

# The use of the ketogenic diet in the treatment of psychiatric disorders

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## Abstract

**Introduction:** The ketogenic diet (KD) is a high-fat, low-carbohydrate, and moderate-protein diet that has shown benefit as a treatment in neurologic disorders and may serve as a therapeutic option in individuals with psychiatric disorders.

**Methods:** A search was conducted using EBSCOhost and PubMed databases for studies relating to ketogenic or low-carbohydrate diets and psychiatric disorders.

**Results:** A total of 32 experimental or observational studies were identified by initial search strategies, 14 of which met the criteria to be included in this analysis. Although specific diet formulations varied somewhat between studies, they all generally examined low-carbohydrate dietary intake with the goal of producing a ketotic state. The studies included in this review indicated the KD was beneficial in reducing symptoms associated with various psychiatric disorders.

**Discussion:** This review summarizes the available evidence regarding the efficacy of the ketogenic diet in psychiatric disease states. Data from the studies analyzed demonstrated a positive response in individuals who were able to remain on the diet, regardless of the disease state. However, there is a need for more data to clearly define the specific benefits the KD may provide.

**Keywords:** ketogenic diet, low carbohydrate diet, psychiatric disorder

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## Introduction

The 2015-2020 Dietary Guidelines for Americans recommends, based on percentage of calories, a diet that consists of 20% to 25% fat, 45% to 65% carbohydrates,

and 10% to 35% protein.<sup>1</sup> In contrast, the ketogenic diet (KD) is a high-fat, low-carbohydrate diet, with the protein component remaining the same. By restricting carbohydrates, lipolysis is activated, creating ketones to use as the body's primary energy source rather than glucose. The original KD consists of approximately 80% fat from long-chain fatty acids, which are found in animals or plants (eg, dairy products, avocados, vegetable oils, nuts, fatty fish), 15% protein, and 5% carbohydrates. To date, several variations of the original KD have been introduced, such as lowering the caloric intake from fat to 60% to 70%, switching the fat to medium-chain triglycerides, and increasing the carbohydrates to 10% to 20% while placing no restrictions on the amount of fat or protein.<sup>2,3</sup> Specific examples include the modified Atkins diet (MAD; 15% carbohydrates with unlimited amounts of protein and fat) and the "John Radcliffe Diet" (71% of calories coming

from a combination of medium-chain, long-chain, and saturated fats, 19% from carbohydrates, and 10% from protein).<sup>4</sup> Regardless of the diet plan, the intent is to switch the body's fuel source from glucose to fat via the production of ketones, a process known as ketosis. As a result, the energy balance in the brain is significantly altered. It is hypothesized that ketone bodies, such as  $\beta$ -hydroxybutyrate (BHB), are more efficient in producing energy per gram of oxygen compared with glucose.<sup>5</sup>

Several theories for using the KD to treat psychiatric medical conditions have been proposed. It is believed that the KD alters the  $\gamma$ -aminobutyric acid (GABA) to glutamate ratio in the brain, favoring GABA. Hypothetically, this increase in GABA may help compensate for the imbalanced GABA levels of a person with schizophrenia, consequently alleviating symptoms such as hallucinations and delusions.<sup>6</sup> Ketogenic diets are also thought to decrease reactive oxygen species and increase adenosine triphosphate and phosphocreatine levels, thus boosting metabolic efficiency, which may provide benefit for individuals taking medications with a higher risk of weight gain. This may reduce inflammation in the brain, which may lead to symptomatic relief in multiple disease states, including Alzheimer disease.<sup>7</sup> Another theory involves ketosis limiting apoptosis and neuronal excitability, which may explain the theory behind successful reports of the KD in individuals with epilepsy.<sup>8,9</sup> The metabolic changes associated with seizure reduction can also be applied to potential efficacy in patients with autism spectrum disorder (ASD) because of positive changes in the gut microbiome.<sup>10</sup> In bipolar disorder, acidic plasma is thought to stabilize mood by reducing intracellular sodium and calcium.<sup>11</sup> By inducing relative hypoglycemia in patients with narcolepsy, the KD increases activation of orexin-containing neurons to improve daytime sleepiness.<sup>12</sup> The purpose of this systematic review is to examine the clinical impact of the KD on various psychiatric disease states. The reviewed studies provide supporting evidence for the potential benefit of using the KD in the treatment of Alzheimer disease, anorexia nervosa, ASD, bipolar disorder, MDD, narcolepsy, and schizophrenia.

