

2021

Complementary and Alternative Medicine (CAM) for Individuals with Epilepsy

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COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) FOR INDIVIDUALS WITH
EPILEPSY

by

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A thesis submitted in partial fulfillment of the requirements
for Honors in the Major Program in Nursing
in the College of Nursing
and in the Burnett Honors College
at the University of Central Florida
Daytona Beach, FL
Spring Term 2021

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Abstract

Individuals with epilepsy manage the clinical manifestations of the condition, primarily seizure-related activity, with daily use of pharmacologic agents, making it one of the most common neurological conditions treated with drug therapy for symptom management. Pharmacologic agents for epilepsy, also known as anti-epileptic drugs (AEDs), are commonly prescribed to treat seizures and neurologic conditions associated with epilepsy but can lead to a reduced quality of life and many unwanted side effects. Complementary and alternative treatments can also provide relief from seizures associated with epilepsy. The purpose of this literature review was to evaluate the effectiveness of complementary and alternative treatments compared to pharmacological treatment for individuals with epilepsy. A literature review examining different alternative treatments, such as physical activity, medical cannabis, neurostimulation, and various diets, and their benefits on seizure reduction, seizure frequency, and the quality of life was conducted from various online databases. Research articles published from 2003 to 2020 that focused on the benefits of complementary and alternative therapies in controlling the clinical manifestations of epilepsy were included for synthesis. Results from 10 studies that used a complementary or alternative therapy as a treatment for epilepsy, alone or in combination with pharmacological therapy, were compared for effectiveness on clinical manifestations. Seventy percent of the studies analyzed show at least a fifty percent reduction in seizure frequency. The studies suggest that complementary and alternative therapies can be effective as monotherapy or as adjuvant agents for reducing seizure frequency, reducing seizure duration, and improving quality of life. Although benefits were found in each study, many studies were performed on animals or had small sample sizes, indicating the need for further research.

DEDICATION

For my family and close friends whose support has allowed me to be successful and grow as an individual.

ACKNOWLEDGMENTS

I would like to thank all of those who have guided me throughout the process of developing my Undergraduate Honors Thesis, as well as throughout my endeavors in nursing school. I would like to thank both of my sisters, Angela and Rachel, as well as my parents and my significant other, Josh, for giving me support throughout this process. I would like to thank my thesis chair, Dr. Leslee D'Amato-Kubiet, for her guidance and kindness throughout developing this review. I would also like to thank my committee member, Dr. Angeline Bushy, for guidance throughout this review. Thank you to the College of Nursing, faculty, and staff that have provided me with an unforgettable and educational experience that I will take with me throughout the rest of my nursing career. Finally, I would like to thank Burnett Honors College for their guidance while developing my thesis.

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Introduction

Epilepsy affects nearly 50 million individuals worldwide and is one of the most common neurological conditions in world populations (Farrukh et al., 2020). Although there is no cure for epilepsy, there are many prescriptive pharmacologic agents, known as antiepileptic drugs (AEDs), that help individuals manage the clinical manifestations of the condition. There are more than 20 AEDs currently available for the management of clinical manifestations associated with epileptic related neurologic events (Cross, 2004). To determine which AED is appropriate, variables, such as age, sex, and comorbid conditions, are considered when selecting an agent for monotherapy or combined therapy, often used in severe cases unresponsive to monotherapy. Although AEDs are the first-line therapy for individuals with epilepsy, approximately 33% of individuals with epilepsy continue to have seizures (Asadi-Pooya et al., 2019). Frequent seizures and the use of multiple AEDs is associated reduced quality of life (Walker et al., 2012). Complementary and alternative medicines (CAM) and herbal supplements can also be used for the treatment of epilepsy, although their use and effectiveness in people with epilepsy is poorly understood.

The use of CAM and the combination of CAM with traditional AEDs has dramatically increased in recent years. Although prescriptive pharmacologic therapies are widely used for people with epileptic events, the use of complementary or alternative therapies (CAM), such as medical cannabis and other herbs, neurostimulation, the ketogenic diet, acupuncture, and exercise, are not widely accepted by the general population or health care providers. A number

of these therapies are used with or without prescriptive pharmacologic medications to treat epilepsy effectively (Kneen & Appleton, 2006). Despite the rates for CAM therapies growing rapidly, less is known about their effectiveness and their benefits or risks in providing relief of symptoms to people with epilepsy, indicating the need for further research.

Background

Epilepsy is a neurological condition defined as the occurrence of two or more unprovoked and unpredicted seizures occurring more than 24 hours apart (Thijs et al., 2019). Abnormal, excessive, or simultaneous electrical discharge of the cerebral cortex that causes a transient occurrence of signs or symptoms is known as an epileptic seizure (Cross, 2004). This activity ultimately results in altered behavior, sensation, consciousness, and awareness of an individual. Epilepsy varies from person-to-person, with some seizures lasting only a couple of seconds and others lasting minutes. Epilepsy is considered resolved for individuals who have an age-dependent syndrome but have passed a certain age and are seizure-free and for individuals who have been seizure free for 10 years with no antiseizure medications for 5 years. (Thijs et al., 2019). The causes and comorbidities of epilepsy can be determined to provide care that is holistic and allows for the best possible management of seizures.

Approximately 60% of cases of epilepsy do not have a known cause (cryptogenic epilepsy) (Solomon & McHale, 2012). Seizures are thought to arise from one of five main conditions: genetic (idiopathic epilepsy), metabolic or structural (symptomatic epilepsy), inflammatory, or infectious. Altered sodium and glucose, phenylketonuria, drug poisoning, renal failure, withdrawal from ETOH, and environmental factors can all cause metabolic-related epilepsy (Alireza Zali et al., 2018). Epilepsy related to structural abnormalities could be a result of traumatic brain injuries, congenital brain defects, and lesions on the brain (Alireza Zali et al., 2018). Other causative conditions leading to seizures include genetic conditions, such as tuberous sclerosis, and inflammatory and infections, such as cerebral vasculitis or meningitis (Solomon & McHale, 2012).

