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Review

Exploring the Rationale for the Use of the Ketogenic Diet in the Treatment of Mental Health Disorders

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Abstract

***Background*:** The ketogenic diet (KD) was developed in the 1920s as a treatment for pediatric epilepsy and is emerging as a possible treatment option for certain mental health disorders. There is a link between certain mental health disorders and epilepsy, suggesting some commonality among underlying mechanisms.

***Methods*:** The literature relating to mental disorders and the KD is sparse. The authors attempt to a narrative review of the existing literature to show that there may be validity to studying the KD as a treatment for certain mental health disorders.

***Results*:** Various types of mitochondrial dysfunction and impaired oxidative metabolism have been identified in many mental health disorders (bipolar disorder, major depressive disorder, autism, schizophrenia, and others). Mitochondrial deficits may affect neuroplasticity and cause synaptic dysfunction, which could change brain structure and function in a way that might affect behavior. The KD has been associated with epigenetic changes in the genes associated with mitochondrial function. Chronic oxidative stress and inflammation have also been implicated in mental health disorders and may be reduced by the KD. The KD regulates

glutamatergic transmission and may initiate extracellular changes as well, in a manner similar to pharmacological agents used to stabilize moods. The KD may be difficult for patient adherence and has been associated with many and potentially severe adverse effects. The role of the KD in addressing treatment-resistant pediatric epilepsy is established and epilepsy is comorbid with a number of mental health conditions.

***Conclusions*:** There is a paucity of literature on this subject and there is no robust clinical evidence in support of the use of the KD for treating mental disorders but there are indications that the KD can reduce systemic inflammation, improve cerebral mitochondrial metabolism, and enhance endogenous antioxidation, all of which may be helpful in treating certain mental health conditions. The KD is also associated with serious health risks and clinicians must weigh risks versus benefits.

Keywords

Diet; ketogenic diet; ketosis; mental health disorder; mitochrodrial dysfunction

1. Introduction

Developed in the 1920s as a treatment for pediatric epilepsy, the ketogenic diet (KD) is a high-fat, low-protein/low-carbohydrate diet, often described in terms of the ratio of lipids to non-lipids, ranging from 2:1 to 6:1. [1] The 4:1 KD showed more antiepileptic benefit in a study of 76 patients with refractory childhood epilepsy compared to the 3:1 KD diet, although patients with fewer gastrointestinal (GI) symptoms better tolerated the latter. [1] A Cochrane review of randomized clinical trials showed that the KD showed promising results for treating pediatric epilepsy, albeit with certain GI side effects. [2] With the advent of anticonvulsant therapy in the late 1930s, the KD fell out of favor until it regained recognition in the 1990s as a potential treatment option for drug-refractory epilepsy. [3] Less rigorous variations on the KD are popular among consumers for weight loss.

In addition to its role in the treatment of pediatric epilepsy, the KD is emerging as a possible treatment option for certain mental health conditions. There is a well-established link between certain mental health disorders and epilepsy, [4] which suggests that there may be some commonality in terms of underlying mechanisms. Evidence suggesting that certain mental health disorders may have an underlying metabolic mechanism suggest the possible role of diet-based therapy. The KD is controversial in that it is associated with potentially severe side effects and the safety of the diet must be considered for each individual patient and balanced against potential benefits. From a scientific point of view, it is important to better understand if and how the KD might address symptoms of certain mental health disorders if only to better understand the mechanisms of these disorders.

The objective of this narrative review is to survey the literature for the current status of research on the possible role of the KD in the treatment of certain mental health disorders.

2. Materials and Methods

This is a narrative review exploring the rationale behind the possible use of the KD in the treatment of certain types of mental health disorders. The KD has known risks and safety must be considered before embarking on this diet for mental health or other conditions.

3. Results

3.1 The Brain's Response to the Ketogenic Diet

The KD causes ketones (acetone, acetoacetate, and beta-hydroxybutyric acid) to increase [5] and glucose to deplete, causing the body to enter ketosis. Restricted intake of carbohydrates promotes fatty acid oxidation and subsequent conversion into ketone bodies, which then acts as the primary energy source in place of glucose. Evidence of ketosis can be obtained by a simple urine test. (Diet-induced ketosis should be distinguished from ketoacidosis caused by starvation, alcohol toxicity, diabetes, and other conditions; the latter is a potentially life-threatening condition. [6]) Ketone bodies are efficient energy producers. [7]

The human brain requires large amounts of energy for housekeeping functions, maintaining resting and action potentials, and for synaptic transmissions. [8] As much as half of all energy in the brain is dedicated to housekeeping tasks. [9] The brain's constant or cyclical release of neurotransmitters and neuropeptides consumes energy as well. [9] Despite these high demands, the brain stores comparatively low reserves of glucose and lipids in comparison to other tissues composed of myocytes and adipocytes, respectively. With a typical Western diet, the brain depends almost exclusively on glucose for its energy while the body's periphery may use fats as well as glucose for fuel. The "selfish brain theory" posits that when glucose supplies are low, the brain prioritizes its need for glucose above all other areas of the body. [10] Eating in accordance with the KD forces the brain to use ketone bodies as its main source of energy, diverting it away from glucose and launching various enzymatic cascades that fundamentally change how the brain metabolizes fuel. It has been proposed that an increase in acetone levels in the brain might reduce seizures due to the anticonvulsant effects of acetone. [11]

3.2 The Brain, the Ketogenic Diet, and Mental Disorders

To meet its consistent high demand for energy, the healthy brain relies on glucose as its primary source of fuel, using mitochondrial functions to convert glucose into the usable energy form of adenosine triphosphate (ATP). Various degrees of mitochondrial dysfunction and impaired oxidative metabolism have been identified in certain mental health disorders including bipolar disorder, depression, autism, schizophrenia, and others. [12] Oxidative stress appears to be one of the primary contributors and possible cause of mitochondrial dysfunction. More specifically, the lack of oxidizing agents lowers the availability of electronic acceptors during oxidative phosphorylation, thereby diminishing the electrochemical gradient needed to drive ATP production in the mitochondria. Mitochondrial deficits may play a role in neuroplastic and synaptic dysfunction, may change brain structure and function, and, in that way, could affect behavior. [13] Chronic oxidative stress is present in certain mental disorders, which are likewise

associated with both chronic inflammation and a high level of circulating proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). [12]