## Methods

A search was conducted using EBSCOhost and PubMed databases for studies published through July 2020, with the following keywords: *ketogenic diet*, *low carbohydrate diet*, and *psychiatric disorder*. Initial search results were limited to studies with abstracts published in the English language that were conducted in human participants. Duplicate citations were removed during article screening, and references of pertinent articles were reviewed for the purpose of gathering additional references. Studies

without abstracts, literature reviews, and letters to the editor describing case reports with limited details were excluded. Studies describing interventions in nonpsychiatric disorders (eg, epilepsy) were excluded. Studies that did not discuss dietary intake consisting of a low-carbohydrate or ketogenic diet (generally defined as at least 60%-80% of total daily calories from dietary fat with reduced consumption of carbohydrates), and studies that solely used dietary supplements or medical food interventions to produce ketosis were excluded. The Figure highlights the literature review process. The authors summarized the studies by the formulation of the KD listed (if provided) and the efficacy associated with a KD intervention.

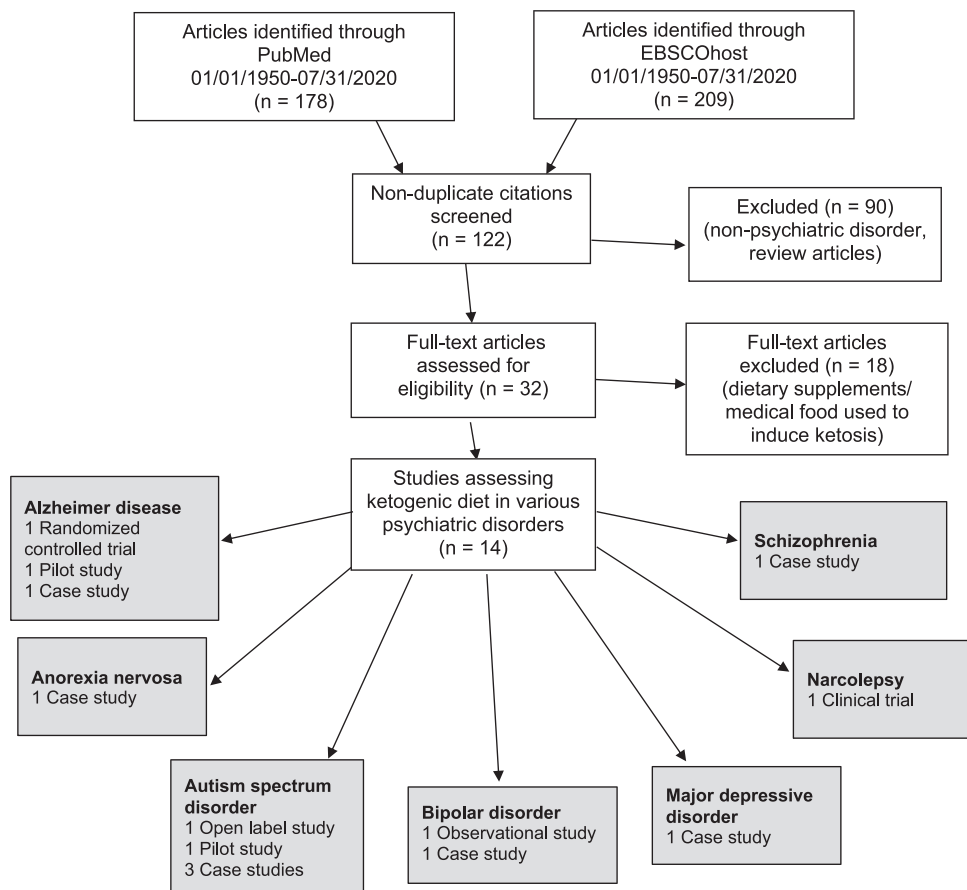
## Results

The initial search produced 178 citations in PubMed and 209 in EBSCOhost. Duplicates were removed, and 90 articles were excluded. After reviewing the abstracts, 32 full-text publications were retrieved. Studies that did not describe a low-carbohydrate diet or KD intervention in psychiatric disorders were excluded, which resulted in 14 experimental or observational studies. These studies examined the KD in psychiatric disorders, specifically Alzheimer disease, anorexia nervosa, ASD, bipolar disorder, MDD, narcolepsy, and schizophrenia. A summary of the results is presented in the Table.