Understanding different types of epileptic clinical manifestations is beneficial to providing holistic and therapeutic care aimed at the prevention of seizures. Seizures are typically divided into two different categories: generalized seizures, where the entire brain is affected by electrical activity, or focal (partial) seizures, where seizures originate from one area of the brain (Cross, 2004). The classification is further broken down into subcategories. Absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizure are classified as generalized seizures. Absence seizures provoke a ‘trace-like’ state which manifests as a blank state and a brief upward rotation of the eyes lasting anywhere from 3 seconds to 30 seconds (Alireza Zali et al., 2018). An absence seizure will end with three distinct clinical manifestations: mild eyelid clonus, loss of muscle tone, and oral automatism (Alireza Zali et al., 2018). Myoclonic seizures are sudden, shock-like twitches that typically occur upon waking up or before going to bed and result in a brief loss of consciousness. Seizures often occur in clusters lasting from a few minutes to a few hours. Repetitive, jerky movements across both sides of the body, along with the presence of clonic movement of the chest and urinary incontinence characterize a clonic seizure (Alireza Zali et al., 2018). A tonic seizure is characterized by rigid muscle contraction. Tonic-clonic seizures, also known as the grand mal seizures, include two distinct phases: the tonic phase and the clonic phase. The tonic phase leads to the contraction of the respiratory muscles, ultimately leading to stridor and cyanosis, as well as urinary inconsistency and tongue bite (Alireza Zali et al., 2018). Deep respirations, muscle relaxation, and altered level of consciousness are all associated with the clonic phase (Alireza Zali et al., 2018). Classic clinical manifestations of an atonic seizure include the sudden reduction of muscle tone or “drop attacks”, which can result in injuries

(Cross, 2004). If a tonic-clonic seizure occurs longer than five minutes without recovery between attacks, the seizure is considered status epilepticus and is a medical emergency.

The clinical manifestations that occur during a focal (partial) seizure correlate with the location of the abnormal electrical activity and the actions of the brain occurring at the location. For example, the temporal lobe is responsible for feelings, emotions, memories (Solomon & McHale, 2012). Individuals with temporal lobe epilepsy often experience epigastric sensations, such as butterflies in their stomach, odd smells or tastes, and altered level of consciousness after a seizure has occurred (Solomon & McHale, 2012). Typically, temporal lobe epilepsy responds well to pharmacologic therapies. The frontal lobe is responsible for cognitive functions, voluntary movement, and speech. Although frontal-lobe epilepsy is also location-dependent, strange movements, such as head turning and thrashing around, and impaired speech can occur (Solomon & McHale, 2012). People with epilepsy experiencing sight-related symptoms, such as rapid eye blinking and seeing patterns, flashing lights, or colors, are often diagnosed with occipital-lobe epilepsy (Solomon & McHale, 2012). However, since seizures from the occipital lobe can spread to another lobe and change the characteristics of the seizures, it is often challenging to diagnose. Tingling, warmness, and other sensory symptoms are often associated with parietal-lobe epilepsy. With this type of epilepsy, individuals commonly report their extremities feeling bigger or smaller.

Pharmacologic therapies are commonly used to manage the clinical manifestations of epilepsy, with the goal of eliminating seizures and minimizing side-effects affecting quality of life. Over two dozen medications to treat the clinical manifestations of epilepsy are available

worldwide, yet only 66% of individuals in high-income countries respond well to the medications (Thijs et al., 2019). Antiepileptic drugs (AEDs) are divided into categories based on their mechanism of action: sodium channel blockers, GABA-A receptor activators, NMDA receptor blockers, AMPA receptor blockers, calcium channel blockers (including T-channel blockers and N and L-calcium blockers), H-current modulators, and neuronal potassium channel openers (Alireza Zali et al., 2018). Some pharmacologic therapies can be used for both generalized and focal seizures, while others are for specific types of epilepsy. Individualized therapeutic plans are formulated according to the individual's age, sex, comorbidities, epilepsy type, and tolerability, in order to reduce clinical manifestations of seizure activity. For example, valproate and clonazepam are commonly used for the treatment of myoclonic seizures, while absence seizures specifically respond well to ethosuximide, valproate, and clonazepam.

The failures of two antiseizure drug schedules to achieve adequate seizure freedom is known as drug-resistant epilepsy. In individuals with epileptic related seizures do not respond well to antiepileptic drugs (AEDs), non-pharmacological therapies, such as certain diets, Vagal nerve stimulation, exercise, acupuncture, surgical operations, and medical cannabis are also available (Kneen & Appleton, 2006). Diets such modified Atkins and ketogenic could improve seizure control in some individuals. Vagal nerve stimulation (VNS), which is performed with a neuro-stimulating device, has been approved by the Food and Drug Administration (FDA) for the management of focal-onset epilepsy for those older than the age of 12 that are not fit candidates for surgical operations (Alireza Zali et al., 2018). Surgical procedures, such as anterior callosotomy, lesionectomy, focal resection, lobectomy, hemispherectomy, and multiple

subpial transections have also proven to be effective for focal epilepsies, although they are not the first-choice alternative therapy.

In addition to pharmacologic and non-pharmacologic drug therapies for epilepsy, herbal therapies have also shown to be effective in the prevention of seizures. Up to 90% of individuals with epilepsy in developing countries do not receive care for their condition, motivating researchers to investigate the effect of plant-based therapeutics on seizure activity (Sucher & Carles, 2015). Extracts, such as flavonoids, (furan) coumarins, phenylpropanoids, and terpenoids, have been shown to exhibit anticonvulsant effects. Some plant extracts were reported to have similar effects to that of synthetic drugs. For example, *Aegle marmelos*, *Delphinium denudatum*, *Ficus religiosa*, and *Nymphaea alba* were reported to have an effect that is similar to the AED phenytoin (Sucher & Carles, 2015).

