurveda, Qi Gong, or Tai Chi in HD as there had been for PD.³⁵ This may in part relate to the fact that the overall prevalence of HD in Asia is much lower (0.40/100,000) compared to that in Europe, North America and Australia (5.7/100,000).³⁶

Conclusion: There is insufficient evidence to recommend any particular alternative system or Chinese herb for the management of HD. Based on one small Class III study, further studies of the herb YGS for the management of chorea should be considered.

Nutraceuticals and dietary adjustments

Multiple lines of evidence support a role for oxidative stress, inflammation, and mitochondrial dysfunction as part of a pathogenic cascade across neurodegenerative diseases. While mutant huntingtin protein lowering and DNA-based therapies are receiving much attention in HD disease modification, several industry-led trials have been conducted over the recent years in HD to specifically target certain components of cell destruction. Likewise, many nutraceuticals and diets are touted as impacting oxidative stress, excitotoxicity, and metabolic or mitochondrial impairment.³⁷

Antioxidants

Compelling animal data have demonstrated that striatal degeneration in HD may be secondary to excessive activation of glutamate-gated ion channels.³⁸ In studies of a neuron-like cell line, antioxidants were found to be able to protect against glutamate-induced cytolysis.³⁹ Two lipophilic, centrally active antioxidants were studied in HD: d-alpha-tocopherol (vitamin E) and idebenone. Both studies met Class I level of evidence criteria, but neither demonstrated improvement on the pre-defined primary outcomes of cognition or activities of daily living (ADLs).^{40,41} CoQ10 is an antioxidant and cofactor related in mitochondrial electron transfer. Two large studies of CoQ10 were stopped for futility after failing to demonstrate a difference compared to placebo on the rate of functional decline in HD.^{42,43}

Conclusion: Based on two studies with Class I evidence, it has been determined that CoQ10 does not slow the functional decline of patients with HD. From the expanded literature review of antioxidants, there is no further evidence to support the use of other antioxidants to help ameliorate HD symptoms or rate of progression. There is similar evidence against the use of vitamin E and idebenone based on Class I studies.

Mediating neurotoxicity

Excessive glutamate-mediated neurotoxicity (and likewise insufficient GABA) may play a role in the pathophysiological cascade of HD among

other degenerative diseases.⁴⁴ AOAA can increase brain GABA content through inhibiting GABA-T.⁴⁴ In a study with Class II level of evidence, AOAA supplementation did not show benefit in HD for chorea, gait, cognition, or mood after a 4-month trial. It was proposed that the potential side effects of AOAA (ataxia and drowsiness) may preclude it from being increased to a dosage high enough to inhibit CNS GABA-T activity.⁴⁴ In a study of a GABA precursor (glutamic acid), which crosses the BBB more readily than AOAA, motor or cognitive benefits were again not seen.⁴⁵

The popularity of cannabis and cannabinoid use in HD among other diseases has spread significantly throughout the United States over the last few years with the increasing number of states making cannabis products legal for medicinal or even recreational purposes. The Cannabinoid Receptor 1 (CB1) is widespread throughout the central nervous system and is densely present in basal ganglia structures.⁴⁶ Proposed effects of cannabinoids on oxidative stress and neuroinflammation make them attractive candidates for research in HD and other degenerative diseases, but the potential impact of CB1 receptors on GABA and basal ganglia signaling also has implications for the management of chorea, dystonia, and other hyperkinetic movements.⁴⁶ In HD, the CB1 receptors lose their functionality, which leaves the CNS more vulnerable to cytotoxic damage. Loss of CB1 receptors has been shown to correlate in one study with increased mutant huntingtin protein levels.⁴⁶

A study has been conducted on cannabidiol in HD. Over 6 weeks, an average of 700 mg/day did not show improvement in chorea scores, although no significant side effects were seen.⁴⁷ Likewise, no significant improvement with the synthetic cannabinoid agonist nabilone for motor UHDRS scores when compared to placebo in 44 patients was observed.⁴⁸ However, the drug was again described as well tolerated, and there was some improvement in chorea (a secondary outcome). Sativex (an extract of THC and CBD) had similarly negative findings.⁴⁹ This again confirmed that safety and tolerability were present, but there was no difference found on motor, cognitive, behavioral, or functional outcome measures.