### Alzheimer Disease

Three studies assessing the effects of the KD on Alzheimer disease were included. A case study by Morrill and Gibas<sup>13</sup> described alleviating mild Alzheimer disease symptoms of forgetfulness, delayed word recall, and frequent misplacement of objects in a 71-year-old female patient by using the KD. This low-carbohydrate, high-fat diet produced sustained plasma ketones between 0.5 and 2 mg/dL, indicating moderate-level, nutritional ketosis. The PEAK Brain Training Mobile Application for cognitive training in addition to guided low-impact exercises were used. The Montreal Cognitive Assessment (MoCA) score was used to measure change in cognition. By the end of the study, the patient's MoCA score increased from 21 to 28, showing a positive correlation between the diet and an improvement in symptoms.

In 2017, Taylor and colleagues<sup>14</sup> assessed the feasibility and efficacy of the KD in participants with Alzheimer disease. This was a 3-month-long study, in which 10 of 15 total participants completed. After the study intervention period, there was a 1-month washout period where participants resumed their regular diet. Ketosis was



**FIGURE:** Systematic review process

evaluated using serum BHB levels, as well as a urine ketone test. The Mini-Mental State Examination (MMSE) and Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) were performed at baseline and throughout the 3-month study period to determine the effect of the KD. Ten participants’ ADAS-cog scores changed significantly from baseline, with a mean improvement of 4.1 points (25.5 vs 21.4,  $P < .02$ ). MMSE scores in those who completed the study significantly improved (25.2 vs 26.3,  $P < .05$ ). Following the 1-month washout period, participants were readministered the ADAS-cog and MMSE exams, which resulted in a return to mean baseline scores of 25.3 (ADAS-cog) and 25.1 (MMSE) for 9 participants. The participants continued cholinesterase inhibitors during the study. Diarrhea was the most common side effect reported. No serious adverse events occurred, and laboratory and electrocardiogram results were within normal limits.

A randomized, controlled trial to assess the impact of the KD on Alzheimer disease symptoms was published by Ota and colleagues.<sup>15</sup> Twenty Japanese patients with mild to moderate Alzheimer disease were either started on a ketogenic diet formula containing medium-chain

triglycerides (MCTs) or an isocaloric placebo formula containing emulsified long-chain triglycerides as a substitute for MCTs. Changes in symptom severity were measured by the Wechsler Memory Scale-revised (WMS-R), the Wechsler Adult Intelligence Scale-3rd edition (WAIS-III), the Stroop test, and the Trail Making Test (TMT). In a post-hoc analysis, there were significant improvements in the WMS-R in the digit-symbol coding category ( $P < .05$ ), as well as in the logical memory (both immediate and delayed) in the WAIS-III test ( $P < .05$ ). The study participants were allowed to continue their antedementia drugs (eg, cholinesterase inhibitors and *N*-methyl-*D*-aspartate receptor antagonists) at the same dose during the study. Diarrhea was the only reported side effect.

## Anorexia Nervosa

Scolnick and colleagues<sup>16</sup> published a case report detailing the effects of the KD on a 29-year-old female with a 15-year history of anorexia nervosa. A KD of 2:1 to 1:1 ratio of fats to carbohydrates was used, and a KD nutritionist provided dietary education. After 3 months on the diet, the patient reported improvement but was still experiencing compulsions associated with anorexia. Ketamine IV