Mitochondrial dysfunction, generally classified as either a cytopathy or an encephalomyopathy, arises due to mutations in the mitochondrial DNA or nuclear DNA, the pathways of which are currently being elucidated. [12, 14] In a healthy state, the antioxidative efforts of glutathione (GSH) and thioredoxin help clear out reactive oxygen species (ROS) and reactive nitrogen species (RNS), both of which result naturally from the body's oxidative phosphorylation process. [15] When GSH and thioredoxin are unable to clear ROS and RNS, chronic oxidative stress develops. This may be exacerbated by the activation of certain inflammatory cells, such as microglia, which may stimulate the further production of ROS and RNS. [16] In turn, oxidative stress launches transcription factors, such as NF-Kβ and activated Protein 1, which produce proinflammatory cytokines and other species, which then activate other cells to produce more ROS and RNS in the form of superoxide, nitric oxide (NO), and peroxynitrite. [17, 18] This forms the "autotoxic loop" [18] in which chronic inflammation is maintained as a result of proinflammatory cytokines. [19] See Figure 1. In this way, chronic oxidative stress is linked with chronic systemic inflammation. [18] Once chronic inflammation is well established in the periphery, it is hypothesized that inflammatory signals to the brain are transmitted based on the observation that systemic inflammation can lead to chronic neuroinflammation. [20, 21] Proinflammatory cytokines may use any of several pathways to the brain, including the vagus nerve, endothelial cells of the blood-brain-barrier, or possible transport by way of circumventricular organs, such as portions of the pituitary gland for example, which lack a barrier to the brain. [22, 23]

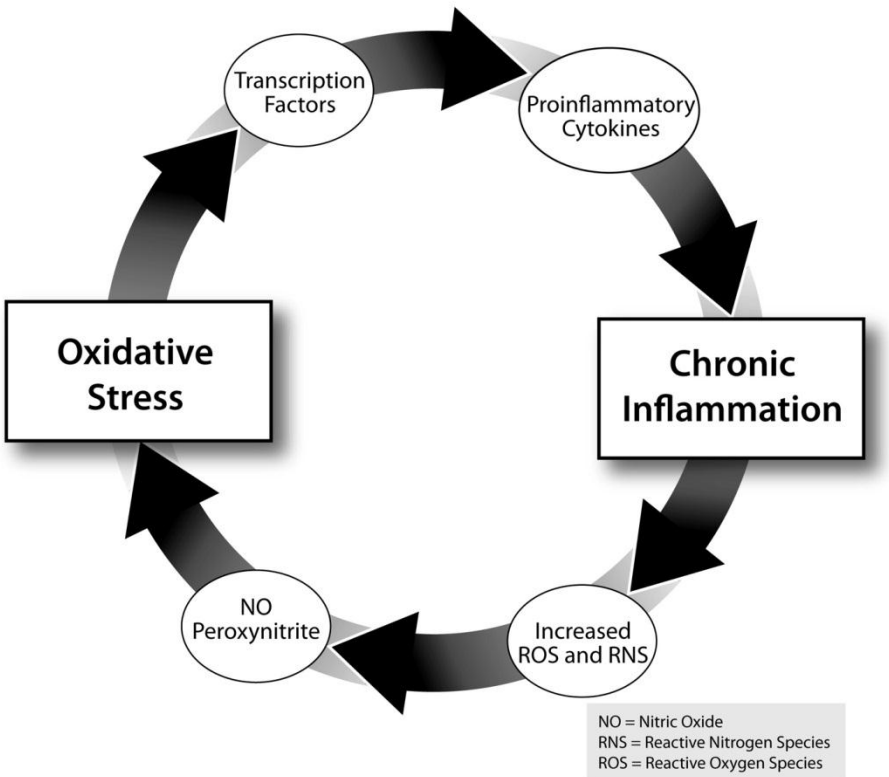

Figure 1 The autotoxic loop demonstrates the link between oxidative stress and chronic inflammation (Art courtesy of Todd Cooper).

The KD has been or is being explored for a potential role in the treatment of many conditions, including amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and others. [5] The KD has been proposed for autosomal dominant polycystic kidney disease. [24] The underlying assumption is that cellular energy status is involved in many disorders and aberrant energy production has been associated with heart disease, [25] aging, [26] epilepsy, [27] Alzheimer's disease, [28] and cancer. [29] Energy production and metabolic pathways may likewise be involved in mental health disorders, such as bipolar disorder, depression, schizophrenia, [30] autism spectrum disorder, [31] and attention deficit hyperactivity disorder. [32] Circulating ghrelin is available as acyl ghrelin and des-acyl ghrelin which play different roles. In a murine study, des-acyl ghrelin has an anxiogenic effect on non-stressed animals, but under stress, the effect changes to an anxiolytic effect. [33] The KD decreases the levels of plasma of both acyl and des-acyl ghrelin in pediatric patients. [34] The role of ghrelin in psychiatric disorders, in particular anxiety, is being elucidated. [35]

The KD regulates glutamatergic transmission and controls glutamatergic toxicity by inhibiting vesicular glutamate transport vesicles. [36] The KD may also increase gamma-aminobutyric acid (GABA) and GABAergic transmission, which has been associated with anxiolysis. [37] The KD has been associated with epigenetic changes in genes associated with mitochondrial function [38-40] but further work is needed to elucidate the effects of the KD on mitochondrial biogenesis. Cerebral hypometabolism is a characteristic of several mental disorders, including depression. [41] Ketosis may also cause certain extracellular changes which would decrease intracellular sodium levels, thereby steadying the resting state of the action potential, which is a property of many mood-stabilizing agents. [41]