Conclusion: There is insufficient evidence to recommend cannabis products in the management of HD. Three studies with Class I level of evidence did not demonstrate definitive benefit of cannabis products, but some encouraging results with regard to safety and tolerability as well as ongoing accumulation of anecdotal reports and increasing popularity and demand across the United States for use for various motor and non-motor symptoms suggest a need for larger controlled trials. Caution needs to be applied as the safety profile of cannabis products is primarily studied in short-duration studies. The long-term effects on cognition and mental health, especially in people with existing neurodegenerative disorders, are not established.

Metabolic dysfunction

HD is a hypercatabolic state resulting in energy deficiency and weight loss. Animal models have demonstrated anti-dyskinetic effects of compounds that are in the highly unsaturated fatty acids (HUFA) class.⁵⁰ HUFA and creatine supplementation in rat models have slowed motor deterioration and significantly reduced brain atrophy and improved survival by 20%.⁵⁰ Both compounds influence various receptors, ion channels, muscle function, and various enzymes.⁵⁰

Creatine supplementation has been studied in multiple RCTs, including one trial that meets Class I level of evidence criteria.⁵¹⁻⁵⁴ That trial tested a creatine dose of 5 g/day with no improvement in motor, cognition, or coordination ability.⁵¹ A later trial, CREST-E, used a higher dose up to 40 g/day.⁵² Not only was no benefit seen at that higher dose, but also gastrointestinal side effects occurred with higher likelihood.

With regard to fatty acids, eicosapentaenoic acid (EPA) is the most studied. There are promising data on EPA from four RCTs, two of which meet criteria for Class I level of evidence.⁵⁵⁻⁵⁸ While significant improvement in motor functioning was not demonstrated in all trials, one trial did demonstrate an improvement in the presence of orofacial dyskinesia and MR imaging demonstrated improvement in progressive cerebral atrophy that is the natural history of HD.⁵⁷ The two patients on placebo and screened with MRI had an increase in ventricular size, while the two patients on EPA had a decrease in ventricular size after 6 months.⁵⁷ There is also an abnormal brain energy profile in HD patients, and supplementation with triheptanoin (a metabolic intermediate of branched-chain amino acids) was able to improve this abnormal profile.⁵⁹ When a combination of fatty acids was used (up to 8 g daily), there was an improvement in overall dyskinesia and UHDRS-motor scores. However, the functional scales and cognitive-behavioral outcomes were not significantly improved.

Levocarnitine is also a regulator of lipid metabolism with reported antioxidant properties. The two studies targeting levocarnitine in patients with HD demonstrated that levocarnitine supplementation may only be beneficial in those with hypocarnitinemia.^{60,61}

Conclusion: There is Class I evidence that creatine does not slow down disease progression or improve symptoms of HD. Subsequent trials have been conducted and further support these recommendations. More data are needed to clarify recommendations surrounding fatty acid supplementation. Two Class I studies demonstrate no significant benefit from these compounds, and this is reflected in the AAN guidelines. Since that publication, more data have come out to suggest that fatty acid supplementation should be studied more for the potential to impact dyskinesias as well as the overall rate of cerebral atrophy. Levocarnitine may only be helpful for a certain subset of HD patients with specific metabolic abnormalities.

Dietary changes

As HD is a systemic disease, patients often have metabolic changes and challenges particularly with unintentional weight loss and muscle wasting. HD is also an energy-deficient state, and it is important to find ways to provide proper high-calorie nutrition to HD patients.⁶² Clinically, a higher baseline BMI has been positively associated with slower rates of deterioration in multiple domains: motor, functional, and cognitive.⁶³

Typically, high calorie diets are recommended for patients with HD to meet metabolic demands. Diets that contain high levels of certain antioxidants and nutrients have raised interest in neurodegenerative disease, as have ketogenic diets. Ketogenic diet was suggested to delay weight loss in a mouse model of HD, but human studies are not available.⁶⁴ High-protein diets are generally well tolerated, but while the

increased calorie count does improve body weight, there was no significant change in motor or cognitive functioning.^{65,66}

