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Review

Non-pharmacological Interventions for Intractable Epilepsy

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ABSTRACT

In 30% of epileptic individuals, intractable epilepsy represents a problem for the management of seizures and severely affects the patient's quality of life due to pharmacoresistance with commonly used anti-seizure drugs (ASDs). Surgery is not the best option for all resistant patients due to its post-surgical consequences. Therefore, several alternative or complementary therapies have scientifically proven significant therapeutic potential for the management of seizures in intractable epilepsy patients with seizure-free occurrences. Various non-pharmacological interventions include metabolic therapy, brain stimulation therapy, and complementary therapy. Metabolic therapy works out by altering the energy metabolites and include the ketogenic diets (KD) (that is restricted in carbohydrates and mimics the metabolic state of the body as produced during fasting and exerts its antiepileptic effect) and anaplerotic diet (which revives the level of TCA cycle intermediates and this is responsible for its effect). Neuromodulation therapy includes vagus nerve stimulation (VNS), responsive neurostimulation therapy (RNS) and transcranial magnetic stimulation therapy (TMS). Complementary therapies such as biofeedback and music therapy have demonstrated promising results in pharmacoresistant epilepsies. The current emphasis of the review article is to explore the different integrated mechanisms of various treatments for adequate seizure control, and their limitations, and supportive pieces of evidence that show the efficacy and tolerability of these non-pharmacological options.

Contents

1. Introduction . . . 952
2. Metabolic therapies . . . 952
   2.1. The ketogenic diet (KD) . . . 952

Abbreviations: ASDs, Antiepileptic drugs; ATP, Adenosine triphosphate; BBB, Blood-brain barrier; CKD, Classic ketogenic diet; CSF, Cerebrospinal fluid; EEG, Electroencephalography; EMG, Electromyography; GABA, Gamma-aminobutyric acid; KB, Ketone bodies; KD, Ketogenic diet; LC, Locus coeruleus; LCFA, Long-chain fatty acids; MAD, Modified Atkin's diet; MCT, Medium-chain triglyceride; MEP, Maximal evoked potential; NTS, Nucleus tractus solitaries; PPAR, Peroxisome proliferator-activated receptor; PUFAs, Polyunsaturated fatty acids; ROS, reactive oxygen species; SMR, Sensorimotor rhythm; TCA, Tricarboxylic acid cycle; TMS, Transcranial magnetic stimulation; VNS, Vagus nerve stimulation; RNS, Responsive neurostimulation.

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2.1.1. How the brain uses ketone bodies (KB) as an energy source? . . . 953
2.1.2. Mechanisms underlying antiepileptic potential of ketogenic diet . . . 953
2.2. Modified Atkin's diet (MAD) therapy . . . 955
2.3. Anaplerotic diet . . . 955
3. Neuromodulation therapy . . . 957
3.1. Vagus nerve stimulation (VNS) . . . 957
3.2. Responsive neurostimulation therapy (RNS) . . . 957
3.3. Transcranial magnetic stimulation (TMS) therapy . . . 957
4. Complementary therapies . . . 958
4.1. Biofeedback therapy . . . 958
4.2. Music therapy . . . 959
5. Conclusion . . . 959
CRediT authorship contribution statement . . . 960
Declaration of Competing Interest . . . 960
Acknowledgement . . . 960
References . . . 960

1. Introduction

Epilepsy is the 4th most common neurological disorder and described as a brain condition characterized by a long-lasting predisposition to epileptic seizures (Fisher et al., 2014). Epilepsy is treated with commonly available antiseizure drugs (ASDs) either as a monotherapy or in the combination of two or more drugs. About one-third of epilepsy patients have intractable epilepsy, also referred to as "refractory" or "uncontrolled epilepsy." ILAE (International League Against Epilepsy) explained drug-resistant epilepsy as "failure of adequate trials of the two tolerated and appropriately chosen and used ASDs schedule (either as monotherapy or combination) to achieve sustained seizure freedom" (Kwan et al., 2010). In these patients, combination therapy of > 2–3 drugs fail to show any therapeutic response; hence, referred to as intractable. Various hypotheses or mechanisms are proposed behind the development of drug-resistance in epilepsy such as transporter hypothesis, alteration of target hypothesis, gene variant hypothesis, and remodeling of neural network (Tang et al., 2017; Kwan et al., 2011). Transporter hypothesis which states that overexpression of the multi-drug resistant transporters leads to resistance because these transporters throw the drugs out of the cell hence keeping them away from their site of action. The target hypothesis states that alteration or modification in the target cellular regions (ion-channels or receptors) leads to the development of resistance against the antiepileptic effect of the target drug. Gene variant hypothesis postulated that changes in the respective genes that regulate either pharmacokinetic or pharmacodynamic behavior of the drug cause or show resistance to the antiseizure drugs (ASDs). Moreover the neural network hypothesis assumes that seizure-induced neuromodulation also triggers the remodeling of the neuronal networks and as a result downregulation of the physiological antiseizure system which hinders the ASDs from reaching the target neuronal region (Kwan et al., 2011; Tang et al., 2017). In various refractory (or intractable) epilepsy cases, dietary therapy remains effective for reducing incidences of seizures in children (Miranda et al., 2012) and as well as in adolescents and adults (Klein et al., 2010). Approximately 50–60% reduction in seizures is observed in dietary manipulated children, with a ketogenic diet (KD) treatment (Nei et al., 2014). Along with KD, an anaplerotic diet has also shown promising results in ameliorating the metabolic anomalies of the disease. In addition to metabolic therapies, brain stimulation therapies have proven efficacies in the management of epilepsy and improvement of quality of life. Among the renowned brain stimulation therapies are; (1) vagus nerve stimulation (VNS) which is an FDA approved therapy procedure for pharmacoresistant epilepsy and has a beneficial effect on cognitive parameters, (2) transcranial magnetic stimulation (TMS) therapy has shown therapeutic potential in epilepsy and can also serve as a biomarker for the diagnosis of epilepsy (Kimiskidis, 2016), and (3) Responsive neurostimulation therapy is also an FDA approved procedure for intractable epilepsy. Complimentary therapies comprise biofeedback therapy that empowers the patient to normalize its abnormal EEG patterns, and music therapy where listening to Mozart's music has proven helpful in controlling the epileptiform discharges (Hughes et al., 1998). This review article segmented into three parts. In the first part, the impact of metabolic therapy on the brain and its counteracting mechanism in pharmacoresistant epilepsy has been elaborated. In the second part of the article, all the efficacy of available brain modulation therapies are highlighted, then in the third part, complementary therapies are discussed (see Tables 1 and 2).

Table 1
A summarized data about therapeutic indication, adverse effects, and contraindication of Ketogenic diet.

Indication	Undesirable effects	Contraindications
Dravet syndrome	Early-onset complications;	Pancreatitis
Doose syndrome	Hypoproteinemia	Liver failure
Lennox-Gastaut Syndrome	Hyperuricemia	Disorders of fat metabolism
Juvenile-myoclonic seizures	Hypertriglyceridemia	Primary carnitine deficiency
Infantile spasms	Hepatitis	Porphyria
Glut-1 deficiency	Dehydration	Pyruvate-carboxylase deficiency
Temporal lobe epilepsy	Aspiration	Carnitine translocase deficiency
Frontal lobe epilepsy	Pneumonia	
West's syndrome	*Late-onset complications*;	
Pyruvate-dehydrogenase deficiency	Osteopenia	
Angelman syndrome	Nephrolithiasis	
	Hydronephrosis	
	Iron-deficiency anemia	

References (Baby et al., 2018; Kass et al., 2016; Kossoff et al., 2018; Luat et al., 2016; Peng et al., 2019; Stenger et al., 2017; Zhang et al., 2016).