Recent studies suggest medical cannabis provides people with epilepsy an alternative treatment for seizures, resulting in improved cognitive and behavioral function and the reduction of seizure frequency and intensity (Markle & Nativio, 2019). Medical cannabis could provide an opportunity for nearly 470,000 Americans to benefit from a seizure-free life (Markle & Nativio, 2019). However, many of the herbal therapies have not been assessed for their efficiency, safety, or cost-effectiveness. The Holistic Theory of Nursing provides guidelines for preparing an individualized treatment plan that is both and tailored to the individual. Individual considerations are a mainstay of therapy when developing a treatment plan.

To treat individuals with epilepsy effectively and therapeutically, planning involves assessment of the individual's financial situation, culture, age, medical history, religious beliefs,

and geographic location to the nearest pharmacy, market, and acute care facility. Holistic nursing focuses on healing the person, rather than treating their clinical manifestations. In the holistic nursing theory, healing is based on a person's interconnectedness of the mind, spirit, body, emotions, relationship, environment, and social interactions (Petiprin, 2020). The physical needs of each individual, as well as their psychological and spiritual needs, are addressed in this theory, allowing health care providers to develop a plan of care specific and detailed to each person's situation and clinical manifestations associated with epilepsy. The holistic theory allows providers to build a stronger relationship with each individual with epilepsy and acts as a guide to promote healing and health (Petiprin, 2020).

Epilepsy affects millions of individuals around the world. Nearly 30% of individuals with epilepsy experience intractable epilepsy, where combination therapy of two or more drugs does not show a therapeutic effect on an individual (Alqahtani et al., 2020). Uncontrolled epilepsy can severely affect an individual's quality of life. Although pharmacological therapies are common for individuals with epilepsy, many alternative and complementary therapies, including medical cannabis and other herbs, neurostimulation, the ketogenic diet, acupuncture, and exercise, have also been proven to have significant therapeutic effects on the clinical manifestations of the condition. Each therapy needs to be researched further to determine the effects it has on individuals with epilepsy.

Problem

The clinical manifestations of seizure activity in individuals with epilepsy are often difficult to control. Although pharmacologic therapies are typically used to control signs and symptoms associated with epilepsy, complementary and alternative therapies can be considered when developing a treatment plan to prevent seizures from occurring. Complementary therapies, such as electroconvulsive therapy, the ketogenic diet, acupuncture, exercise, and herbal supplements, have not been widely researched. The use of complementary and alternative therapies must be evaluated further to understand the effects they have on people with epilepsy.

The effects that complementary and alternative therapies, as well as the combination of COM therapies with pharmacologic therapies in people with epilepsy is not fully understood. Research demonstrates several alternative therapies can have a positive impact on clinical manifestations of people with epilepsy, leading to a lifestyle free of seizure activity. However, the research is vague and does not convey one therapy is more beneficial than another. Further research is needed to understand complementary and alternative therapies and their effects on the clinical manifestations of epilepsy, as well as the benefits each CAM can provide for the different types of epilepsy.

Evidence suggests complementary and alternative therapies can be effective for treating the clinical manifestations associated with epilepsy and can produce fewer side effects. Herbal AED's produce less side effects than pharmacological AED's. Further research is needed to address many unanswered questions concerning the effectiveness of each complementary and alternative therapies in individuals with epilepsy.

Purpose

The purpose of the literature review is to examine the risks and benefits of complementary and alternative therapies in people diagnosed with epilepsy. Evidence showing improvement in the clinical manifestations related to CAM used with epilepsy are sparse. Additionally, knowledge about the combination of CAM with traditional AEDs on the clinical manifestations associated with epilepsy indicates the need for further research into mechanisms of action of CAM agents and dosing quantities to prevent harm. Most of the research conducted is still experimental and focuses on neuropeptides interference, microRNA activity, and tools to regulate electrical activity, rather than benefits of complementary therapies, such as alternative diets, exercise, or herbal therapies. Alternative and complementary therapies for individuals with epilepsy can be useful and a better understanding of the effects they have on preventing and interrupting seizures would be of value to the individual with epilepsy and the healthcare provider prescribing therapy.

Method

A comprehensive review of the literature was performed using research articles available from 2003 to 2020 regarding the use of complementary and alternative therapies and their relationship in managing clinical manifestations associated with epilepsy. The focus was the use of alternative therapies, such as herbal therapy for individuals with epilepsy. Databases used to search for articles included EBSCO host databases, Medical Literature On-Line (Medline), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsychInfo databases. Searches will use a combination of the following terms: Epilepsy*, seizure*, alternative*, complementary*, clinical manifestations*, benefit*, therapies*, and, treatments*. Inclusion criteria consisted of 1) published research in English, 2) complementary and alternative therapies compared to prescriptive agents, and 3) complementary and alternative therapies used to control clinical manifestations associated with epilepsy. Articles excluded focused solely on pharmacological therapies available to individuals with epilepsy and treatments that did not include the use of complementary and alternative therapies.

The data was compiled into tables to synthesize the relationship between the benefits of complementary and alternative treatments in controlling the clinical manifestations of epilepsy. Additional information on the benefits of complementary and alternative treatments was tabled based on the information obtained. Data showed the evidence for the use of complementary and alternative therapies on the clinical manifestations of the clinical manifestations in people with epilepsy.

Results

Twelve studies related to complementary and alternative therapies on the clinical manifestations of epilepsy were included in the literature review. Of the twelve studies reviewed, nine studies proved to be effective and three proved to be inconclusive. The studies suggest complementary and alternative treatments can be effective treating the clinical manifestation of epilepsy, however, the data was limited. Many of the studies included complementary and alternative treatments in addition to pharmacological regimens, indicating adjuvant agents to pharmaceutical drug therapy can control clinical manifestations associated with epilepsy. The effectiveness of complementary and alternative therapy use alone for managing the clinical manifestations associated with epilepsy is of value but poorly understood. Additionally, many studies had small sample sizes, focused on an individual type of epilepsy, or used animal testing, which did not translate to human variants.