3.3 Mental Disorders and Brain Energy Metabolism

Mental disorders in the United States and other countries remain prevalent conditions, a substantial burden on the healthcare system, and a source of personal distress and societal loss. Safe, effective, broadly reliable treatments for these disorders have proven elusive and many such disorders resist treatment. In fact, treatment-resistant depression (TRD) is a well-known condition, which is by definition intractable. Even with diligent efforts and the advantages of modern healthcare, many patients with mental health disorders never achieve symptomatic remission. [42] While the KD has been suggested for its role in treating mental health disorders, there are comparatively few studies, no large controlled trials, and relatively little scientific attention. [5]

The Research Domain Criteria (RDoC) by the National Institutes of Mental Health (NIMH) offers a new framework for the study of mental health conditions by defining specific cognitive and motivational domains of brain function that allow mental health conditions to be more systematically evaluated. [43] RDoC attempt to blend neurobiological with psychological factors, [44] and have been challenged for their "biological fundamentalism." However, the RDoC have led to a neurobiological exploration of anhedonia, appetite depression, sleep disorders, and suicidal ideation. For example, recent work by Hesmati and Russo suggest that anhedonia, a core symptom of major depressive disorder (MDD), may be associated with dysregulation of the mesolimbic dopamine (reward) circuit. [45] This theory has recently been extended to anhedonia in schizophrenia, although the latter's mesolimbic dopamine dysfunction is characterized more by disorganization rather than the deficiency typical in MDD. [46, 47] This has led to the recognition

that many mood disorders have a systemic component or even a systemic foundation. A few associations have been unexpected, such as obesity and MDD (metabolic syndrome affects both populations at disproportionately high rates). [48] Thus, the symptoms of MDD may be explicable and controllable when approached systemically, which opens the door to potential dietary interventions.

There is a paucity of literature relating to human studies of the KD and various mood disorders and even preclinical research is limited. [5] Yet there are reasons to think the KD may have some promise in the treatment of some of these disorders, for example treating anxiety, depression, bipolar disorder, autism spectrum, attention deficit disorder, and schizophrenia spectrum disorders. Mental health disorders and epilepsy are often comorbid and appear to share some of the same underlying mechanisms. Anecdotal evidence and clinical observation have reported that when the KD is used for control of epilepsy in a patient with mood disorders, the mental health improves as well. Some of these d disorders will be discussed briefly below. Medication therapy is available for many of these disorders with varying degrees of safety and effectiveness. See Tables 1, 2, and 3.

3.3.1 Anxiety Disorders

Various anxiety disorders are identified in the literature: generalized anxiety disorder, social anxiety disorder, and panic disorder. People with generalized anxiety disorder are excessively anxious about daily events in multiple domains of life (home, work, finance, social), typically manifesting in physical symptoms (stomach pain, restlessness, headaches, and so on). [49] On the other hand, panic disorder is episodic and may occur with or without a distinct trigger. Panic attacks are characterized by a trigger and the rapid onset of intense fear, typically lasting about ten minutes. Physical symptoms (trembling, dyspnea, tachycardia, dizziness, nausea, and others) may accompany the episode. People with panic disorder may become overly preoccupied with their condition and live in such fear of another episode that they modify their behavior and limit their social interactions to avoid putting themselves at risk of a new episode. [49] There is considerable overlap in the incidences of various anxiety disorders and epilepsy, in that the lifetime incidence of anxiety is 11.2% in people without epilepsy and 22.8% in people with epilepsy. [50] The 12-month prevalence of generalized anxiety disorder among U.S. adults (age range 18 to 64 years) is 2.9% with a lifetime prevalence of 7.7% for women and 4.6% for men. In contrast, the 12-month prevalence for panic disorder among U.S. adults is 3.1% and lifetime prevalence is 7.0% for women and 3.3% for men. [51]

Cognitive behavioral therapy is the first line of treatment for anxiety disorders, which may be supplemented by pharmacological therapy, such as with benzodiazepines. [49] While the etiology of anxiety disorders remains to be elucidated, evidence suggests anxiety can be associated with unusual brain activitiy, variations in brain structure, altered neuronal processes, and genetic factors. [52] Functional magnetic resonance imaging (fMRI) studies show that anxiety directs blood flow toward the ventromedial prefrontal cortex and hippocampus. [53]

Table 1 Short overview of mental disorders and their most commonly prescribed pharmacological treatments. Note that off-label prescribing is not unusual in the pharmacological treatment of mood disorders. [41, 50, 54-62, 63-65]

Mental Disorder	Lifetime Prevalence in US	Medication Therapies	Effectiveness	Comments
Generalized anxiety disorder	7.7% (women) and 4.6% (men)[50]	Benzodiazepines more effective than SSRIs [54]	Long-term more effective than short term[55]	Benzodiazepines are associated with tolerance and dependence and must be used under close clinical supervision
Social anxiety disorder	Up to 12% [56, 57]	SSRIs, SNRIs, TCAs Benzodiazepines not recommended	2-6 wk before onset of action (SSRI, SNRI) Both SSRI and SNRI are more effective than TCA. [58, 59]	Withdrawal symptoms possible with SSRI discontinuation Some SSRIs and SNIRs inhibit CYp450 enzymes and may have drug-drug interactions
Panic disorder	7.0% (women) and 3.3% (men). [60]	SSRIs and/or Benzodiazepines	2-6 wk before onset of action (SSRI, SNRI)	Benzodiazepines are associated with tolerance and dependence
Major depressive disorder	13.23% [61]	Antidepressants: SSRIs SNRIs TCAs Atypical antidepressants MAOIs	2-6 wk before onset of action (SSRI, SNRI)	Often comorbid with other mental health conditions and/or substance use disorder MAOIs should not be taken in a diet high in tyramines, thus patients should avoid aged or strong cheeses and cured meats Some may be contraindicated during pregnancy; some antidepressants carry black-box warning for suicide risk
Bipolar disorder	4.4% [62]	Carbamazepine Valproate Lithium	Carbamazepine and valproate can be effective in treating hypomania and mania; lithium is effective in treating severity and frequency of mania and may help prevent bipolar depression and decrease risk of suicide	Gabapentin and pregabalin are also anticonvulsants, but they do not appear to be effective for this condition[41]