2. Metabolic therapies

2.1. The ketogenic diet (KD)

Classic ketogenic diet KD (CKD) includes a high proportion of fats, an adequate amount of proteins, and low content of carbohydrates. Most of CKD is available with 4:1 ratio of fats to protein and carbohydrates 0.85–90% of energy comes from fat and the remaining 10–15% from carbohydrates and protein. The other modified variants of the ketogenic diet are modified Atkin's diet (MAD), medium-chain triglyceride diet (MCT), and low glycemic index

Table 2
Comparative difference between the classic ketogenic-diet (CKD), Modified Atkin's diet (MAD), and Triheptanoin diet about composition, usage, and mechanism.

Classic Ketogenic diet (CKD)	Modified Atkin's diet (MAD)	Triheptanoin-based diet (Anaplerotic)
The first use reported in the 1920s.	The first use reported in 2002.	The first use reported in 2002.
About 90% of energy comes from fats and remaining from proteins and carbohydrates.	About 10–20 g carbohydrates/day allowed.	It allows approximately 35% of the daily caloric regimen from triheptanoin.
Restricted in amounts of fluids, carbohydrates, and proteins.	Less-restrictive	Less-restrictive
Requires hospitalization for initiating the therapy.	It does not require hospitalization.	Simply added to the normal diet.
It induces its action by providing alternative fuel to the brain.	Like CKD, by providing an alternative energy source to the brain it exerts its action.	By boosting-up the TCA-cycle, it exerts its effect.

References (Baby et al., 2018; Calvert et al., 2018; Kossoff and Dorward, 2008; Rezaei et al., 2019; Wehbe and Tucci, 2019).

treatment. The fundamental purpose of these variants is to increase palatability and adherence to the dietary regimen (Ye et al., 2015). From the time of Hippocrates, it is known that fasting has a beneficial effect on reducing the frequency of seizures. In the 1920s Wilder at Mayo Clinic (USA) observed that fasting exerts its antiepileptic effect through ketosis. So, to simulates the body's metabolism during fasting, Dr. Wilder developed a ketogenic diet (KD) for patients with epilepsy (Wilder, 1921). However, after the discovery of phenytoin, the interest in this dietary regimen declined. In the early 1980s, KD had undergone its revival. Dr. John Freeman of John Hopkin's Hospital played an influential role in reviving the use of KD, especially in pediatric patients with refractory epilepsy (Freeman et al., 2007). From the last 20 years, this non-pharmacologic therapeutic option undergoes a revival, particularly in patients having refractory epilepsy. Because these patients are resistant to two or three ASDs and there are less than 5% chances of freedom from seizures by adding other ASDs (Williams and Cervenka, 2017). Accordingly, in these resistant patients, manipulation with KD proves beneficial in reducing seizures frequency. KD is a high-fat diet with low carbohydrate content. The human central nervous system (CNS) does not use fat as primary fuel but when we do not consume carbohydrates for approximately three to four days, then this condition enforces our CNS to find alternative energy sources (Kim et al., 2019). The ketogenic diet induces the production of ketone bodies and changes metabolism from glycolysis to beta-oxidation. Muscles and other tissues utilize fatty acids as a primary energy source, and β-oxidation of these fatty acids causes production of Acetyl-CoA which is metabolized by mitochondria into ketone bodies. Ketone bodies can cross the blood–brain barrier (BBB) and hence can be consumed by the brain as an alternative energy source.

2.1.1. How the brain uses ketone bodies (KB) as an energy source?

The brain uses glucose as the primary fuel for driving out energy but other substrates can be used by the brain when their adequate levels are present in the blood. For example, acetate, β-hydroxybutyrate, pyruvate, fructose diphosphate, lactate, and acetoacetate are such substrates (Sokoloff, 1973). The brain uses various ketone bodies like acetoacetate and β-hydroxybutyrate as an alternative source of energy during ketotic states, e.g., during fasting or when an individual is consuming a diet rich in fats and restricted in carbohydrates. Randle originally described the utilization of secondary metabolizing substrates as an energy source other than glucose in 1963 (Randle, 1963). When the level of KB in the blood rises to 4 mM, then these ketone bodies meet approximately 70% of the brain energy demand (Owen et al., 1967). These conditions lead to increased oxidation of long-chain fatty acids (LCFA) into KB by the liver. The conversion of fatty-acids by the liver is necessary as LCFA is not able to cross the blood–brain barrier. The brain contains specific enzymes like succinyl-CoA that convert ketone bodies into acetyl-CoA, a step mandatory for utilization of ketone bodies as a metabolic fuel. Carnitine (water-soluble amine) is responsible for the transportation of LCFA across mitochondrial membrane for β-oxidation. β-oxidation is a process through which fatty acids are metabolized into acetyl-CoA. It is proposed that the metabolism of fatty acids will decrease in carnitine deficiency, thus reducing the anti-seizure effect of the ketogenic diet. However, many ASDs (like valproic acid) reported to deplete the level of carnitine (El Mously et al., 2018; Linek, 2019). The liver generates KB but is not able to utilize it as an energy source because of the deficiency of enzymes required for the metabolic conversion of KB (Sokoloff, 1973). This acetyl-CoA subsequently enters into the TCA cycle (tricarboxylic acid cycle or Krebs cycle), inside the mitochondria where oxidative phosphorylation of acetyl-CoA generates ATP and CO_2 as by-products (Auvin, 2016). The overall depictive summary KD, metabolism, and end products presented in Fig. 1.

2.1.2. Mechanisms underlying antiepileptic potential of ketogenic diet

Scientific studies have clinically demonstrated that adequate seizure control by ketogenic diet is mediated with the amount of ketonemia produced. It has been established that seizures are controlled progressively with the initiation of therapy i.e. within 1–3 weeks, because of constantly increasing levels of ketone bodies in the blood (Rho et al., 2002), and this ketotic effect subsides when the patient consumes glucose. In 1933, Keith observed in rabbits that acetoacetate protects against thujone-based seizures (Keith, 1933). Later, it has been shown that β-hydroxybutyrate block seizure activity in epileptic mice (Kim et al., 2015). Various studies have indicated that KD is more efficacious in infants or children (Rho et al., 1999) because of age-related modifications in the expression of monocarboxylic acid transporters, which are responsible for the transportation of KB across the BBB (Morris, 2005; Pierre and Pellerin, 2005). And another factor is that as compared to children, adults show poor compliance with KD therapy. Following are the main mechanisms responsible for antiepileptic effects of KD;

a) *Increase in GABAergic neurotransmission:* Many antiseizure drugs produce their effect by increasing the inhibitory activity of GABA. It has been proposed that ketogenic diet control seizures by increasing the synthesis of GABA and altering the metabolism and transport of glutamate. Yudkoff et al. have shown that the ketotic state alters the metabolism of amino acids (glutamate and aspartate) in both glial cells and neuronal cells (Yudkoff et al., 2005). Normally glutamate can be either converted into GABA or transformed into aspartate by a reaction that utilizes oxaloacetate. As KD induces metabolic changes and causes oxaloacetate to condense with the acetyl-CoA along with incorporation into the Krebs cycle. Hence, depriving the availability of oxaloacetate to convert glutamate into aspartate. So, more and more glutamate is metabolized into GABA (Yudkoff et al., 2005). A study conducted by Dahlin et al. in children with intractable epilepsy, who were fed with KD for about 4 months, found that there is no significant change in the level of glutamate; however, the concentration of GABA in CSF is increased (Dahlin