**TABLE: Impact of the ketogenic diet (KD) in the treatment of various psychiatric disorders**

Source	Study Characteristics	Intervention	Outcomes
<b>Alzheimer Disease</b>			
Morrill and Gibas <sup>13</sup> (2019)	Study design, duration: case report, 10 wk Setting: OP N = 1	Low-carb, high-fat diet to produce sustained plasma ketones between 0.5 and 2 mg/dL	MoCA score increased from 21 to 28 Biometric changes: HOMA-IR decreased by 75% from 13.9 to 3.48 TG decreased by 50% from 170 to 85 mg/dL VLDL decreased by 50% from 34 to 17 mg/dL HbA1c decreased from 5.7% to 4.9%
Taylor et al <sup>14</sup> (2018)	Study design, duration: pilot study, 31 mo Setting: OP N = 15	KD, targeted macronutrient composition (70% fat), including MCT (10% total fat), 20% protein, and restriction of carbs (<10%); diet ratio of 1:1 (lipid to nonlipid)	60% Reported some ketosis Serum $\beta$ -hydroxybutyrate levels (mmol/L): Baseline: 0.11 1 mo: 0.52 2 mo: 0.34 3 mo: 0.31 ( $P < .001$ ) Returned to 0.12 in 1-mo washout period MMSE ( $P < .05$ ) and ADAS-Cog ( $P < .02$ ) scores improved
Ota et al <sup>15</sup> (2019)	Study design, duration: RCT, 12 wk Setting: OP N = 20	MCT-ketogenic formula	No immediate benefit, but significant benefits in patients at 12 wk in WMS-R and WAIS-III ( $P < .05$ )
<b>Anorexia Nervosa</b>			
Scolnick et al <sup>16</sup> (2020)	Study design, duration: case report, 6 mo Setting: OP N = 1	KD, 2:1 to 1:1 ratio of fats to carbohydrates	Restrictive eating obsessions and compulsions stopped Continual improvement observed for >6 mo
<b>Autism Spectrum Disorder</b>			
Lee et al <sup>10</sup> (2018)	Study design, duration: open-label clinical trial, 6 mo Setting: OP N = 15	Modified ketogenic gluten-free diet regimen with supplemental MCT	ADOS-2 improvement at 3 mo: >7 units: 6 participants >3 units: 2 participants Little/none: 7 participants ADOS-2 improvement at 6 mo: Sustained improvement: 10 participants
Evangelidou et al <sup>17</sup> (2003)	Study design, duration: pilot study, 6 mo Setting: IP N = 30	John Radcliffe diet	Improvement in CARS score ranged from minor to significant in 60% of patients
Herbert and Buckley <sup>18</sup> (2013)	Study design, duration: case report, 8 y Setting: OP N = 1	GFCF KD	CARS score decreased from 49 to 17 Intelligence quotient increased by 70 points
Zarnowska et al <sup>19</sup> (2018)	Study design, duration: case report, 6 mo on diet, 10 mo observation Setting: OP N = 1	Low-carbohydrate, moderate protein, high-fat, KD	Intellect on WISC-R improved from baseline in the 16 mo following KD implementation

**TABLE: Impact of the ketogenic diet (KD) in the treatment of various psychiatric disorders (continued)**

Source	Study Characteristics	Intervention	Outcomes
El-Rashidy et al <sup>20</sup> (2017)	Study design, duration: case-control study, 6 mo Setting: IP N = 45	MAD (n = 15) and GFCF diet (n = 15) vs control (n = 15)	CARS score mean decrease: MAD 41.7 → 33.7 (P = .0001) GFCF 39.17 → 34.27 (P = .001) Control no change ATEC score mean decrease: MAD 58 → 44 (P = .003) GFCF 64.13-42.13 (P = .0001) Control 62.82 → 61.60
<b>Bipolar Disorder</b>			
Campbell et al <sup>21</sup> (2019)	Study design, duration: observational analytic study Setting: OP N = 141	KD, omega-3 enriched, or vegetarian	Reports of significant mood stabilization or remission of symptoms were substantially higher for the KD than for other diets
Phelps et al <sup>11</sup> (2013)	Study design, duration: case series, 7 mo Setting: OP N = 2	KD, 70% fat, 22% protein, 8% carbs	Mood stabilization exceeded the improvement achieved with medication
<b>MDD</b>			
Cox et al <sup>22</sup> (2019)	Study design, duration: case report, 12 wk Setting: OP N = 1	KD, 65% fat, 25% protein, 10% carbs	PHQ-9 score decreased Biometric changes: HbA1c dropped from 8% to 5.4% Average daily glucose measurements declined from 216 to 96 mg/dL HOMA-IR and TG/HDL ratios improved by 75%
<b>Narcolepsy</b>			
Husain et al <sup>12</sup> (2004)	Study design, duration: clinical trial, 8 wk Setting: OP N = 9	KD, consisting of <20% carbs/d	NSSQ total score decreased by 18% (P < .0019)
<b>Schizophrenia</b>			
Kraft and Westman <sup>23</sup> (2009)	Study design, duration: case report, 12 wk Setting: IP N = 1	KD, <20 g carbs/d	Auditory and visual hallucinations stopped Continual improvement observed for 12 mo

ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADOS-2 = Autism Diagnostic Observation Schedule Second Edition; ATEC = Autism Treatment Evaluation Checklist; CARS = Childhood Autism Rating Scale; GFCF = gluten-free-casein-free; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; IP = inpatient; MAD = modified Atkins diet; MCT = medium-chain triglycerides; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NSSQ = Narcolepsy Symptom Status Questionnaire; OP = outpatient; PHQ-9 = Patient Health Questionnaire; RCT = randomized control trial; TG = triglycerides; T2DM = type 2 diabetes mellitus; WAIS-III = Wechsler Adult Intelligence Scale-3rd edition; WISC-R = Wechsler Intelligence Scale for Children-Revised; WMS-R = Wechsler Memory Scale-revised.

infusions were initiated after 3 months of the KD intervention, with a total of 4 infusions given during 14 days. The Patient Health Questionnaire (PHQ-9) score, a 9-item depression screening tool, decreased from 13 to 6 after the initial infusion and decreased to 2 after the third infusion. Six months after ketamine infusions the patient

continued to sustain a KD diet. The patient's weight remained stable, and she claimed to be free of any anorexia obsessive thoughts and behaviors by the end of the study; however, eating disorder rating scales were not used to monitor progress. The patient did not experience any side effects with the KD.

## Autism Spectrum Disorder

Five studies assessing the effects of the KD on ASD were included. Lee and colleagues<sup>19</sup> studied the efficacy of a modified ketogenic, gluten-free diet regimen with supplemental MCTs in 15 children ages 2 to 17 years with ASD. At 3 months, substantial improvement, defined as a decrease of greater than 7 units in the Autism Diagnostic Observation Schedule, second edition (ADOS-2) total score, was observed in 6 participants. Moderate improvement occurred ( $>3$  units) in 2 participants, and minor or no improvement ( $\leq 3$  units) was observed in 7 participants. A total of 8 of 15 participants who responded to the KD improved their overall score by at least 4 points. An improvement in Childhood Autism Rating Scale (CARS) scores was also reported at 3 months. At 6 months, 10 participants achieved a sustained decrease in ADOS-2 total scores. Medications for comorbidities were continued during the study. Common side effects occurred in the first 2 to 4 weeks of diet initiation and included diarrhea (18.8%), vomiting (18.8%), fatigue (18.8%), constipation (12.5%), dehydration (12.5%), weight loss (12.5%), acidosis (6.3%), and hypoglycemia defined as blood glucose  $<50$  mg/dL (6.3%).

A pilot study performed by Evangelidou and colleagues<sup>17</sup> included 30 children ages 4 to 10 years with autistic behavior on the high-fat (71%), low-carb (19%) John Radcliffe diet. The diet was applied for 6 months, with 4-week periods of continuous administration followed by 2-week diet-free intervals. Patients were evaluated via CARS scores after 6 months. Significant improvement ( $>12$  unit reduction in CARS score) was recorded in 2 patients, average improvement ( $>8$  to 12 unit reduction) occurred in 8 patients, and minor improvement (2 to 8 unit reduction) was observed in 8 patients. Twelve patients did not demonstrate a decrease in CARS scores. Haloperidol was given at least 6 months before the initiation of a KD and was continued after the diet was completed, but no increased dosages were needed. Behavioral treatments were not given. No adverse effects were reported.

Herbert and colleagues<sup>18</sup> described a 4-year-old female patient with severe regressive autism and a history of epilepsy for whom drug therapy was deemed ineffective. After being placed on a gluten-free, casein-free (GFCF) KD, she showed a reduction in ASD symptoms. During a follow-up period lasting more than 8 years, the patient achieved a decrease in CARS score from 49 to 17, representing a change from severely autistic to non-autistic. The patient also had an increase in her intelligence quotient (IQ) of 70 points. The patient remained on anticonvulsant therapy; however, doses were able to be reduced without an increase in seizure frequency.

Żarnowska and colleagues<sup>19</sup> studied a 6-year-old female patient with high-functioning autism who responded poorly to several behavioral and pharmacologic interventions during a period of 16 months. The patient was placed on a low-carbohydrate, moderate-protein, high-fat KD. One month following initiation of the diet, marked improvements were reported in behavior and intellect (including hyperactivity, attention span, abnormal reactions to visual and auditory stimuli, use of objects, adaptability to changes, communication skills, fear, anxiety, and emotional reactions). Intellect was measured via WISC-R scores: Full Scale IQ increased from 82 to 99, Verbal Scale IQ increased from 102 to 113, and Performance Scale IQ increased from 62 to 83 during the 16 months following initiation of the KD. Improvements continued until the end of the observation period. Pharmacologic treatment was not needed during the study period, and there were no side effects observed.