Autism spectrum disorder	1 in 59 children in the USA[63]	Antipsychotics: Risperidone Apripiprazole (Abilify) Antidepressants Stimulants Methylphenidate (Ritalin) Anticonvulsants	Only symptomatic relief	Prevalence has increased 15% in two years; the gender gap (boys have autism more frequently) is narrowing
Attention deficit hyperactivity disorder	8.7% [64]	Stimulants Methylphenidate (Ritalin) Amphetamines		69.3% of those diagnosed take medications[64]
Schizophrenia spectrum	<1% [65]	Antipsychotics 2nd generation such as aripiprazole, clozapine, quetiapine, risperiodone and others 1st generation Chrlopromazine Fluphenazine Haloperidol Perphenazine		Electroconvulsive therapy (ECT) may be used for non-responders to drug therapy

MAOI=monoamine oxidase inhibitor

SNRI=serotonin-norepinephrine reuptake inhibitor

SSRI=selective serotonin reuptake inhibitor

TCA=tricyclic antidepressant

Table 2 Commonly prescribed pharmacological therapies and current indications. Note that there is frequent off-label prescribing of drugs for mental health disorders. [66-68] The list is alphabetized by drug name. Brand names are those used in the U.S.; these drugs may be marketed under other brand names in other markets.

Agent or Class	**Brand names in USA**	**Indications, Off-label Use, Currently Being Studied**
Apiprazole	Abilify	Autism spectrum disorder Bipolar disorder Major depressive disorder Schizophrenia Off-label: Generalized anxiety disorder, social phobia, attention-deficit hyperactivity disorder, dementia, eating disorders, insomnia, obsessive-compulsive disorders, personality disorders, post-traumatic stress syndrome, substance use disorder, Tourette's syndrome
Atypical antidepressants (bupropion, trazodone, mirtazapine, nefazodone, vilazodone, vortioxetine)	Wellbutrin, Desyrel or Oleptro, Remeron, Serzone, Viibryd, Brintellix	Major depressive disorder
Benzodiazepines (alprazolam, cobazam, clonazepam, clorazepate, chlordiazepoxide, diazepam, estazolam, lorazepam)	Xanax, Onfi, Klonapin, Tanxene, Librium, Valium or Diastat, Prosom, Ativan	Generalized anxiety disorder Panic disorder
Carbamazepine	Tegretol	Bipolar disorder
Chlorpromazine	Thorazine Largactil	Schizophrenia spectrum
Clozapine	Clozaril	Schizophrenia spectrum
Fluphenazine	Prolixin	Schizophrenia spectrum
Gabapentinoids (gabapentin, pregabalin)	Neurontin, Lyrica	All off label Autism spectrum disorder. The literature reports on the use of pregabalin in GAD, bipolar mania, and some forms of treatment-resistant manifestations of bipolar disorder
Haloperidol	Haldol	Schizophrenia spectrum
Lithium	Eskalith, Lithane, Lithobid, Lithonate, Lithotabs	Bipolar disorder

MAOIs (isocarboxazid, phenelzine, selegiline, tranylcypromine)	Marplan, Nardil, Emsam, Parnate	Major depressive disorder
Methylphenidate	Ritalin, Concerta, Daytrana, others	Autism spectrum disorder Attention deficit hyperactivity syndrome
Perphenazine	Trilafon	Schizophrenia spectrum
Quietiapine	Seroquel	Bipolar disorder Schizophrenia spectrum
Risperidone	Risperdal	Autism spectrum disorder Schizophrenia spectrum Bipolar disorder
SNRIs (desvenlafazine, duloxetine, venlafaxine, milnacipran, levomilnacipran)	Pristiq Cymbalta Effexor Savella Fetzima	Social anxiety disorder Major depressive disorder Autism spectrum disorder
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	Celexa, Lexapro, Prozac, Luvox, Paxil, Zoloft	Generalized anxiety disorder Social anxiety disorder Panic disorder Major depressive disorder Autism spectrum disorder
Stimulants (amphetamine, amphetamine/ dextroamphetamine, dextroamphetamine, dexmethylphenidate, lisdexamfetamine,	Adderall, Dexedrine, Dyanavel, Evekeo, ProCentra, Vyvanse, Ritalin, and others	Attention deficit hyperactivity syndrome
TCAs (amitriptyline, clompramine, desipramine, doxepine, imipramine, Maprotaline, nortriptyline, protriptyline, trimipramine)	Elavil, Anafranil, Norpramine, Sinequan, Tofranil, Ludiomil, Pamelor, Vivactil, Surmontil	Social anxiety disorder Major depressive disorder Autism spectrum disorder
Valproate	Depakote	Bipolar disorder

GAD=generalized anxiety disorder

Table 3 Frequently prescribed pharmacological treatments for various mood disorders and safety considerations. Most of these drugs carry at least one black-box warning.