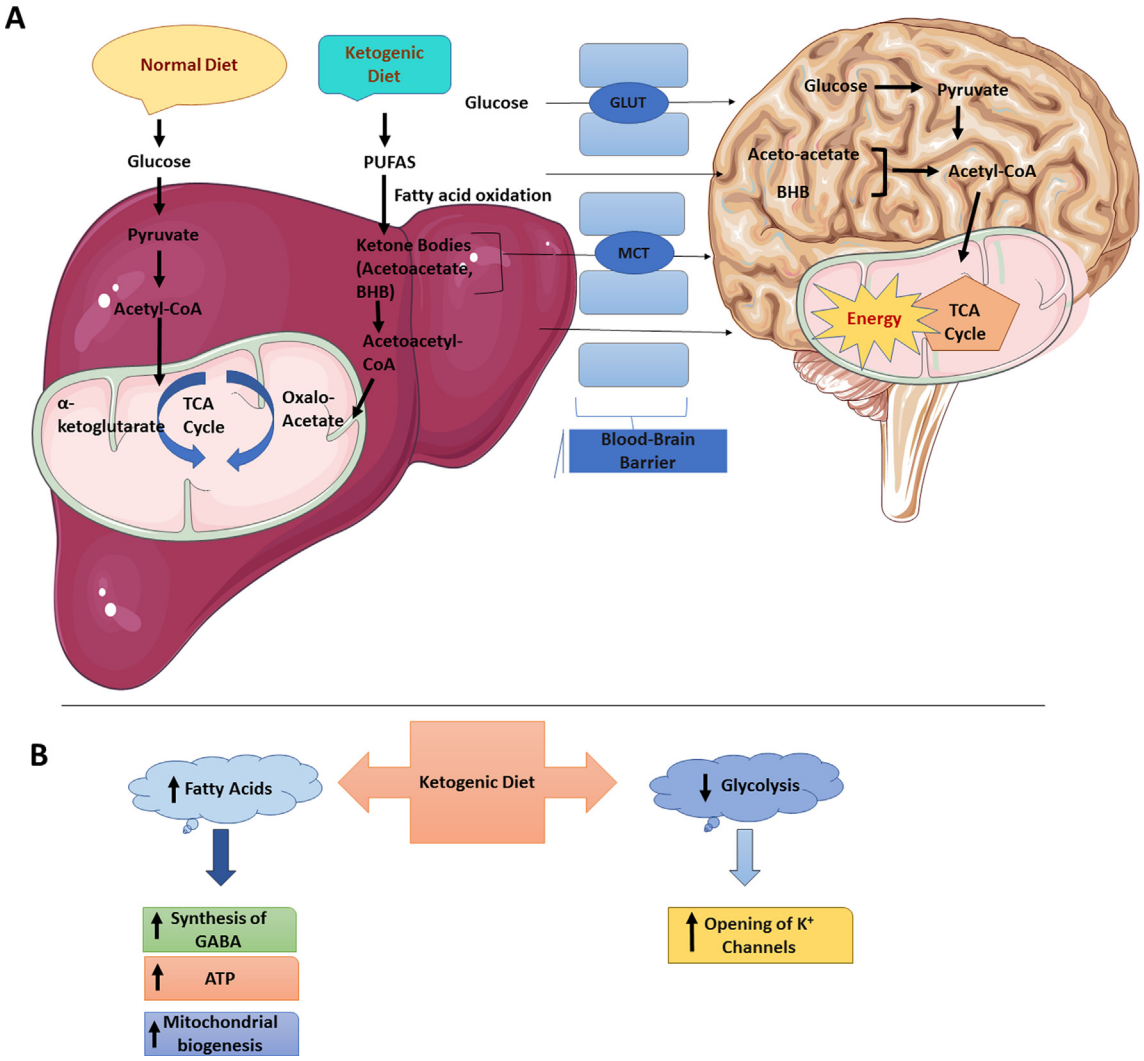

Fig. 1. Metabolic fate and antiepileptic effects of ketone bodies **A**. Normally, glucose is used as a metabolic energy source and converted to pyruvate which is later transformed into Acetyl-CoA in the mitochondria and pass through the TCA cycle for the generation of ATP. But when the level of fatty acids is high then ketone bodies i.e., generated in the liver transformed into aceto-acetyl CoA. Then this aceto-acetyl CoA alternatively incorporated into the TCA cycle to produce ATP. These ketone bodies can pass through the blood–brain barrier employing transporters MCT and are utilized to produce ATP for meeting the energy demands of the brain. **B**. ketogenic-diet leads to an increase in the level of fatty acids and decreases the process of glycolysis in the brain. Alteration of these biochemical pathways result in various possible antiepileptic effects such as increase synthesis of GABA (ketone bodies are precursors for the synthesis of neurotransmitters), enhanced synthesis of ATP which increase the production of adenosine which itself have antiepileptic effects, increase mitochondrial biogenesis cause decreased production of ROS and also increase the opening of K^+-channels.; TCA cycle = tricarboxylic acid cycle; ATP = adenosine triphosphate, MCT = monocarboxylic acid transporters, BHB = β-hydroxybutyrate, ROS = reactive oxygen species, glut1 = glucose transporters.

et al., 2005). Another study conducted in rats fed with a ketogenic diet for about three weeks observed an increased level of glutamate and glutamine in the brain (Bough et al., 2006), as these neurotransmitters then utilized for the synthesis of GABA.

b) *Adenosine:* Several lines of studies have shown that adenosine possesses antiepileptic activity owing to the activation of A_1R (adenosine receptors) in the brain that inhibits the glutaminergic system. Another action of A_1R is that it causes hyperpolarization of the neuronal membrane by the opening of K^+-channels (Dunwiddie and Masino, 2001). Ketogenic diet results in increase formation of ATP (a precursor for the formation of adenosine) and thus, increasing the level of adenosine which subsequently surge activation of A_1R. Masino and colleagues have shown further than adequate ketogenic diet consumption results in increase stimulation of A_1R with a decrease in incidences of seizure frequency (Masino et al., 2012).