Ketogenic Diet

The ketogenic diet has been widely studied as an alternative treatment in relation to treating the clinical manifestations for individuals with epilepsy. The ketogenic diet is a diet consisting of high fat, low carbohydrates, and moderate-protein intake (Baby, Vinayan, Pavithran & Grace Roy, 2018). Rather than using glycolysis for energy, this diet shifts human metabolism to use fatty acids and ketones (Roehl, Falco-Walter, Ouyang & Balabanov, 2019). The majority of evidence supports that the ketogenic diet improves seizure frequency, as well as seizure severity and overall quality of life. All four studies analyzed in the literature review were shown to have a major impact on seizure frequency. Two studies focused on how the ketogenic diet affects the clinical manifestations of adults with epilepsy, while the other study focused on

how the ketogenic diet impacts children with pharmco-resistant epilepsies. The other study compared the ketogenic diet to other diets, including the modified Atkins diet and low Glycemic Index Therapy diet (Sondhi, et al., 2020).

In one study, twenty-nine individuals (16 women and 13 men) between the ages of 11 and 51 were placed on the ketogenic diet with the ratio of 4 grams of fat to 1 gram of carbohydrates and protein (Nei, Ngo, Sirven & Sperling, 2014). Of the twenty-nine individuals, fifteen individuals had a reduction in their seizure frequency, with thirteen experiencing a seizure reduction more than 50% and six experiencing a seizure reduction of more than 80% (Nei, Ngo, Sirven & Sperling, 2014). Another study compared the quality of life in adults with epilepsy following the modified ketogenic diet with 15 grams of carbohydrates daily (MKD-15) with adults with epilepsy consuming 50 grams of carbohydrates daily (MKD-50). Out of the 55 participants who met criteria, 87% (n= 48) reported improvements in their quality of life and 60% (n= 33) reported having improvements in the seizure frequency (Roehl, Falco-Walter, Ouyang & Balabanov, 2019), proving that the ketogenic diet is effective for both seizure frequency as well as overall quality of life.

Another study focused on how the ketogenic diet affects Indian children with refractory epilepsy and is limited in the amount of evidence it provides. Although the results show forty-four out of the seventy-four children reported more than an 50% reduction in their seizure frequency, this study was limited to children between the ages of 1 months to 13 years, only included children with a certain ethnicity, and only included children with certain types of seizures (Baby, Vinayan, Pavithran & Grace Roy, 2018). Although the majority of studies have

shown beneficial effects of the ketogenic diet on the clinical manifestations associated with epilepsy, further research is needed to confirm due to small sample sizes and the limited research on the ketogenic diet in relation to specific types of seizures.

Neurostimulation

Approximately 30% of individuals with epilepsy experience drug resistant epilepsy (DRE), leading to complications such as increased mortality, decreased quality of life, and social, work, and stigma problems (Gil-Lopez et al., 2020). Evidence supports that neurostimulation can be an effective alternative for individuals with drug-resistant epilepsy, but data is limited. The three studies analyzed included different types of neurostimulation- deep brain stimulation (DBS), trigeminal nerve stimulation, and auricular vagus nerve stimulation. Out of the three studies analyzed, two were shown to be an effective alternative treatment for individuals with epilepsy and one study was shown to be inconclusive due to the small sample size and animal testing. Two of the three studies involve invasive neurostimulation techniques (deep brain stimulation and vagus nerve stimulation), while one study focused on a non-invasive neurostimulation technique (external trigeminal nerve technique). Two studies focused on the effects of neurostimulation on humans, while one focused on the effects of neurostimulation on monkeys.

One study focused on the effects of external trigeminal nerve stimulation on individuals older than the age of eighteen. External trigeminal nerve stimulation (ETNS) is a non-invasive type of neurostimulation conducted with bilateral adhesive skin electrodes (Gil-Lopez et al., 2020). In this study, twenty participants were randomly assigned in the external trigeminal nerve

stimulation group and twenty participants were randomly assigned to the control group. After one year of treatment, 10 participants (50%) in the ETNS group responded to treatment and 0% in the control group responded to treatment (Gil-Lopez et al., 2020). Additionally, the ETNS group showed a decrease by -41.79% from baseline in seizure frequency after 6 months of treatment and -43.5% from baseline in seizure frequency after one year of treatment (Gil-Lopez et al., 2020). Frontal lobe epilepsy was shown to be less responsive to treatment compared to temporal lobe epilepsy.

Another study focused on the effects of transcutaneous auricular vagus nerve stimulation for pediatrics with intractable epilepsy (He et al., 2013). Initially, fourteen participants began transcutaneous auricular vagus nerve stimulation using a ear vagus nerve stimulator. Thirteen participants completed the 24-week study without changing their pharmacological regimens. The baseline seizure frequency was compared 8 weeks after undergoing treatment, 9 to 16 after undergoing treatment, and 17 to 24 weeks after undergoing treatment. The results showed reductions in seizure frequency during the three 8-week periods: 31.83% after 8 weeks, 54.13% from weeks 9 to 16 and 54.21% from weeks 17 to 24 (He et al., 2013). Four out of the fourteen participants responded to treatment during the first 8 weeks (28.57%) and seven out of the thirteen participants responded to treatment during the second and third 8-week periods (53.85%) (He et al., 2013). Figure 1 and 2 show the responder rate and the decrease in seizure frequency experienced during this study. Another study determined that low frequency stimulation had a stronger effect on the number of seizures than high frequency stimulations (Sherdil, Chabardes, David, & Pierrat, 2020). Data is limited within this study because of the small sample size (n= 3) and animal testing.