Drug	Side Effects	Black-box Warnings	Rare Side Effects, Comments
Apiprazole	Weight gain, vision disturbances, nausea, vomiting, constipation, drooling, headache, dizziness, drowsiness, restlessness, anxiety, insomnia, and common cold symptoms	Elderly patients with dementia-related psychosis are at an increased risk of death May increase risk of suicidality in children, adolescents, and young adults	Tardive dyskinesia Pathological gambling and other compulsive behaviors
Atypical antidepressants	Constipation, lightheadedness, dizziness, dry mouth	May increase risk of suicidality in children, adolescents, and young adults	Bupropion should not be used in people with seizures or with eating disorders; nefazodone should not be used in people with liver dysfunction; vortioxetine may increase risk of bleeding Serotonin syndrome
Benzodiazepines	Drowsiness, confusion, trembling, impaired coordination, vision disturbances, feelings of depression	None	Tolerance, dependence Withdrawal symptoms
Carbamazepine	Nausea, vomiting, dizziness, drowsiness, swollen tongue, loss of balance/coordination. Rash or skin reactions (which may become life threatening) may occur in 1 to 6 out of 10,000 new users.	Serious dermatological reactions, aplastic anemia and agranulocytosis,	May be contraindicated with certain antidepressants
Lithium	Hand tremors, increased urination, thirst, diarrhea, vomiting, drowsiness, muscle weakness, loss of coordination	Lithium toxicity which can occur at doses near the therapeutic range	Serotonin syndrome
MAOI	Nausea, diarrhea, constipation, headache, drowsiness, insomnia, dry mouth, dizziness, and lightheadedness	May increase risk of suicidality in children, adolescents, and young adults	Potential food interactions Potential drug interactions Serotonin syndrome Withdrawal-like symptoms upon abrupt discontinuation
Methylphenidate	Nervousness, agitation, anxiety, insomnia, stomach pain, loss of appetite, weight loss, and nausea	Can be abused and lead to dependence	Dependence

Risperidone	Headache, dizziness, tremors, agitation, anxiety, depressed mood, diarrhea, constipation, upset stomach, weight gain, "common cold" type symptoms (stuffiness, sneezing, sore throat)	Elderly patients with dementia-related psychosis are at an increased risk of death	Tardive dyskinesia, neuroleptic malignant syndrome
SNRI	Dizziness, nausea, tiredness, anxiety, agitation, insomnia, constipation, hypertension, elevated heart rate	May increase risk of suicidality in children, adolescents, and young adults	Some SNRIs inhibit CYp450 enzymes and may cause pharmacokinetic drug-drug interactions Serotonin syndrome
SSRI	Digestive discomfort, drowsiness, nervousness, agitation, sleep disorders, heart rhythm disorders (prolonged QT interval), and somnolence. Serotonin toxicity may occur at elevated doses or in combination therapy with other drugs that increase serotonin levels.	May increase risk of suicidality in children, adolescents, and young adults	Many of these drugs are not approved for use in pediatric patients with certain disorders Some SSRIs inhibit CYp450 enzymes and may cause pharmacokinetic drug-drug interactions Serotonin syndrome
Stimulants (amphetamine-based drugs)	Sleep problems, decreased appetite, delayed growth (in children), headaches, stomachaches, rebound irritability, tics, and moodiness	High potential for abuse, administration for prolonged periods of time may lead to drug dependence Risk of serious cardiovascular events and sudden deaths in patients with heart problems	Dependence
TCA	Blurred vision, constipation, hypotension, weight gain or loss, elevated heart rate, restlessness, dry mouth, racing heart, increased appetite, weight gain, decreased libido, and hives	May increase risk of suicidality in children, adolescents, and young adults	
Valproate	Nausea, vomiting, stomach pain, diarrhea, dizziness, weakness, headaches, tremors, blurred or double vision, sleepiness, hair loss, weight gain, and changes in appetite	Hepatoxicity; teratogenicity; pancreatitis	Can cause birth defects; contraindicated in pregnant women

GAD=generalized anxiety disorder; MAOI=monoamine oxidase inhibitor; MDD=major depressive disorder; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

It is thought that anxiety involves dysfunctional neurotransmission, in that the nervous system's healthy balance of GABA to glutamate is disrupted; glutamate causes neuronal hyperexcitability which may manifest into symptoms of anxiety and GABA acts to counterbalance these excitatory effects. [69] GABA is the body's primary inhibitory neurotransmitter and, as such, is present in high concentrations in all regions of the brain and spinal cord (about a third of all CNS neurons are GABAergic) but is not present outside of the central nervous system (CNS). GABA acts on three types of receptors: $GABA_A$, $GABA_B$ and $GABA_C$, of which $GABA_A$ is known to play a role in anxiety, epilepsy, alcoholism, and other psychiatric disorders. [70] The $GABA_A$ receptor may be modulated by the effects of endogenous neurosteroids as well as endogenous or exogenous benzodiazepines. [71]

3.3.2 Depressive Disorders

According to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) types of depressive disorder include disruptive mood dysregulation disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance-induced depression, and major depressive disorder (MDD). MDD is prevalent, one of the most severe forms of depression, and may potentially be treated with the KD. Symptoms of MDD include diminished interest in life, decreased pleasure, weight changes, insomnia or hypersomnia, fatigue, feelings of worthlessness or guilt, difficult concentrating, and suicidal ideation. The 12-month and lifetime prevalence of MDD from the DSM-5 is 5.28% and 13.23%, respectively (95% confidence interval [CI], 12.64-13.81). MDD has significant comorbid associations including substance use disorder, panic disorder, generalized anxiety disorder, and other personality disorders. [61] Depressive disorders occur frequently in people with epilepsy, with a reported prevalence of 11% to 62%. [72, 73]MDD may deteriorate into treatment-resistant depression with associated profound and clinically severe changes in neurological function as well as related dysfunction. Treatment-resistant depression lacks a consensus definition but is a recognized clinical entity. [74]

It has been observed that MDD patients have elevated levels of interleukin-1β (IL-1β), TNFα, and IL-6 which suggest both inflammation and increased macrophage activity. [75-77] There may be specific groups of MDD patients in which other types of cytokines are more dominant. [78] Oxidative stress is considered a major contributor to MDD, which leads to elevated production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which, in turn, compromise the body's antioxidative defenses. [79] MDD patients are observed to have deficient stores of vitamin E, [80] higher lipid peroxidation in the brain, [81, 82] and oxidative damage to peripherally circulating lipids. [65-70] In patients with MDD, the oxidative stress markers in the periphery have been observed to correlate to the duration and severity of the depressive disorder. [82, 84, 85] Chronic inflammation has been associated with MDD and remission of depression is characterized by a return to more normal inflammatory markers, such as cytokine levels. [86] Many diseases with an inflammatory component (such as cardiovascular disease, autoimmune disorders) or inflammatory conditions (postpartum period) have been associated with clinical depression. [87]