c) *Opening of ATP-sensitive Potassium (K_{ATP}) channels:* Another potential mechanism by which ketone bodies (KB) or ketogenic diet (KD) induce antiepileptic activity is via activation of K_{ATP}. Glycolysis is inhibited by consuming ketogenic diet and ketone bodies are metabolized by mitochondria and thus, giving alternate sources of ATP. This metabolic shift decreases the production of ATP by the process of glycolysis. Various membrane-proteins are associated with glycolysis and ATP is compartmentalized between cell membrane. Several intracellular pumps utilize ATP generated by the process of glycolysis for maintaining ion concentration. This K_{ATP} also utilizes glycolytic ATP and is linked between metabolism and neuronal excitability. Increased intracellular ATP actively blocks K^+ channels (active state) thus increases neuronal excitability. While during metabolic deprivation states (i.e. during ischemia or hypoxia) these K^+ channels remain passively open. Furthermore, it has been observed that by adding either acetoacetate or BHB to brain slices of mouse

reduces neuronal excitability rate which is mediated by the opening of K^+ channels. The mechanism behind the opening of K^+ channels are the reduced intracellular levels of ATP and also activation of the G-Protein (Lutas and Yellen, 2013). Furthermore, akin type of K_{ATP} is present in pancreatic β-cells that maintain a hyperpolarized state, and their regulation via increase blood glucose levels after meals alter the level of insulin release through the modulation of Ca^{++} channels that input in the depolarization (Bennett et al., 2010). This K_{ATP} also has a burst of activity in dentate granules of the hippocampus and respiratory neurons (Tanner et al., 2011).

d) *Mitochondrial biogenesis and reactive oxygen species:* Changes in production of reactive oxygen species (ROS) and mitochondrial metabolism are the key pathological factors involved in the development of epilepsy, and KD affects both phenomena. KD augments the cellular energy reserves by increasing the generation of ATP mainly by causing an increase in mitochondrial biogenesis. It is well known that KD increases the number of mitochondria in cells of the brain because a supplemental number of mitochondria is required for the production of ATP from fats, however, in case of glycolysis the high number of mitochondria are not required as the initial process of glycolysis takes place in the cytoplasm. KD also reduces oxidative stress by increasing the production of reduced glutathione (GSH) from mitochondria. This reduction in oxidative stress is an important adaptive mechanism because a decrease in glutathione level is supposed to occur in epilepsy (Rogawski et al., 2016), primarily due to increased oxidative stress in patients with epilepsy (Mueller et al., 2001). By acutely applying ketone bodies to slices of the brain increases the activity of an enzyme catalase in response to hydrogen peroxide (H_2O_2). It is well known that KD deploys its neuroprotective effect mainly by reducing the oxidative stress at the level of mitochondria (Kim et al., 2010). Another probable mechanism by which KD mitigates ROS production by increasing the expression of mitochondrial uncoupling proteins (UCP). UCP is co-linked with Co-Enzyme Q and regulates the production of ROS. It is also proposed that fatty acids present in KD stimulate the production of transcription factors that would enhance the expression of UCP (Rogawski et al., 2016).

e) *Polyunsaturated fatty acids (PUFAS):* When the patient receives a high-fat diet, it promotes the oxidation of fatty acids and alters the level of PUFS in the body. It has been known that PUFAS affects various ion channels e.g. it blocks Na^+-channels and Ca^{++}-channels and causes the opening of K^+ channels, thus producing antiepileptic effect (Vreugdenhil et al., 1996). PUFAS also reduces seizures by affecting PPAR (peroxisome proliferator-activated receptor) that controls the transcription of numerous genes that affect metabolism and energy. Fenofibrate, a substrate for PPAR, has been shown to have antiepileptic activity (Porta et al., 2009). However, the effect of the ingestion of PUFAS on anti-seizure activity is still controversial.

f) *Glucose restriction:* KD with a restricted carbohydrate diet also gives a neuroprotective effect. It was reported in a study that the administration of 2-D-deoxy glucose (2-DG), an analog of glucose that does not undergo glycolysis, to adult rats for continuous seven days prevented them from the neurotoxic effect of kainate (an excitotoxic). It was identified by the authors that 2-DG protects the cell against cell death provoked by glutamate or ROS. 2-DG treatment also induces the expression of stress-responsive proteins that guards the cell against oxidative stress (Gasior et al., 2006; Lee et al., 1999).

2.2. Modified Atkin's diet (MAD) therapy

MAD is a less restrictive version of the classic KD therapy, but is efficacious for controlling seizures. This MAD therapy induces ketosis in the same way as classic KD but with less restriction (Kossoff et al., 2006). The composition of MAD is such that approximately 65% of calories come from the fats as compared to classic KD which contains 90% of fats. In MAD initially ~ 10–20 g of the carbohydrates allowed. Carbohydrates in all forms are allowed as compared to the low-glycemic index diet which only allows carbohydrates having glycemic index less than 50 (Kossoff and Dorward, 2008). This MAD therapy is feasible to use as compared to CKD. Because the former allows the patient to take the unrestricted amount of the fluids, fats, and proteins hence, it is more compliant. Another benefit of MAD is that it does not require hospitalization and can be started as an out-patient service because it is tolerable and has fewer side effects (Park et al., 2018). A study conducted by Atkin's foundation has reported that approximately 65% of the patients have a 50% reduction in the number of seizures. A similar study conducted in Korea has reported similar findings of about 50% reduction of seizures in 43% of patients and > 90% decrease in the frequency of seizures in about 36% of patients (Kossoff and Dorward, 2008). It was concluded from the recent metanalysis that KD and MAD do not vary significantly in terms of reducing the seizure frequency at month 3 and month 6, with reductions of approximately $\geq$ 50 percent and $\geq$ 90 percent respectively (Rezaei et al., 2019). The latest study has shown that MAD interacts significantly with the ASDs and reduces their serum concentration as compared to that of the pre-diet data value (Kverneland et al., 2019). However, a large data study is required before concluding any interaction between dietary and medication therapy. There are reduced chances of cardiometabolic risk factors with MAD therapy compared with the former dietary regimen (de Souza Neves et al., 2020). Only minor side effects observed like headache, gastrointestinal symptoms, and weakness. Since some of the MAD studies indicate that a strict first month increases effectiveness, a rational approach would be to continue with the KD and then later turn to the MAD (Kossoff et al., 2013).

2.3. Anaplerotic diet

Anaplerosis is the act of replenishing the substrates of the TCA cycle. The anaplerotic agents increase the level of ATP, maintain the potential gradient across the neuronal membrane by providing the $NADH/H^+$ and increase neurotransmission by providing intermediates for the synthesis of inhibitory neurotransmitter. It is well known that the deficit of the TCA-cycle intermediates causes hyperexcitability (Willis et al., 2010).

It is known since decades that epilepsy is a chronic disorder of the brain which occurs due to various pathological causes i.e., an imbalance between inhibitory and excitatory neurotransmitters, genetic alterations, inflammation and due to metabolic anomalies in the brain (like the malfunctioning of the glycolytic cycle, TCA cycle, ETC (electron transport chain). It was an early belief that energy depletion tends to occur during seizure activity and consequently to cause neuronal injury. By using PET (positron emission tomography) after administration of the ^{18}F-fluorodeoxyglucose, it was observed that hypermetabolism tends to occur throughout seizures and hypometabolism in between the seizures (Tan et al., 2015). Due to which abnormalities in the energy balance observed in the epileptic brain. ATP deficiency is particularly observed in the epileptic zone as ATP is required for maintaining a potential gradient across the neuronal membrane. $NADH/H^+$ that is produced during the TCA cycle maintains a potential gradient (Kovac et al., 2013). Glucose consumption is increased during seizures because of increased demand but its metabolism does not increase propor-

tionately in between the seizure events. Neurotransmission is increased during seizures due to which not only the metabolic load increases, because of an increase in the reuptake and clearance of neurotransmitters which requires ATP, but also the depletion of the TCA cycle intermediates and its metabolic derivatives (neurotransmitters) occurs. Oxaloacetate and α-ketoglutarate that are the reactants of the TCA cycle are also precursors for the synthesis of various neurotransmitters like GABA, glutamate, and aspartate. Due to the diminution of the TCA cycle reactants there is a decrease in the production of $NADH/H^+$ and $FADH_2$ which depletes the ATP stores and ultimately compromises the ATP-dependent neuronal activities.