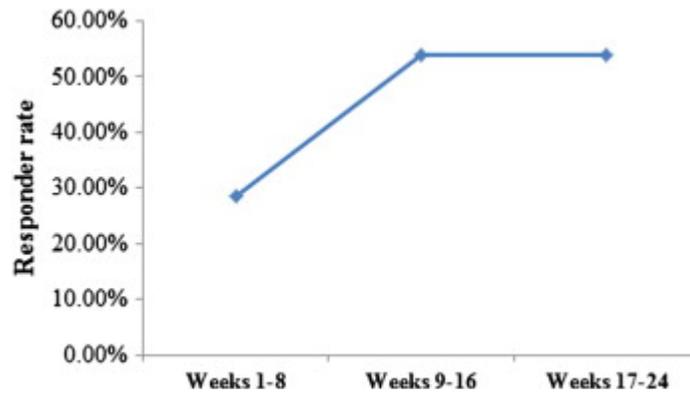


Figure 1. Responder rate after 8, 16, and 24 weeks (He et al., 2013)

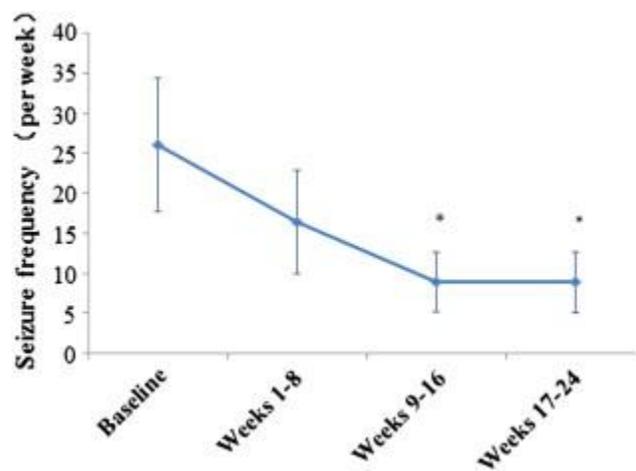


Figure 2. The decrease in seizure frequency (He et al., 2013)

Physical Activity

Although the number of clinical studies is limited, research over recent years has shown physical activity is effective alternative therapy with beneficial effects for epilepsy. Clinical research has found that regular exercise may reduce seizure frequency and increase psychological and cardiovascular health in individuals with epilepsy (Campos et al., 2017). The studies analyzed used Wistar rats as test subjects, proving both to be inconclusive. In one study, the Wistar rats were divided into four different groups: control, epilepsy, epilepsy with forced

exercise, and epilepsy with voluntary exercise (Campos et al., 2017). The seventy-one Wistar rats were given 350 mg/kg of pilocarpine hydrochloride to induce seizures. Seizure frequency was recorded during two different periods. During the first period, the observed number of seizures was 9.50 for the epilepsy group, 8.93 for the epilepsy with forced exercise group, and 11.67 for the epilepsy with voluntary exercise group. During the second period, the observed number of seizures was 6.86 for the epilepsy group, 6.60 for the epilepsy with forced exercise group, and 4.25 for the epilepsy with voluntary exercise group (Campos et al., 2017). Figure 3 shows the decrease in the number of seizures from the first period to the second period between epilepsy, epilepsy with forced exercise, and epilepsy with voluntary exercise groups. Another study conducted on 20 Wistar rats also showed physical activity to have positive effects on induced seizures. This study consisted of fifteen 3-day cycles- the rats would run on the treadmill the first day, swim on the second day, and rest on the third day (Setkowicz & Mazur, 2006). Results showed that the rats experienced decreased susceptibility to frequently induced seizures, but is limited on the data it provides. Further research is needed to confirm that physical exercise is beneficial to individuals with epilepsy due to small sample sizes and animal studies.

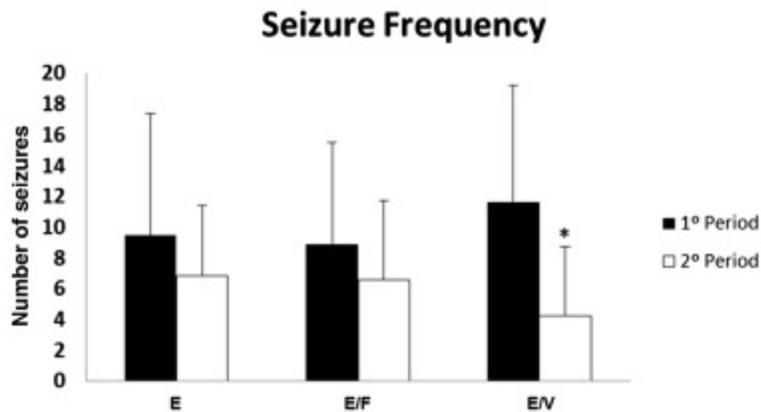


Figure 3. Epilepsy with forced exercise, and epilepsy with voluntary exercise groups (Campos et al., 2017)

Medical Cannabis and CBD

Cannabis is the most widely studied herbal therapy in relation to treating the clinical manifestations of epilepsy, however, mixed results regarding the effectiveness have been found. Two components of Marijuana have shown to have anticonvulsant effects- non-psychoactive cannabidiol (CBD) and psychoactive Δ 9-tetrahydro-cannabinol (THC) (Hausman-Kedem, Menascu, & Kramer, 2018). Most studies show that CBD has a greater role in reducing one's seizure frequency than THC. CBD is thought to have an antiepileptic mechanism by inhibiting excitatory neurotransmission, although the mechanism is still unclear (Hausman-Kedem, Menascu, & Kramer, 2018).

In one study, 57 children and adolescents between the ages of 1 to 20 years with refractory epilepsy were given Cannabis oil in addition to their other therapeutic therapies for at least three months. Twenty out of the forty-six (43.5%) included for analysis, including two participants that experienced seizure exacerbation, had a seizure reduction between 0 to 49%, ten

participants had a seizure reduction of 50 to 75%, fourteen participants had a seizure reduction of 75 to 99%, and two participants were completely seizure free (Hausman-Kedem, Menascu, & Kramer, 2018). The results showed several participants experienced a significant reduction in their seizure frequency (56.5%), while others did not (43.5%). Medical cannabis was proven to be more effective in the younger ages group (<10 years) and those on a higher CBD dose. Nearly 50% participants experienced adverse reactions, which was the main reason for treatment cessation (Hausman-Kedem, Menascu, & Kramer, 2018). Although the results suggest that adding CBD-enriched medical cannabis to the daily pharmacological therapy can be effective for children and adolescents, many components need to be explored further to determine cannabis' true effectiveness in improving seizure frequency.