The KD's effect on systemic inflammation might be a partial explanation for current interest in its use in the treatment of people with MDD. A preclinical study found that rats on the KD exhibited fewer signs of depressive behavior. [88]

3.3.3 Bipolar Disorder

Bipolar disorder is a biphasic disorder in which symptoms wax and wane with alternating energy levels, which may offer the clearest observable correlation with mitochondrial energy fluctuations. For example, the manic phase of bipolar disorder is characterized by increased brain energy while the depressed phase corresponds to decreased brain energy. [89] Mitochondrial dysfunction underlies a variety of mental health conditions (autism, anxiety disorder, dementia, Down syndrome, depression, and others) and many such conditions are comorbid with each other (for example, depression and dementia). [90] Mitochondria produce the energy necessary for brain function, allow synaptic plasticity, produce important molecules (such as hormones), and oversee the housekeeping of neurotransmissions. When mitochondria malfunction, individuals may exhibit cognitive deficits, intellectual disability, mental health disorders, and/or neurodegenerative disease. [90] Bipolar patients have been observed to have a higher prevalence of mitochondrial disorders than the general population [91], abnormalities in brain and lymphocyte distribution of mitochondria as well as aberrant mitochondrial morphology. [92] In fact, mitochondrial dysfunction is emerging as a new target for drug development in the treatment of bipolar disorder. [38]

Elevated levels of C-reactive proteins have been observed in acute mania and remission phases of bipolar disorder. [93] A meta-analysis found bipolar patients had higher concentrations of tumor necrosis factor-alpha (TNFα) but not higher levels of other cytokines, such as various interleukins, transforming growth factor-beta 1 (TGF-β1) and TNF2. [94] There may be a role for anti-inflammatory agents in the treatment of bipolar disorder and certain omega-3 fatty acids, curcumin, and other substances are being investigated. [95] People with bipolar disorder have been observed to have altered levels of catalase (CAT), superoxide dismutase (SOD), and glutathione. [96] Compared to controls, people with bipolar disorder have greater lipid peroxidation, more damage to the DNA and RNA, and elevated nitric oxide (NO) levels. [97] Furthermore, evidence suggests that the severity of the disorder is correlated to the severity of oxidative stress. [98, 99] Improved oxidative defenses and reduction in oxidative stress have been linked with remission in bipolar disorder. [100]

Bipolar disorder is often treated with certain medications aimed at reducing convulsions, such as carbamazepine, valproate, and lithium. However, the anticonvulsants gabapentin and pregabalin do not appear to be effective in treating bipolar disorder. [41] Two case studies in the literature describe patients diagnosed with bipolar disorder who went on the KD and maintained ketosis for a minimum of two years, over which time their bipolar symptoms improved to the extent that they could discontinue their mood-stabilizing drug regimen. [101]

3.3.4 Autism Spectrum Disorder

The DSM-5 describes autism spectrum isorder as a neurodevelopmental disorder characterized by persistent deficits in social (verbal and nonverbal) communication and social interaction and narrowly restricted, repetitive patterns of behaviour, interests, and activities. It is diagnosed four times more often in males than females. In searching for a better understanding of the physiology associated with autistic behaviors, the bidirectional microbiota gut-brain axis has emerged as an intriguing area for research. GI symptoms and alterations in the gut microbiota frequently parallel

cerebral disorders. [102] The gut microbiome may be involved in the pathogenesis of autism spectrum disorder and is considered an important new therapeutic target. [103] In fact, the gut microbiome could play a role in the production, expression, and turnover of neurotransmitters, such as GABA, serotonin, and others. [103]

Abnormal expression of pro- and anti-inflammatory cytokines have been observed in the brain, gut, and peripheral blood of children with autism. [104-110] Likewise, disorders of the immune system have been observed in children with autism, [110, 111] along with chronic oxidative stress. [112-114] In about 30% to 50% of children with autism, particularly those with more severe forms, there is evidence of mitochondrial dysfunction. [114-117] Both metabolic and mitochondrial dysfunction underlie autism and epilepsy, although the exact relationship between autism and epilepsy remains to be elucidated. [118, 119] About 30% of children with autism have epilepsy; conversely, about 15% to 30% of children with epilepsy have autism. [120, 121] While epilepsy is not a causative factor for autism, epilepsy and autism share certain neuronal networks. [118] Genetic mutations in the $GABA_A$ receptor subunit have been identified in children with epilepsy and autism, leading to the hypothesis that dysfunctions in GABAergic signaling are a common molecular mechanism in both epilepsy and autism. [122] It has been hypothesized that the KD would provide certain neuroprotective benefits for people with autism although to date no large-scale randomized studies have been conducted. [123]

3.3.5 Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder, involving neuropsychological deficits (including working memory, self-regulation of affect, internalization of speech, and behavioral analysis) combined with a lack of behavioral inhibitions. [124] It occurs in about 29% of pediatric epileptic patients, making it the most frequently reported mental health condition among children with epilepsy. [125] There is an approximately equal sex distribution of ADHD in patients with epilepsy, but ADHD is three or more times more common for males in the general population. [126] It has been observed that when children with epilepsy went on the KD to improve their seizure symptoms, there was a marked improvement in their ADHD symptoms as well. [127] To date, most studies on the relationship of the KD and ADHD have been carried out in animals. [32, 128, 129]

3.3.6 Schizophrenia Spectrum

The DSM-5 defines schizophrenia spectrum, along with other psychotic disorders, by abnormalities in one of more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior, i.e., catatonia, and negative symptoms such as anhedonia, lack of emotional affect, and severely curtailed speech and movement. The relationship between schizophrenia and epilepsy remains to be elucidated. Neuroinflammation has been implicated in the etiology of schizophrenia [130, 131] and immunological defects have been observed in these patients. [132] The role of Th-17 cells in schizophrenia is being elucidated. [131] Chronic systemic inflammation occurs in schizophrenia and it is thought that the greater degree of inflammation and oxidative stress, the greater the degree of cognitive impairment in the first schizophrenic episode. [133] Patients with schizophrenia have oxidative damage to their DNA, [134, 135] overproduction of ROS and RNS,

decreased antioxidative defenses, [136] and oxidative stress in the brain and cerebrospinal fluid[137] as well as in the plasma and the periphery. [138-140] See Figure 1.