For overcoming the ATP deficit during seizures, a different approach is followed that is by supplementing the body with the substrates that will eventually increase ATP synthesis. Therefore, supplementing the body with ATP yielding substances such as glucose, lactate, pyruvate, and with other intermediates of the TCA cycle (like α-ketoglutarate, succinate, oxaloacetate, malate and fumarate) leads to *anaplerosis* i.e., it causes de novo synthesis of the TCA cycle substrates (Baby et al., 2018).

Pyruvate is the end-product of glycolysis that pass through the TCA cycle by converting to acetyl-CoA. It also replenishes the TCA cycle (anaplerosis) through carboxylation catalyzed by an enzyme pyruvate carboxylase by converting it to oxaloacetate, and this anaplerotic pathway followed naturally. Studies have reported that intraperitoneal administration of 250–500 mg per kg of pyruvate in rats, reduced the death rate in chronic seizures. Similarly, pyruvate administration (preferentially as Na-pyruvate) exerted a propitious effect in patients with Leigh syndrome by reducing the occurrence of seizures (Koga et al., 2012). Na-pyruvate when given with vitamin C and vitamin E ameliorated the mitochondrial impairment and reduced the seizures in mice (Simeone et al., 2014). Many studies have reported the beneficial effects of the addition of these metabolites into diets e.g. in case of cyanide poisoning, α-ketoglutarate is administered to decrease the seizures. Similarly, supplementation with either oxaloacetate or α-ketoglutarate reduced the seizures in mice that occur due to kainic-acid. Reports have shown that succinate supplementation reduced seizures (McDonald et al., 2019) in the rats following pentylenetetrazole administration (Yue et al., 2002).

A well known anaplerotic agent such as Triheptanoin is a medium-chain triglyceride containing three uneven 7-carbon atoms fatty-acid chains. It crosses the double-membrane of mitochondria and undergoes β-oxidation, thus converted into acetyl-CoA and propionyl-CoA. This latter one is transformed into methyl malonyl-CoA and ultimately into succinyl-CoA which is an anaplerotic substance (Wehbe and Tucci, 2019). On the other hand, heptanoate used for the synthesis of 5-carbon containing fatty-acids will ultimately transformed into ketone-bodies having 5-carbon atoms i.e., β-ketopentanoate and β-hydroxypentanoate. These ketone bodies can cross the blood–brain barrier and are used as a source of energy in the absence of glucose (Gu et al., 2009). A recent study has reported that supplementation with triheptanoin simulates the effects of ketogenic-diet even in the presence of standard carbohydrates level (Fogle et al., 2019; Wehbe and Tucci, 2019). Replenishing of TCA-cycle intermediates augments the syn-

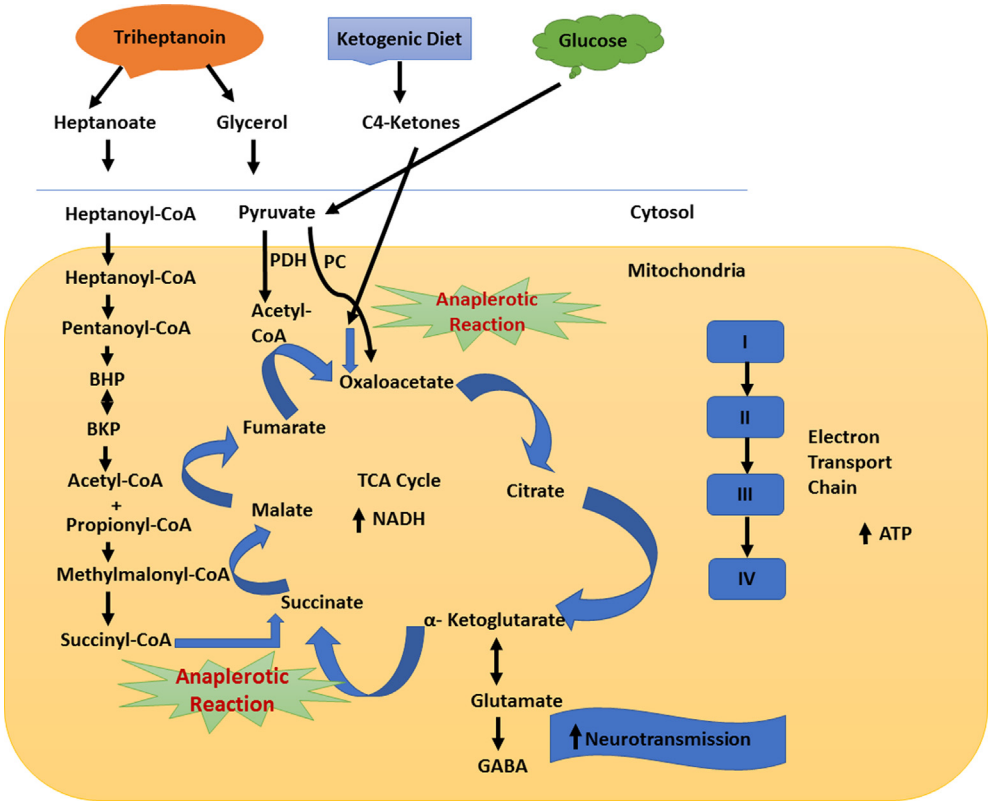

Fig. 2. Anaplerotic effect of Pyruvate, Triheptanoin, and Ketogenic diet. The pyruvate metabolized into acetyl-CoA by an enzyme pyruvate dehydrogenase which later condenses with the oxaloacetate to form citrate. Furthermore, pyruvate can be metabolized into the oxaloacetate directly by enzyme pyruvate carboxylase i.e., an anaplerotic reaction. On the other hand, triheptanoin metabolized into heptanoate and glycerol. Later, heptanoate converted into propionyl-CoA and acetyl-CoA. Then propionyl-CoA converted into succinyl-CoA which is an anaplerotic agent. And keto-diet metabolized into C_4-ketones which then converted into acetyl-CoA which then replenish the TCA cycle. When there is increased formation of TCA intermediates through anaplerosis then, there is an increase in neurotransmission as these TCA cycle intermediates are precursors for the formation of neurotransmitters. Triheptanoin (anaplerotic agent) by replenishing the TCA intermediates could increase the level of ATP. Hence keeping the neuronal membrane potential stable and decreases the neuronal firing rate. PC = Pyruvate carboxylase, PDH = Pyruvate dehydrogenase, BHP = β-hydroxypentanoate, BKP = β-ketopentanoate.

thesis of ATP which essentially causes the stabilization of membrane potential and contributes to the anticonvulsant mechanism of the triheptanoin and substrates of the TCA-cycle as shown in Fig. 2. Besides its anaplerotic effect, studies have shown that triheptanoin also enhances the utilization and oxidation of glucose in the epileptic brain (McDonald et al., 2019). In various metabolic disorders, most likely in patients with GLUT-1 and pyruvate carboxylase deficiency, this triheptanoin based diet has shown promising results in ameliorating the metabolic abnormalities of the disease (Mochel, 2017; Wehbe and Tucci, 2019). Only some of the side effects relating to the gastrointestinal system like diarrhea and bloating are observed (Borges et al., 2020).