El-Rashidy and colleagues<sup>20</sup> randomized 45 children ages 3 to 8 years diagnosed with ASD into 3 groups. A total of 15 children received a ketogenic MAD, 15 children received a GFCF diet, and 15 received balanced nutrition as the control group. All patients were assessed via neurologic examination, anthropometric measures, CARS score, and Autism Treatment Evaluation Test before and after 6 months following initiation of the diets. Both intervention groups showed significant improvement in Autism Treatment Evaluation Test and CARS scores at 6 months ( $P < .0001$ ,  $P < .003$ ), and the ketogenic MAD group showed better results in cognitive awareness ( $P = .0001$ ) and sociability ( $P < .034$ ) when compared to the GFCF group. Five patients in the MAD group were not included in the data analysis because of poor compliance.

## Bipolar Disorder

Two articles evaluated the effects of the KD in bipolar disorder. Campbell and Campbell<sup>21</sup> completed an analytic observational study that used online bipolar disorder forums to retrieve data from patients. A total of 85% of the 141 study participants' self-reported comments demonstrated positive effects on mood while following a ketogenic diet. Reports of mood stabilization or relief of symptoms were significantly higher ( $P < .0001$ ) for patients on the KD compared with other diets, such as omega-3 enriched or vegetarian. Additionally, study participants reported a decrease in depression, improved clarity of thought and speech, weight loss, and increased energy overall.

Phelps and colleagues<sup>11</sup> described the effects of the KD on bipolar disorder in 2 patients who experienced a decrease in quality of life despite taking medication for mood stabilization. A 69-year-old female experienced confusion due to lamotrigine, and a 30-year-old female wanted to



discontinue lamotrigine because of concerns about becoming pregnant while taking this medication. The KD formulation consisted of 70% fat, 22% protein, and 8% carbohydrates. Both patients maintained ketosis for 2 to 3 years, successfully discontinued their mood stabilizers, and demonstrated significant subjective improvement. There were no adverse effects of the KD reported in either case.

## Major Depressive Disorder

Cox and colleagues<sup>22</sup> reported the effects of the KD in a 65-year-old female with a 26-year history of both type 2 diabetes and MDD. The intervention consisted of a KD formulation with 65% fat, 25% protein, and 10% carbohydrates during 12 weeks. The PHQ-9 was used. The patient's scores decreased substantially from a baseline score of 17 (moderately severe) to 0 (no symptoms reported). The patient's quality of life dramatically improved with the use of the KD. Additionally, the patient's HbA1c decreased from 8% to 5.4%, and her average daily glucose readings were lowered from 216 to 96 mg/dL. Although specific details were not provided, the patient was able to reduce her medications by 75% by the end of the study, which included a SSRI.

## Narcolepsy

An experimental study by Husain and colleagues<sup>12</sup> evaluated the effects of a low-carbohydrate KD on sleepiness and narcolepsy symptoms. Nine participants with a diagnosis of narcolepsy were asked to adhere to the Atkins diet plan, and their symptoms were assessed during an 8-week period. At the end of the 8 weeks, the combined Narcolepsy Symptom Status Questionnaire score of all participants showed a statistically significant decrease of 18% (161.9 to 133.5,  $P = .0019$ ) from baseline. Patients reported less daytime sleepiness. The participants were taking optimal doses of stimulant medications. There were no serious adverse events reported, but 4 patients experienced mild and self-limiting side effects (eg, headache, leg cramps, irritability, and difficulty with concentration). No adverse changes were noted in vitals or laboratory tests.

## Schizophrenia

Kraft and Westman<sup>23</sup> described the effects of the KD on a 70-year-old female with a 17-year history of schizophrenia. Her medication regimen at the time of the study was risperidone 4 mg by mouth at bedtime. The goal of the case report was to evaluate if the KD would lessen the patient's schizophrenia symptoms (paranoia, disorganized speech, and hallucinations). This particular KD consisted of a restriction of less than 20 g of carbohydrates per day. The patient reported diminished auditory and visual

hallucinations approximately 8 days after initiation of the diet. She had no recurrences during the course of the 12-month intervention period. The patient experienced weight loss (approximately 10 kg) and noted increased energy while following the KD. Two additional case reports about the KD in patients with schizophrenia have been published as letters, but these were excluded from this review because of insufficient details.