Another study focused on the efficacy of CBD added to antiepileptic drugs (AED) for the treatment of seizures associated with Lennox-Gastaut syndrome, a severe form of epilepsy. Participants between the ages of 2 and 55 years old were divided into two groups: one was placed on a 20 mg/kg/ day oral solution of CBD and the other group had the matched placebo (French et al., 2017). Each group was tolerated for 2 weeks, followed by a 12-week dose maintenance. Although the results show a significant difference in seizure frequency between the CBD group versus the placebo group (44% versus 22%), this study is limited because it only focused on one type of epilepsy (French et al., 2017). Another study showed similarities, where 36.5% of individuals experienced a decrease in their seizure frequency and included epilepsies with different causes (Devinsky et al., 2016). More research is needed to determine if CBD is effective in all mild, moderate, and severe forms of epilepsy.

Discussion

Studies examined in this thesis offer insight into complementary and alternative treatments for the clinical manifestations of epilepsy. Research findings showed the benefits of using complementary and alternative therapies for the clinical manifestations of epilepsy; however, results were often mixed. Although many of the studies presented with limitations and mixed results, the majority of the studies revealed positive effects complementary and alternative therapies have in minimizing the clinical manifestations of epilepsy, making it an effective form of treatment.

Pharmacologic treatments are often the first-choice therapy to treat the clinical manifestations associated with epilepsy but can leave a negative impact on an individual's quality of life, sigma, relationships, and social life. Additionally, nearly 30% of individuals with epilepsy on multiple antiepileptic drugs (AEDs) experience intractable epilepsy, where the combination of two or more pharmacological drugs does not control their clinical manifestations (Alqahtani et al., 2020). The side effects of many pharmacologic treatments and many individuals not achieving seizure freedom on pharmacological treatments alone and exploring other treatment options is essential. There are many non-pharmacological treatments available to help with the clinical manifestations of epilepsy, including neurostimulation, the ketogenic diet, medical cannabis, and physical activity. Complementary and alternative therapies open up a new opportunity for individuals with epilepsy to achieve seizure freedom. More research is imperative to help individuals eliminate seizures, while minimizing the side-effects affecting quality of life.

The studies analyzed offered a variety of different alternative and complementary treatments available to individuals with epilepsy. More than 70% of the studies analyzed in this literature review showed benefits in improving the seizure frequency and the clinical manifestations associated with epilepsy. One study showed that CBD-enriched cannabis could be a very promising alternative treatment for the clinical manifestations of epilepsy, with 56% of participants experiencing a reduction in their seizure frequency (Hausman-Kedem, Menascu, & Kramer, 2018). Two studies on CBD oral solution and cannabidiol proved to be effective for reducing seizure frequency, however, less than 50% of the participants experienced a reduction in their seizure frequency and many adverse effects were reported (Devinsky et al., 2016) (French et al., 2017). One study compared the ketogenic diet to the modified Atkins diet and low Glycemic Index Therapy diet for drug-resistant epilepsies and found that the ketogenic diet has the biggest impact on seizure reduction (Sondhi, 2020). Additionally, some forms of neurostimulation, including transcutaneous auricular vagus nerve stimulation, external trigeminal nerve stimulation, and deep brain stimulation, has also proven to be effective on seizure frequency, but data is limited (He et al., 2013) (Serdil, Chabardes, David, & Piallat, 2020) (Gil-Lopez et al., 2020). Although many of the studies portrayed the same benefits with alternative and complementary treatments, many had small sample sizes or were tested on animals, indicating the need for further research.

Although many of the studies had limitations, this literature review provides information on a variety of different alternative treatments that have shown positive effects on the clinical manifestations associated with epilepsy. The studies show to have a positive effect on seizure frequency, duration, and overall quality of life. Studies in the future should include a variety of

different types of seizures, as well as a variety of different ages (children, adolescents, and adults) should be put more into consideration. Some studies compared alternative therapies to a placebo group to determine the effectiveness. These studies showed the benefits of alternative therapies, but failed to show how effective they were compared to pharmacological therapies. Comparing and contrasting pharmacological therapies to alternative and complementary therapies may help prove how beneficial the alternative treatments can be.

Complementary and alternative therapies are becoming more and more popular and can be used in a variety of different diseases. Many studies added complementary and alternative therapies to pharmacological therapies and examined their effects. For example, one study added CBD to participants' regular pharmacological therapies. The results showed a median seizure frequency drop of 74 per month, proving that CBD is effective for seizure frequency when added to AEDs (He et al., 2013). While this was proven to be effective, more studies need to focus on alternative therapies alone.

In conclusion, there should be further studies on alternative and complementary treatments used in controlling the clinical manifestation associated with epilepsy. Further studies can help determine which CAM therapy is the most beneficial for which type of seizure, for certain age groups, and in comparison, or in conjunction with pharmacological therapies. The evidence presented supports that complementary and alternative therapies are effective in treating the clinical manifestations associated with epilepsy. Therefore, these options should be available and offered as a treatment option to individuals with epilepsy. Complications were shown in two of the CBD studies, with more than 75% of participants reporting having adverse

effects (French et al., 2017) (Devinsky et al., 2016). However, all the CBD studies still proved to be effective in reducing seizure frequency. The majority of the studies analyzed showed positive effects on managing the clinical manifestation of epilepsy, suggesting that individuals should use CAM therapies to better manage their symptoms.

Limitations

This literature review contained several limitations. Several of the studies had small sample sizes, were tested on animals, were compared to a placebo rather than pharmacological agents, and were focused on a certain population, such as pediatrics or only individuals with refractory epilepsy. A number of studies focused on the pediatric population alone, while others included both the pediatric and adult population. Some studies focused on certain types of epilepsy, such as a severe form of epilepsy, further limiting the data provided. Knowing which alternative medicine is beneficial to which type of seizures is important to understand and is something that can be researched further.

The sample sizes ranged from $n=3$ to $n=170$. The smallest sample size group explored deep brain stimulation on three monkeys (Sherdil, Chabardes, David, & Piallat, 2020). Although the results showed that having a low frequency stimulation had a positive effect on seizure frequency and duration, the reliability of the finding is limited due to the small sample size and animal testing. The largest sample size group explored which diet was most beneficial for seizure frequency: The Ketogenic diet, the Modified Atkins diet, or the Glycemic Index Therapy diet. The ketogenic diet was shown to have the most positive effect on seizure frequency, with a 66% reduction (Sondhi et al., 2020).