3. Neuromodulation therapy

3.1. Vagus nerve stimulation (VNS)

VNS used as a non-pharmacological treatment in patients of intractable epilepsy. This stimulation therapy is suggested for Lennox-Gastaut Syndrome, atonic and tonic seizures, Tuberous-sclerosis complex associated seizures, multifocal epilepsy (Giordano et al., 2017), infantile spasms, and in hypothalamus hamartoma syndrome (Khawaja et al., 2017). Only those patients are eligible for VNS therapy who failed to respond to one or more antiseizure drugs and not fit for surgery. The antiepileptic effect of VNS is due to its afferent nerve endings. The afferent fibers enter medulla at a point of nucleus tractus solitarius (NTS). In turn, NTS directly innervates the nucleus of locus coeruleus (LC) which is the principal site in the brain for providing noradrenaline. Hence, NTS may control the release of noradrenaline by giving its projections to LC. In 1998, Krahl et al. showed that LC has a significant role in reducing seizures, by experimenting in rats that lesions of LC inhibits the seizure diminishing effect of the VNS that were provoked by corneal shock (Krahl et al., 1998). However, direct stimulation of LC inhibits the development of kindling seizures that occur by electrical stimulation of the amygdala. Several scientific reports have shown that stimulation mediated by VNS also causes an increase in the cerebral blood flow to many of the brain areas especially to cortex, amygdala, thalamus, hippocampus and posterior cingulate gyri cortex (Giordano et al., 2017). VNS causes an increase in the level of inhibitory neurotransmitter i.e. GABA in the cerebrospinal fluid. The density of the $GABA_A$ receptor increase in the patient receiving VNS therapy for years. So, VNS produces its antiepileptic effect by increasing the concentration of noradrenaline for an extended period ~ 80 min, by increasing the cerebral blood flow and increasing the level of GABA. In recent years, the immunomodulatory effect of VNS has been recognized. The afferent fibers activate the cholinergic anti-inflammatory pathway while the efferent fibers inhibit the release of pro-inflammatory thus mediating the anti-inflammatory effects (Aalbers et al., 2012; Sajko and Rotim, 2019).

The VNS is done by a sophisticated device comprising of a pulse generator, a lead wire with 2 platinum electrodes, a tunnelizer that is placed subcutaneously, the programming wand accompanied with software, and a hand-held magnet. The pulse generator that is placed under the left side of the chest wall sends a signal to the vagus nerve via a lead that is whirled around the nerve (Panebianco et al., 2016). The vagus nerve stimulator should be sited on the left side of the chest wall as left vagus nerve innervates the atrioventricular node (AV node) but right vagus nerve innervates the sinoatrial node (SA node) so there is a greater risk of cardiac side effects like arrhythmias and bradycardia from implantation to the right vagus nerve (Giordano et al., 2017). In VNS there is very slow onset of effects lasting months to a year.

Various side effects that are observed due to stimulation of vagus nerve stimulation are dyspnea, coughing, paresthesia, dysphagia, and hoarseness (Giordano et al., 2017; Johnson and Wilson, 2018; Panebianco et al., 2016). Various case reported the most serious cardiac events after implantation of VNS i.e., bradycardia, asystole and syncope (Kato et al., 2018). So, clinicians must consider these side effects even after years of the implantation of the stimulation device (Jaglan et al., 2020). However, VNS therapy has been employed successfully in pregnant women with no evidence of harm to the fetus (Salerno et al., 2016). Epileptic seizures affect neurodevelopment in children and lead to poor quality of life. A retrospective study conducted by Elliot et al., which included 141 children in the study, concluded that VNS is effective and well-tolerated in children less than 12 years of age as it is effective in older patients. VNS therapy is also safe for use in > 3 years of age children as evident in the study of Fernandez et al. (Fernandez et al., 2015).

3.2. Responsive neurostimulation therapy (RNS)

Formerly there are open-loop neurostimulation devices such as vagus nerver stimulation and deep brain stimulation therapy (DBS) that are pre-programmed and they do not immediately respond to the changes in electrophysiologic signals or clinical symptoms of the patients. As compared to the previously mentioned neuromodulation device, RNS (closed-loop) therapy is more effective, tolerable, and immediately modifies itself to the patient's physiological signals and its apparent clinical symptoms (Morrell and Halpern, 2016). This neurostimulation therapy can be adapted as an alternative option for intractable patients who are also not suitable or better candidates for respective surgery. Presently there are only 2 FDA approved neurostimulation devices i.e., VNS and RNS for adjunctive treatment of intractable seizures. Even though seizures are sporadic so a therapy that is intermittent, or responsive and programmable (customized) seems like an attractive treatment option. It was found in several small studies that electrically induced seizures can be either shortened or terminated by giving a short burst of electrical activity at the site of epileptic discharge. The device i.e. implanted intracranially constantly observes the electrical activity of the brain via leads placed at the epileptic foci and immediately provides responsive electric stimulation at epileptic foci. FDA has approved this adjunctive therapy for patients aged $\geq$ 18 years and these patients must follow the following criteria (Ma and Rao, 2018; Matias et al., 2019);

- Resistant to the > 2 ASDs
- Frequent seizures (approximately 3 or more seizures per month in past 3 months) and have disabling seizures i.e., motor, or complex partial seizures and/or 2° generalized seizures
- Not>2 epileptogenic sites

In a study, an estimated 70% reduction in seizures was reported in patients with frontal and parietal seizures (Jobst et al., 2017). Significant improvement in the quality of life is observed in the patients receiving RNS therapy (Matias et al., 2019). This neurostimulation therapy is generally well-tolerated. The risk of infection stated to be 3.7% for each procedure. Only implantation related complications observed like hemorrhage (4.7%) and lead damage (2.6%). RNS is currently incompatible with MRI. Currently, RNS system is the only commercially available form of long-term electrocorticography. In the future, this RNS therapy may find its new application in the detection of the epileptiform activity in response to the various ASDs, which may increase its future usage and benefits (Matias et al., 2019).

3.3. Transcranial magnetic stimulation (TMS) therapy

TMS is a non-invasive tool that has shown substantial effectiveness in seizure control to many non-responsive patients to avail-

able ASDs. This technique is being used for stimulating the brain motor cortex as first demonstrated by Barker in 1980s (Barker et al., 1985) and based upon the principle of Faraday's law i.e., when an alternating current of short-duration passed through a coil, it generates a varying magnetic field that in turn passes through the skull and produces an electric field (secondary-current) which stimulates or depolarizes the neurons of the cortex (Carrette et al., 2016; Reithler et al., 2011). TMS produces a short-lasting current (100–400 μs) that passes through the coil and generates varying magnetic field (1.5–2 T) that produces an electrical field of approximately 200 V/m (Reithler et al., 2011). The generated magnetic field decays as distance increases so the secondary current produced by the magnetic field also decreases hence, there will be limited cortical excitability (Carrette et al., 2016). Different magnetic coils are used for achieving varying degrees of stimulation and depth. A set of 8 coils for the stimulation purpose is widely used. Similarly, the coils of other shapes are also available; for example, H-shaped coils for stimulating deeper brain regions. The excitation of neurons causes the generation of an action potential and this effect can be measured indirectly by muscle evoked potential (MEP) with the help of EMG electrodes, if the area of stimulation is the primary motor cortex (Nitsche and Paulus, 2009).