Mitochondrial dysfunction and energy dysregulation may play a role in the etiology of schizophrenia and schizoaffective disorder. [141] Ultrastructural abnormalities in the mitochondria have been observed in schizophrenic patients, [142] with enlarged mitochondria and morphological changes in the organelles of brain and peripheral blood cells. [143, 144] Brain energy levels can be affected in people with schizophrenia by NO's effect on mitochondrial activity, ATP production, [145] and the formation of peroxynitrite, which causes oxidative damage to mitochondrial structural proteins and enzymes as well as damage to membrane lipids. [14, 146, 147] Most pharmacological treatments for schizophrenia treatment suppress dopamine, but medications are not effective for all patients and are associated with side effects, which may be severe. [148] The majority of patients with schizophrenia are obese, [149] although the possible association of schizophrenia and obesity remains to be elucidated.

The literature reports case studies on two patients with schizoaffective disorder found symptoms decreased when the patients went on the KD, returned when they went off the diet, and decreased again with resumption of the KD. [150] One of these patients was a 33-year-old man who reported a dramatic decrease in auditory hallucinations and delusions, and an improved mood and higher energy level after three weeks on the KD. Maintaining the diet (with a few breaks when symptoms returned) allowed him to make other positive changes in his life as well, in that he was able to complete some online studies, move into his own apartment, and start dating. [150] In another case report, a 70-year-old woman experienced resolution of long-standing symptoms of schizophrenia with the use of the KD. [151] Large-scale randomized clinical trials have not been conducted for more authoritative levels of evidence. It has been proposed that the KD shifts the brain's ratio of GABA to glutamate in favor of GABA; GABA production in the brain is disrupted in schizophrenics. The shift occurs by suppressing catabolic reactions and increasing GABA synthesis. Furthermore, ketosis may activate brain astrocyte metabolism, subsequently promoting glutamate breakdown/removal while enhancing the conversion of glutamine to GABA. Thus, the KD may help increase cerebral GABA levels and, in that way, reduce schizophrenic symptoms. [152]

3.4 Safety of the Ketogenic Diet

Some may associate ketosis—the assumed and expected result of following the KD—with hyperketonemia, which can be lethal in in extreme circumstances. Pathological ketoacidosis typically occurs in patients with Type I diabetes and differs from what might be called the "physiological ketosis" induced by dietary changes like the KD. Ketogenic changes in human metabolism are unique to our species and likely exist to help humans cope with famine by decreasing glucose demand and insulin levels during periods of deprivation. The KD artificially creates such "famine" conditions while still allowing reasonable caloric intake; similar changes can be brought about by fasting for several days or stark caloric restriction. [153]

Although lifestyle changes such as major dietary modifications are thought to be relatively benign interventions, safety must still be considered. This is particularly important with the KD. Diets that restrict carbohydrates may be problematic in that they typically result in a lower intake of vegetables, grains, and fruits, all of which have recognized nutritional benefits for overall health.

[154, 155] Adverse effects of the KD include GI problems (which typically are worst in the first weeks of the diet and gradually diminish over time), hyperlipidemia, [156] and renal calculi. [157] Cardiovascular adverse effects are recognized as well, in that QT-interval prolongation on an electrocardiography (ECG) has been reported in up to 15% of pediatric patients on the KD and is potentially arrhythmogenic. [158]

The role of macronutrients in heart health remains controversial. The Prospective Urban Rural Epidemiology (PURE) study was a large epidemiological cohort study of dietary intake of 135,335 individuals in 18 nations with a mean follow-up of 7.4 years. [159] It found higher carbohydrate intake was associated with an increased risk of total mortality but not the risk of cardiovascular morbidity or mortality. A cross-sectional analysis of the PURE study (n=125,287) reported that reducing the intake of saturated fatty acids and replacing them with carbohydrates had an adverse rather than beneficial effect on serum lipid levels. [160] However, a study of 15,428 U.S. adults reported that diets both high and low in carbohydrates were associated with increased mortality and that diets the least risk was associated with diets offering a 50% to 55% total carbohydrate intake. [161] Studies about low-carbohydrate diets in general and the KD in particular are sometimes confounded by the ratio of saturated to unsaturated fat consumption (which is thought to play a potential role in making some diets healthier than others) and the limitation that studies are often short term. A meta-analysis of 40 studies (n=1,141 obese patients) reported that low-carbohydrate diets were effective in causing significant weight and body mass index (BMI) reduction, reduced systolic and diastolic blood pressure, and reduced plasma triglycerides and increased high-density lipoprotein cholesterol; all of which are considered favorable. [162] However, many of these benefits are framed within the context of obese individuals seeking weight loss and its attendant health benefits; it is not clear if these diets would have the same advantageous cardiac benefits in normoweight or underweight individuals.

Adherence to the KD can be challenging, as it demands rigorous attention to food preparation, unusual food combinations and eating patterns, large categories of restricted foods, and a limited ability to dine out. Poor or erratic adherence to the diet may diminish the depth and consistency of ketosis the patient experiences. [163] Testing strips available over the counter may be used for at-home urine tests to confirm ketosis. Overall, for motivated patients (or their caregivers) and under supervision of a physician, the KD may confer benefits on appropriate patients with certain types of mental disorders. [164] Its benefits include its neuroprotective, antioxidant, and anti-inflammatory effects on the central nervous system. [74]

Despite the possibility that the KD may be a nonpharmacological treatment modality or an adjunctive therapy for mental health conditions, studies have been few, small, and typically uncontrolled. Those studies of the KD in the literature rarely report serum ketone levels or ketone levels in urinalysis, making comparisons across studies difficult. Many mental health conditions make dieting difficult in that they are associated with mania, impulsivity, recklessness (meaning patients will likely abandon the diet), or profound apathy, while certain mental conditions may reduce appetite or trigger binge eating. The KD can be extremely demanding for patients, so adherence is likely imperfect. Clinicians must assess relative risk versus benefits for this sort of intervention in an individual patient. Comparative evaluations are challenging in that there is no "standard KD" and metrics for mental health outcomes can vary among studies. See Table 4.