Three studies in this research were performed on monkeys or Wistar rats. Although all three showed positive effects on clinical manifestation associated with epilepsy, the studies were not performed on humans, making the results inconclusive. Further trials need to be performed on humans to better understand the benefits that alternative and complementary therapies offer. In addition to small sample sizes and animal studies, many of the alternative and complementary treatments were compared to a placebo group, rather than pharmacological agents. Without comparing alternative and complementary treatments to pharmacological agents, it can be difficult to determine if the CAM therapies are as effective as the agents. Providing further research comparing pharmacological therapies to CAM therapies would be beneficial in determining which is best for treating certain types of seizures.

Implications for Nursing

Pharmacological agents often leave individuals with unwanted side effects, affecting their overall quality of life. Many alternative and complementary therapies can offer individuals seizure freedom without the effects of pharmacological treatments. Continuing research of the alternative therapies for the clinical manifestations of epilepsy is imperative, so that individuals can receive the greatest seizure reduction, with the least number of adverse effects. Individuals with epilepsy should be educated on the various alternative therapies available as treatment options for the clinical manifestations of epilepsy. Health care facilities should implement alternative and complementary treatments for managing the clinical manifestations associated with epilepsy. Further research is needed to understand the effectiveness of alternative and complementary therapies in comparison to pharmacological therapies on the clinical manifestation of epilepsy.

Table of Evidence

Authors Year	Study Purpose	Study description	Results	Complementary or alternative treatment effectiveness 1= not useful 2= inconclusive 3= useful
Nei, Ngo, Sirven, & Sperling (2014)	To test the efficiency of the ketogenic diet in adults with epilepsy	Total of 29 participants included Women= 16 Men= 13 Participants were placed on ketogenic diet ratio of 4 grams of fat to one gram of carbohydrates and protein	Fifteen of the twenty-nine patients (52%) experienced reduction in seizure frequency Thirteen patients (45%) has a seizure reduction more than 50%, with 21% of those experiencing an 80% reduction in their seizure frequency Nine patients (31%) did not have improvement of their seizure frequency, with three experiencing a seizure increase	3 More than half of the participants in this study had a reduction in their seizure frequency This study showed that diets, such as the ketogenic diet, can be beneficial for controlling epilepsy
Hausman-Kedem, Menascu, & Kramer (2018)	To evaluate the efficiency of medical cannabis for the treatment of refractory epilepsy	Total of 57 participants included The participants were between the ages of 1 to 20 years old Participants were treated with Cannabis oil extract with the CBD/THC ratio of 20:1 for at least 90 days	Of the 57 participants, only 46 were included in the efficacy analysis. 20 participants had a seizure reduction between 0 to 49%, 10 participants had a reduction of 50 to 75%, 14 participants had a reduction of 75 to 99%, and 2 were seizure free	3 Of the 46 participants included in this study, 26 participants (56%) experienced a reduction in their seizure frequency. CBD-enriched cannabis extract is a very promising anti-seizure option
Sherdil, Chabardes, David, & Piallat (2020)	To evaluate whether the frequency of stimulation is an important parameter	Total of three monkeys were tested in this study One female monkey, two male monkeys	Low frequency stimulation was shown to have a stronger effect on the number of seizures, as well as	2 This study is very limited on the data it provides.

	that interferes with seizure	This study investigated the effects of low-stimulation (40 Hz) and high-frequency (130 Hz) on three monkeys in which Mesial temporal lobe epilepsy was induced	the duration of the seizures High frequency was shown to have no effect	This study provided a very small sample size and was conducted on monkeys; therefore, another study needs to be done with a larger sample size and examining people undergoing neurostimulation for epilepsy
Gil-López et al (2020)	To determine the efficacy of external trigeminal nerve stimulation in those with focal drug-resistant epilepsy	Total of 40 participants were included Subjects had a median of 15 seizures per month and had tried a median of 12.5 pharmacological therapies Participants were randomized to external trigeminal nerve stimulation or usual medical treatment (20 participants for neurostimulation and 20 for control group) and evaluated at 3, 6, and 12 months Participants were asked to use the stimulation for at least 8 hours a day An external pulse generator was used to deliver external trigeminal nerve stimulation; intensity was set at <10 mA, Frequency 120 Hz, pulse duration 250 μs, and duty cycle 30 sec on and 30 sec off	After one year, 50% of the external trigeminal nerve stimulation responded to treatment The external trigeminal nerve stimulation group experienced a decrease in seizure frequency by 43.5% from baseline Temporal lobe epilepsy responded better than frontal lobe epilepsy (55.56% vs 45.45%)	3 The group undergoing external trigeminal nerve stimulation experienced a dramatic decrease in their seizure frequency, showing that neurostimulation can be an alternative treatment for epilepsy

<p>Campos et al (2017)</p>	<p>Investigate the impact of two types of exercise programs, forced and voluntary, in female Wistar rats with pilocarpine-induced epilepsy</p>	<p>Total of 61 Wistar rats were tested in this study</p> <p>The Wistar rats were divided into four groups: control, epilepsy, epilepsy with forced exercise, and epilepsy with voluntary exercise Control= 20 Epilepsy= 14 Epilepsy with forced exercise= 15 Epilepsy with voluntary exercise= 12</p> <p>An injection of 350 mg/kg was given to induce seizures</p> <p>Forced exercise group: lasted for four weeks with five sessions a week; started from 16 m/min and reaching 22 m/min in the last week</p> <p>Voluntary exercise group: animals were placed in a cage with a voluntary wheel for 30 days with free success to food and water</p>	<p>The results showed that voluntary exercise exerts a positive effect on females with epilepsy</p>	<p>2</p> <p>This study shows that voluntary exercise has a positive effect on females</p> <p>However, the study was conducted on females only, not both males and females, and provides information only about how animals with epilepsy respond to exercise</p> <p>Another study examining the effects of exercise on humans with epilepsy would be of value.</p>
<p>Setkowicz & Mazur (2006)</p>	<p>To assess the effect of long-term physical activity on susceptibility to frequent seizures</p>	<p>Total of twenty rats participated in this study</p> <p>This study consisted of fifteen 3-day cycles; the rats would run on the treadmill the first day, swim on the second day, and rest on the third day</p> <p>Pilocarpine was used to induce seizure in the rats</p>	<p>Results showed that regular physical exercise decreases susceptibility to subsequently seizures</p>	<p>2</p> <p>Although this study suggests physical exercise could reduce seizure frequency, the seizures experienced were induced</p> <p>Examining adults with epilepsy, rather than inducing seizures in</p>