There are various mechanisms through which TMS suppress the epileptic discharges or modify the neuronal activity i.e., by modifying the excitability of the neurons, modifying the function of the ion-channels, altering the synaptic transmission and also by interrupting the ephaptic effects (communication between two neurons using an electrical field that is generated locally) (Ye and Kaszuba, 2019). The stimulator, capable of delivering the trains of closely spaced magnetic pulses to a single scalp site (Wassermann, 1998) is designated as rTMS. Due to the appearance of different physiological effects in different individuals and also due to safety concerns, a line of distinction should be made between low-frequency rTMS (less than or equals to 1 Hz) and high-frequency rTMS (>1 Hz) (Tassinari et al., 2003). High frequency rTMS results in cortical excitability which causes long-term potentiation (LTP) while low frequency rTMS results in cortical diminution which causes long-term depression (LTD) effect. High-frequency rTMS is responsible for inducing seizures in patients as well as in healthy individuals. This harmful or undesirable effect is associated with the stimulus of high intensities, trains of longer intervals, or shorter duration between two train intervals. If focal rTMS of frequency $\geq$ 5 Hz is delivered to the hand area of M_1 (primary motor cortex), it results in the spread of excitation in an individual that is preceded by the increase in the size of MEP in the proximal muscles of the hand. These findings indicate that the high frequency or suprathreshold rTMS can induce the M_1 excitability depending upon the duration and intensity of the train. Both excitatory and inhibitory effects on M_1 motor cortex can be produced by a high-frequency rTMS if applied at or below the RMT intensity (Maeda et al., 2002) (resting motor threshold i.e., the lowest or minimum intensity of a stimulus that is required to provoke an MEP of approximately 50 μV; in a half of 10–20 successive trials while the muscle is at rest (Rossini et al., 2015)). Studies have shown that the low-frequency rTMS might control drug-resistant epilepsy by reducing either the seizure numbers or the epileptiform abnormalities (Fregni et al., 2006; Schiller and Bankirer, 2007). Schiller et al. had demonstrated that in rats, low-frequency electrical stimulation prevents the development of interictal epileptic discharges. Hsu et al. had conducted a meta-analysis of the literature and concluded from their review that low-frequency rTMS has a favorable effect on reducing seizures particularly in patients with cortical dysplasia or either with the neocortical epilepsy (Hsu et al., 2011). Another similar study shows a 30% reduction in the frequency of seizures (Cooper et al., 2018). Small-scale pilot studies have shown the efficacy of rTMS as evident in the literature. However, large-scale controlled multicentered studies are still required for proving the long-term effectiveness and also for clearly elaborating its mechanism of action (VanHaerents et al., 2020).

Along with its therapeutic applications, TMS is also used as a diagnostic tool in epilepsy (Kimiskidis, 2016) i.e.; for determining the action of the antiepileptic drugs on the cortical excitability (TMS-EMG), localization of the epileptogenic region non-invasively (TMS-EMG), probing cortical excitability in patients with epilepsy (TMS-EMG), pre-surgical evaluation of the eloquent cortex (TMS-EMG) and as a biomarker of epilepsy (TMS-EEG). Low-frequency rTMS is regarded as safe for usage in both the healthy and neurologically-impaired individuals. While high-frequency rTMS can lead to different neuropsychological effects, mood impairment, transient hormonal abnormalities, accidental seizures, cognition impairment, pain, and headache (Tassinari et al., 2003; Wassermann, 1998). Drugs that lower the threshold of seizures should be avoided by the individuals undergoing rTMS like tri-cyclic antidepressants, ganciclovir, ketamine, theophylline, alcohol, MDMA, foscarnet, and gamma-hydroxybutyrate (GHB) (Rossi et al., 2009).

However, studies are required for defining the safety of TMS in pediatrics as developmental-regulated changes in CNS may be prone to TMS related adverse events (Rossi et al., 2009). Magnetic field decays rapidly with the distance covered, hence there are lesser chances that TMS exerts any direct effect on the fetus. Studies have reported the safety of TMS in pregnant women with no harmful effect on infants however, pregnant women should not undergo direct stimulation in the lumbar region of the spine unless compelling cause for diagnosis is present (Rossi et al., 2009).

4. Complementary therapies

4.1. Biofeedback therapy

Biofeedback therapy is a non-pharmacological form of treatment that causes the patient to learn their physiological functions of the body (such as skin temperature, heart rate, brain waves, and the muscle tension) and to bring them under voluntary control for healing and cure (Yucha and Montgomery, 2008). In this therapy, various devices employed to provide information about various physiological processes of the body to the patient e.g. electroencephalogram (EEG), electrocardiogram (ECG), electrodermograph, electromyogram, etc.

'*Neurofeedback therapy*' is a type of biofeedback therapy that is solely based on the principle of operant conditioning. In this therapy patient learns how to regulate the abnormal electrical activity of the brain by providing him with the real-time EEG data (Nigro, 2019). A therapist empowers the patient to optimize its abnormal wave patterns through trainings. This therapy is now widely being used in several disorders of the brain like attention-deficit hyperactivity disorder, epilepsy, learning disabilities, cognitive disorders like Alzheimer's disease, and as well as in anxiety and depression (Sterman, 2000).

Learning behavior of the patient depends on the principle of *operant conditioning* e.g. each time the patient's EEG patterns complies with the desired EEG; the patient will be rewarded in the form of gaining scores in the game (Egner and Sterman, 2006), or a ball passing through the loop and when the patient does not give the desired response he will be punished in the form of failure in the game (Miller, 1978). Trained patients increase their EEG frequency bands in the range of 12–15 Hz; this frequency band termed as *sensorimotor rhythm* (SMR). Sterman was the pioneering person who demonstrated that the up-regulation of the SMR frequency band is associated with a reduction in seizures (Sterman,

2000). In 1974, he conducted the first neurofeedback-training in humans. Four patients were involved in the study conducted for six to eighteen months; who were taking three sessions per week. A significant reduction in seizures was observed in these patients (Egner and Sterman, 2006; Sterman, 2000). Finley et al., also observed a reduction in the frequency of the seizures in a 13 yr-old patient when he was trained to increase its SMR (Finley et al., 1975). A condition-reversal study performed by Lubar et al., in patients with epilepsy reported that training of the patients to increase their EEG frequency in the range of 12–15 Hz resulted in a decrease in seizures. Alternatively, during the phase of reversal these subjects were trained to decrease their 12–15 Hz frequency that increased the rate of seizures (Lubar et al., 1981; Walker et al., 2005).