## Discussion

This review summarizes the available literature on the effects of the KD on various psychiatric disorders. Symptom improvement included but is not limited to mood, cognition, communication skills, energy, anxiety, and auditory and visual hallucinations. Other benefits reported included positive biometric changes, such as improved lipid profile, reduced weight, positive change in blood glucose, and decreased HbA1c. These ancillary benefits may facilitate management of comorbid conditions and enhance overall health and well-being.

Niepoetter and Gopalan<sup>24</sup> published a literature review in 2019 on the effect of the KD in autism, depression, anxiety, and schizophrenia in humans and animal models. The authors noted the use of the KD in psychiatric diseases may be a feasible method of treatment and incorporating the KD may allow for a reduction in pharmacologic treatment. Although there appears to be a correlation between the KD and symptom improvement, the evidence is limited. Because there are no well-controlled, large trials investigating the efficacy and safety of the KD for treatment of these psychiatric disorders, more research is needed before such a dramatic change in diet can be considered a primary treatment modality.

There are known challenges and risks associated with this diet intervention. A KD typically consists of approximately 75% fat, 15% protein, and 5% carbohydrates, and strict adherence to the very low daily intake of carbohydrates is required to produce a sustained state of ketosis. It may be challenging to generalize this type of diet for each patient, and long-term sustainability may not be feasible. Side effects of the KD reported in the literature include constipation, nausea, vomiting, diarrhea, fatigue, and hunger and were generally mild and self-limiting. However, this diet has been associated with negative health outcomes, including increased risk of heart disease, hyperlipidemia, and kidney stones.<sup>25</sup>

One of the most important limitations found in this review is the variation in the KD components among studies. Although several experimental studies confirmed a state of ketosis via ketone body testing, most did not. There were numerous versions of the KD used, each with

different macronutrient allotments. For example, some KD plans included daily carbohydrate intake that ranged from 5% to 20% or higher. Some studies added a dietary supplement, such as MCT powders, to the KD to assist in producing ketosis rather than using dietary adjustments alone. Furthermore, the detail in which the studies reported the composition of intervention and control of diets was wide-ranging, and in some cases was lacking. Outcome measures were also variable among the studies. Some used validated objective measures, but others employed more subjective measures, which produces bias. Subjectivity of the results and the different types of tests used make it difficult to directly compare the data between the studies.

Although not included in this review because the study population did not follow a KD, Gardener and colleagues<sup>26</sup> assessed the association between carbohydrate intake and cognitive performance in 666 cognitively normal patients who were genotyped for the apolipoprotein E (APOE) 4 allele. Nearly one third of these patients were determined to be at high risk for developing Alzheimer disease because of carrying the APOE 4 allele. Upon completion of this study, a negative association was discovered between cognitive function and a higher amount of daily carbohydrates consumed in patients with the APOE 4 allele. This may suggest benefits of following a lower carbohydrate diet that is not necessarily ketogenic; however, further investigation is warranted to determine if there is an optimal amount of carbohydrates or level of ketosis required to provide benefit in the treatment of psychiatric conditions.

Another study<sup>27</sup> that did not meet inclusion criteria but is worth noting examined the effects of the KD in 10 female patients ages 19 to 63 years with schizophrenia. The study participants continued their medications and electroconvulsive therapy. The evaluation methods described did not include the specific symptoms listed in the nursing ward checks, the Minimal Social Behavior scale, or the Beckomberg rating scale; however, the authors reported a clinically observed decrease in symptoms after 2 weeks of treatment. Overall, 7 of the 10 patients studied showed improved symptoms while maintaining the KD.

## Conclusion

This review presents the available evidence for the use of the KD in the treatment of several psychiatric disorders. The results are positive, and all studies that met the inclusion criteria showed some form of benefit in those who were able to remain on the diet, regardless of the disease state. However, the small number of study participants is a limitation that prevents generalization. The benefits and risks of the KD should be considered for

each patient before implementing dietary changes. Because the evidence is limited, there is a need for more appropriately controlled, larger trials to clearly define the benefits of incorporating the KD in the psychiatric treatment regimen. Medical food studies were not included in the scope of this article but may be a future area of interest in the treatment of psychiatric diseases. Clinical pharmacists and providers may consider the KD as a potential adjunctive treatment option for patients living with Alzheimer disease, anorexia nervosa, autism, bipolar disorder, MDD, narcolepsy, and schizophrenia. The KD may allow for a reduction in pharmacotherapy and potentially reduce unwanted medication side effects.

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