Table 4 A basic overview of the standard ketogenic diet. Note that there are variations of the keto diet such as the "cyclic keto diet" and "targeted keto diet" and others which allow strictly controlled increases in carbohydrates in advance of exertion. To date, there is no universally recognized standard keto diet but the following table describes broad general rules for ketogenic eating. On the standard keto diet, 75% of calories come from fats, 20% from protein, and 5% from carbohydrates. To achieve and maintain ketosis most dieters restrict their total carb intake to 50 g/day. Dieters can also count "net carbs" which are to total carbohydrates minus the fiber; daily intake of net carbs should be 25 g/day.

Food Category	Foods to Select	Foods to Avoid
Meat	Fatty cuts of grass-fed beef, poultry, pork, lamb, organ meats	Grain-fed beef, processed meats, sausages, cold cuts, meatballs
Fish	Fish are all permitted with emphasis on fatty fish such as salmon and sardines.	Fried fish (because of breading)
Dairy	Butter, full-fat sour cream, full-fat cheeses, heavy cream. Full-fat but unsweetened yogurt.	Milk, low-fat dairy products, margarines, sweetened yogurts
Eggs	Whole eggs, yolks preferred, preferably free-range organic	Egg substitutes
Oils	Olive oil, avocado oil, coconut oil.	Avoid cottonseed, sunflower, safflower, soybean, and canola oils.
Nuts	All including nut butters.	Nut butters with sugar added such as grocery-store peanut butter
Seeds	All	Processed, sweetened seeds
Vegetables	Low-carb only such as broccoli, cauliflower, asparagus, kale, spinach, lettuce.	Avoid starchy vegetables such as potatoes, yams, sweet potatoes, peas, carrots, corn, and cherry tomatoes.
Fruits	Low-carb only such as blueberries, strawberries, raspberries, avocados.	Do not eat bananas, pineapples, grapes, apples, oranges, fruit smoothies, dried fruits.
Sugar	Artificial sweeteners are not recommended and many contain some carbs	Avoid sugar and sweeteners such as honey, maple syrup
Processed food ("junk foods")	None	Avoid all
Grains	Grains must be restricted but grains are not specifically prohibited	Grains (rice, oats, corn, flour, etc.) should be avoided, but may be eaten in very small quantities if daily carb allowance permits
Breads and starches	No bread, rolls, pasta	Avoid all
Beans	None	Avoid all
Alcohol	Hard liquor may be taken straight (tequila, whiskey, scotch, bourbon, vodka, gin, brandy) but avoid beer, wine, mixed drinks, flavored alcohols	
Beverages	Water, tea, coffee	Mixed drinks, smoothies, shakes, sweetened beverages

4. Discussion

The KD has long been recognized as a treatment option for refractory pediatric epilepsy. Its possible role in the treatment of mental disorders may be clinically helpful and suggests that epilepsy and mental health disorders share certain commonalities that may one day help elucidate the pathogenesis of these seemingly diverse and heterogenous conditions. The metabolic dysfunction apparent in both epilepsy and certain mental health disorders is intriguing. Obesity and metabolic syndrome have both been correlated with refractory mental disorders. [165] One suggested explanation for this connection is that a high BMI is associated with increased inflammation which can worsen mental disorders; obesity may also result in disturbed sleep, pharmacokinetic alterations, and reduced bioavailability of prescribed antidepressants. [166] Mitochondrial metabolism increasingly emerges as a factor in both mental disorders and epilepsy. As the KD is further evaluated for its potential benefits in the treatment of mental disorders, a clearer picture may emerge of the pathogenesis of such disorders and their relationship to inflammation, mitochondrial function, and cerebral metabolism.

The KD appears to have the capacity to reduce chronic systemic inflammation and stimulation the endogenous antioxidant defense system. [167] It appears that its anti-inflammatory effect which may be beneficial in the treatment of refractory mental disorders. [168, 169] The role of specific anti-inflammatory and proinflammatory cytokines in mood disorders and epilepsy is not yet elucidated. However, the safety of the KD must also be considered in that it is associated with cardiovascular risks, calculi, hyperlipidemia, and GI symptoms. For certain patients with treatment-resistant mental health disorders or those who find the safety and tolerability of available pharmacological therapy unacceptable, the KD may be a consideration. This topic deserves greater scrutiny as it may shed light on functional processes within the brain associated with specific mental disorders.

5. Conclusions

The KD has long been used as adjunctive therapy for treatment-resistant pediatric epilepsy. Epilepsy is comorbid with a number of mental health conditions, including but not limited to MDD, ADHD, autism spectrum disorder, anxiety disorders, and other and it has been anecdotally observed that patients on the KD with a comorbid mental health disorder achieve symptomatic relief of the latter while on the diet. Despite a lack of robust clinical evidence in support of the KD in mental health disorders, there are reasons to consider that a diet that reduces systemic inflammation, improves cerebral mitochondrial metabolism, enhances endogenous antioxidation, and reduces obesity might be helpful for treating certain psychiatric disorders.

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Author Contributions

JVP provided the original concept, broad research directions, and analysis of the results; AT provided the original concept and helped modify the research directions and provided input on the risks of the KD; JL conducted literature searches and organized the manuscript and developed the graphic for the autotoxic loop; MA and HA provided a critical review of the results and wrote sections on brain metabolism.

All authors read and reviewed the final manuscript with critical input.

Competing Interests

The authors have declared that no competing interests exist.

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