				animals would provide greater insight into the seizure phenomena
Sondhi et al (2020)	To access whether the modified Atkins diet and low Glycemic Index Therapy diet have similar effects of the Ketogenic diet for drug-resistant epilepsy	Total of 170 children between the ages of 1 and 15 participated in this study Children were randomly assigned for one of three diet therapies: Ketogenic diet, modified Atkins diet, or the Low Glycemic Index Therapy diet Ketogenic diet: 52 Modified Atkins: 52 LGIT: 54	One hundred and fifty-eight children completed the trial After the 24-weeks of intervention, the median change in seizure frequency was as follows: Ketogenic diet: 66% reduction Modified Atkins: 45% reduction LGIT: 54% reduction	3 This study suggests anti-convulsant effects in children with varying diets can influence seizure symptoms, and the ketogenic diet has the biggest impact on seizure reduction This study implies there is more than one diet that has positive effects on seizure frequency in children
Roehl, Falco-Walter, Ouyang, & Balabanov (2019)	This study was conducted to evaluate the modified ketogenic diet on seizure frequency, severity, and quality of life	Total of 74 participants between the ages 17 and 70 years old participated in this study; majority white (74%) and female (73%) with focal epilepsy (89%) One group consumed 15 grams of carbohydrate daily (MKD-15), while another group consumed 50 grams of carbohydrate daily (MKD-50) for three months	60% of participants reported at least a 50% reduction frequency in their seizures, 76% reported improvement in their seizure severity, and 87% agreed that it improved their quality of life The results showed that the MKD-15 improved the quality of life in most participants (95%), whereas the MKD-50 only improved some individual's quality of life (69%)	3 This study explores the positive impact of the ketogenic diet on seizure frequency, severity, and quality of life The study had many female participants compared to male participants. Examining similar components with the same age range, but including an even number of males and females could explain the occurrence of seizure more accurately.
Baby, Vinayan, Pavithran, & Grace Roy (2018)	To analyze whether the Ketogenic diet can be beneficial to children in South India	Total of 74 children were enrolled into a Ketogenic diet program, with four who could not complete the process	59.4% reported a seizures reduction of more than 50%	3 This study suggests the Ketogenic diet can be a beneficial and safe

		<p>Baseline seizure frequency was 5 or more times a day for 52 children</p> <p>The diet was continued for a median duration of 10.43 months</p>	<p>25 reported seizure reduction of at least 90%, with 6 children being seizure-free</p>	<p>alternative therapy for children with epilepsy</p>
He et al (2013)	To investigate the safety and efficacy of transcutaneous auricular vagus nerve stimulation for the treatment of pediatric epilepsy	<p>Started with a total of 14 children with intractable epilepsy participated in this study; One child dropped out after 8 weeks and the remaining 13 children completed the 24-week study without a change in the medications</p> <p>Baseline seizure frequency was compared with that after 8 weeks, between weeks 9 to 16, and between weeks 17 to 24</p>	<p>The results showed a significant reduction in seizure frequency compared to baseline:</p> <p>-31.83% reduction after week 8 -54.14% reduction between week 9 to 16 -54.21% reduction between weeks 17 to 24</p>	<p>3</p> <p>This study proves that transcutaneous auricular vagus nerve stimulation, with adjuvant, individual pharmacological therapy, can be beneficial for children</p>
French et al. (2017)	To evaluate efficacy of CBD added to antiepileptic drugs (AED) for the treatment of seizures associated with Lennox-Gastaut syndrome.	<p>Participants were randomized to receive 20 mg/kg/day of CBD oral solution or a matched placebo (86 CBD; 85 placebo) for a 14-week study</p>	<p>The results showed a median seizure frequency drop of 74/month</p> <p>There was a significant drop in seizure frequency for those who took the CBD oral solution compared to the placebo (44% versus 22%)</p> <p>86% of CBD oral solution group experienced adverse effects after 4 weeks of</p>	<p>3</p> <p>This study proves that CBD is effective seizure frequency when added to AEDs</p> <p>However, this study shows that there are many adverse effects associated with CBD oral solution</p> <p>This study also focused on individuals with Lennox-Gastaut syndrome, which is a</p>

			<p>the study, while 69% of the placebo group experienced adverse effects</p> <p>There was one death in the CBD group, considered unrelated to the study</p>	<p>severe form of epilepsy. Other studies should be done to see the results on individuals without Lennox-Gastaut syndrome</p>
Devinsky et al (2016)	To evaluate whether cannabidiol to existing anti-epilpsyic regimens would be safe, tolerated, and efficient in treating the clinical manifestations of epilepsy	<p>214 individuals started the trial; 162 participants had at 12 weeks of follow-up after first dose were included in the safety and tolerability analysis and 137 participants were included in the efficiency analysis</p> <p>Participants were given oral cannabidiol 2 to 5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day</p>	<p>128 out of the 162 participants (79%) in the safety group reported various adverse effects, including somnolence, decreased appetite, diarrhea, fatigue, and convulsions</p> <p>The median reduction in motor seizures was 36.5%</p>	<p>3</p> <p>The study shows that cannabidiol can be effective with reducing seizure frequency, but data is limited</p> <p>Further research is need to investigate cannabidiol true efficacy in reduce seizure frequency</p>

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