The impact of targeted, individualized dietary therapy has been studied in patients with HD. The biologic basis for their study comes from the idea that microRNAs (miRNAs) could potentially be used as a biomarker in HD. miRNAs are small non-coding RNAs and are upregulated in HD.⁶⁷ It is believed to demonstrate a potential impairment in the cholesterol metabolism pathway in HD. Other studies have also demonstrated that certain dietary factors, like a diet high in dairy product, could speed up the rate of phenoconversion, leading to an earlier age of onset.⁶⁸ This individualized diet (rich in uric acids, GABA, antioxidants, and branched chain amino acids) had high adherence over the 12 months of the trial and led to both a noticeable increase in fat mass and a decrease in the expression of miRNAs. Both cognitive and motor status improved in a few of the participants as well.⁶⁵ A similar biochemical improvement was replicated after supplementation of the diets of people with HD with triheptanoin, which is an important intermediate of the Krebs's cycle.⁶⁹ Normally, HD patients more quickly develop muscle acidosis after exercise, but just 4 days of a triheptanoin-enriched diet was able to normalize the muscle pH.⁶⁹

Conclusion: High-calorie diets are typically recommended in HD, but no specific diet can be endorsed at this time. Individualizing diets may be important. More research needs to be done to understand different energy profiles in individual patients and how certain diets could be beneficial to their disease course.

Discussion

CAM modalities are frequently utilized by patients with neurodegenerative diseases, but physicians lack the knowledge and evidence to guide patients into safe practices.⁵ Our review shows a relative paucity of clinical trials examining CAM modalities in HD when compared to other neurodegenerative disorders like AD or PD. Regarding alternative medical systems, almost no data is available possibly due to cultural and epidemiological differences and the relative rarity of the disease. CAM is particularly important for HD as currently there are no good conventional therapies, so the need for other modalities of treatment is even more pressing. Mind-body interventions such as dance and exercise are proposed to impact motor and quality of life in HD, but more evidence supporting specific interventions is needed. Supervised exercise and contemporary dance have been shown to be safe for people with HD, and some motor benefits have been demonstrated, but specific recommendations for class structure, frequency, and range of exercise and dance styles cannot be commented on. More robust trials should be conducted for other mind-body interventions such as acupuncture and Tai Chi for which no clinical trial data were available. A recent qualitative study on yoga reported that patients with HD are interested in yoga participation if it can be tailored to make it safe for them.⁷⁰ Participants in various mind-body interventions tend to enjoy the process but determining the appropriate stage for intervention in HD may also be important to consider for future trials, as advanced patients may not have the same benefits as early stage patients.

Despite having good animal model data and strong biological basis for nutraceutical supplements, there is no evidence supporting disease modification or symptom improvement with any specific supplement in HD clinical trials. Cannabis products, fatty acids, and individualized diets were raised as potential areas worthy of further research.

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Appendix A

“huntington+complementary”: 1
 “huntington+CAM”: 0
 “huntington+integrative”: 1
 “huntington+aromatherapy”: 0
 “huntington+acupuncture”: 0
 “huntington+diet”: 8
 “huntington+nutraceuticals”: 6
 “huntington+dance”: 2
 “huntington+Chinese”: 1
 “huntington+Indian”: 0
 “huntington+herb”: 0
 “huntington+cannabis”: 1
 “huntington+cannabidiol”: 2
 “huntington+reiki”: 0
 “huntington+epigallo”: 0
 “huntington+nabilone”: 1
 “huntington+behavior”: 9
 “huntington+tai chi”: 0
 “huntington+energy”: 5
 “huntington+natural”: 0
 “huntington+breathing”: 0
 “huntington+qi gong”: 0
 “huntington+massage”: 0
 “huntington+meditation”: 0
 “huntington+manipulation”: 0
 “huntington+meditation”: 0
 “huntington+homeopathy”: 0
 “huntington+relax”: 1
 “huntington+fish+oil”: 5
 “huntington+oil”: 1
 “huntington+exercise”: 9
 “huntington+therapy”: 21
 “huntington+vitamin”: 4
 “huntington+supplement”: 3
 “huntington+biofeedback”: 0
 “huntington+osteopathic”: 0
 “huntington+heal”: 0
 “huntington+hypnosis”: 0
 “huntington+plant”: 1
 “huntington+Feldenkrais”: 0
 “huntington+Alexander”: 0
 “huntington+technique”: 1
 “huntington+yoga”: 0
 “huntington+trager”: 0
 “huntington+pilates”: 0
 “huntington+naturopathy”: 0
 “huntington+botanical”: 1
 “huntington+curandero”: 0
 “huntington+espiritista”: 0
 “huntington+hierbero”: 0
 “huntington+shaman”: 0
 “huntington+sobador”: 0
 “huntington+imagery”: 0