In addition to operant conditioning of SMR, slow cortical potentials (SCP) that originate from the cortex are involved in the excitation of the underlying membrane of the cortex and hence involved in seizures. These SCP lasts from several 100milliseconds to seconds. The SCP-negative shifts are observed during and before the development of seizures whereas positive shifts of SCP are involved in inhibition of seizures (Rockstroh et al., 1993; Tan et al., 2009). Rockstroh et al., reported in a study that SCP self-control through the successive biofeedback training can affect the seizures rate (Rockstroh et al., 1993). Kotchoubey et al. conducted a controlled study by dividing the patients into three groups, and compared the SCP group with the MED group (taking newer medications) and RES group (respiratory feedback). The SCP group and the MED group achieved a similar reduction in the frequency of the seizures (Kotchoubey et al., 2001). Both the SMR or SCP neurofeedback training is effective in decreasing the rate of seizures that are neither controlled by other treatment options. Nowadays, qEEG (quantitative electroencephalography) is used to evaluate and quantify the response to neurofeedback therapy. In this, the patient's qEEG compared with the archived qEEG (i.e., obtained from the age-matched healthy individuals' population group).

Neurofeedback therapy has been greatly aided by the recent advances in technology (computer-aided software and applications) that facilitate observing feedback response with greater efficiency and ease. Neurofeedback therapy is considered a safe therapy but some patients may observe mild side effects such as tiredness, headache, anxiety, difficulty in falling asleep, etc. Some of these effects are observed only if therapy is not supervised by a certified and licensed health professional (Hammond, 2007). Lubar et al. have also observed in a double-blind study that improper therapy can also aggravate the symptoms instead of improving in certain cases (Hammond, 2007; Lubar et al., 1981).

4.2. Music therapy

Music therapy recognized as an alternative non-invasive and non-pharmacological therapy for treating epilepsy. The efficacy of music in controlling seizures was first reported by Fernandez et al., by observing in an experiment that a frequency of 1000 Hz is effective in reducing the seizures interval by using the EEG recordings (Liao et al., 2015). Besides that, different studies have reported that listening to Mozart music can affect individual intellectual abilities, which is well-known as the "Mozart effect". This effect was first described by Rauscher et al. (Lin et al., 2011) and the effect of Mozart music in treating epilepsy was described by Hughes et al. in 1998. They demonstrated that Mozart K.448 (i.e., Mozart's Sonata for 2 pianos in D Major K.448) can exert an acute effect on the patient's epileptiform activity in both focal and generalized seizures. As evident from various trials that Mozart's music is also effective in various epileptic syndromes such as in LGS (Lennox-Gastaut Syndrome). Mozart's music is also efficacious in acute condition i.e. in non-convulsive status epilepticus, seizures that were not previously controlled by two anti-seizure medications (Kuester et al., 2010). In addition to Mozart K.448, Lin et al. observed that Mozart K.545 is also effective in reducing the epileptiform discharges. Similarly a Mozart effect is observed from Yanni (acroyali/ standing in motion), a song by Greek composer, because of similar melody, tempo, and structure (Grylls et al., 2018). Various theories define the possible mechanism underlying the antiepileptic effect of Mozart's music. As given follows;

a. Theory of Resonation: Many scientists have proposed that listening to Mozart's music triggers the organization of neurons in the cerebral cortex. Mountcastle was the first one to observe that the neocortex of the brain exists in the form of column cells (Mountcastle, 1957). The immature neurons move from the germinal neuroepithelium (progenitor cells) and organized into cell columns (Rakic, 1988). Hughes et al. found that Mozart's music has a specific organized structure and pattern that is arranged similarly to the cerebral cortex structure (Hughes et al., 1998). Due to which they both (Mozart music and cerebral cortex) resonate with each other and this resonation causes normalization of any suboptimal functioning of the brain cortex.
b. Adaption of Dopaminergic Pathways: Dopamine plays a neuroprotective role in epilepsy because reduced binding of dopamine to its receptors is observed during different types of epilepsy e.g. in juvenile and frontal lobe epilepsy. It had been studied that listening to music enhances the dopaminergic activity in basal ganglia i.e., upregulation of its D2 receptors and also stimulation of the release of dopamine (Liao et al., 2015; Maguire, 2012) Mirror neurons: Different authors have suggested the involvement of mirror neurons in the antiepileptic effect of music. Mirror neurons are discharged when a person performs any motor action like dancing etc. while listening to the music (Liao et al., 2015; Molnar-Szakacs and Overy, 2006). Authors believe that these mirror neurons facilitate our neuronal activity by linking the auditory stimuli with our motor cortex. And these alterations of the motor system by the auditory stimuli are also observed during transcranial magnetic stimulation therapy and in other behavioral studies (Buccino et al., 2005; Maguire, 2012).

This music therapy is effective in following epileptic syndromes and conditions (Liao et al., 2015);

a. Lennox-Gastaut Syndrome, Intractable or drug-resistant epilepsy in children, benign epilepsy, refractory status epilepticus, refractory gelastic seizures;
b. For the prevention of sudden death due to epilepsy, due to its effect on the cardiovascular system and respiration rate (Koelsch and Jäncke, 2015; Metcalf et al., 2019; Scorza et al., 2008);

By the meta-analysis of the literature, Dastgheib et al. have reported that 84% of the patients undergo a significant decreased in epileptic discharges after listening to Mozart's music (Dastgheib et al., 2014). Mozart's music is the most common music type and it has shown effectiveness in different human and animal trials. Hughes et al. have found that in addition to Mozart's music; Liszt's and Haydn's music also exhibits similar antiepileptic properties because of a similar structure of the melody (Hughes, 2002).

5. Conclusion

Epilepsy is a noncommunicable chronic disease of the brain that affects nearly 50 million individuals worldwide of all ages. Around

80% of those individuals live in low- or middle-income countries with limited healthcare facilities. According to estimates, only 70% of the patients with epilepsy can live seizure-free life, if it is properly diagnosed and managed with ASDs. Almost one-third of the patients fail to respond to the existing antiseizure drugs and their disease progresses to intractable epilepsy. The life of these patients is severely affected and the risk of premature death is significantly higher in such patients as compared to the general population. As these patients cannot be managed by the available pharmacological treatment options so, alternative non-pharmacological therapies and methods are employed to take care of such individuals. Some of these therapies such as ketogenic diet and VNS stimulation have been well-characterized and approved for the management of patients with epilepsy while the benefits of other therapies such as biofeedback therapy and music therapy are still being explored. It is important to mention here that 80% of the world's population lives in low-income countries as mentioned above, making it very difficult to explain the use of TMS / VNS / Mozart therapy for such people. In this review, we have summarized these alternative therapies and evaluated their therapeutic potential through available studies. The analysis of these studies has revealed that besides identifying new molecules for the treatment of epilepsy, there is a need to extend our knowledge about these non-pharmacological options to optimize the seizure control in intractable epilepsy.

CRediT authorship contribution statement

Faleh Alqahtani: Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Imran Imran:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition. **Hafsa Pervaiz:** Writing - original draft, Writing - review & editing. **Waseem Ashraf:** Writing - original draft. **Nadia Perveen:** Writing - original draft. **Muhammad Fawad Rasool:** Writing - original draft. **Abdullah F. Alasmari:** . **Metab Alharbi:** Writing - review & editing. **Noreen Samad:** Writing - review & editing. **Saleh Abdullah Alqarni:** Writing - review & editing. **Salim S. Al-Rejaie:** Conceptualization. **Mohammed Mufadhe Alanazi:** Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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