MINKIEWICZ, Magda, MUSIALSKA, Dominika, BOLEK, Michał, FIDYK, Monika, JAGIEŁA, Bartosz and KĘDZIA, Aleksandra. Role of the Ketogenic Diet in Psychiatry: Review of Clinical Trials and Case Studies. Quality in Sport. 2025;41:60265. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.41.60265
https://apcz.umk.pl/QS/article/view/60265

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 12.04.2025. Revised: 25.04.2025. Accepted: 06.05.2025. Published: 11.05.2025.

ROLE OF THE KETOGENIC DIET IN PSYCHIATRY: REVIEW OF CLINICAL TRIALS AND CASE STUDIES

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Abstract:

The ketogenic diet (KD) has gained a lot of recognition as a treatment in refractory epilepsy. Due to its success, more and more researchers have begun to question whether this diet would have a similar positive influence on patients suffering from various psychiatric disorders. This paper explores the use of the ketogenic diet in psychiatric conditions, particularly in mood disorders, schizophrenia, and neurodegenerative diseases. The initial studies have a rather promising outcome, but more evidence needs to be gathered in order to ensure this diet is a safe and credible tool in managing psychiatric symptoms. This review discusses current studies, challenges, and future research directions.

Keywords: ketogenic diet, mental health, psychiatry, mood disorders, bipolar disorder, depression, schizophrenia, neurodegenerative diseases, parkinson's disease, alzheimer's disease

Introduction:

The ketogenic diet (KD) is defined by a high-fat, moderate-protein, and low-carbohydrate composition. The classic KD consists of 4:1 ratio of fats to combined proteins and carbohydrates, which means that fats account for 90% of the total calories, and the remaining 10% of calories comes from proteins and carbohydrates[1]. This approach in dieting leads to the production of ketone bodies from fat sources as a result of insufficient glucose coming from limited carbohydrates intake. Ketone bodies can act as an alternative energy source for the brain, for example, helping to reduce neuronal excitability and the frequency of seizures. Hence, why the ketogenic diet is being used in the treatment of epilepsy, especially in cases when well selected therapy based on antiepileptic drugs has failed [2,3]. The ketogenic diet is also studied as a possible treatment in other medical field – psychiatry. Psychiatric conditions like mood disorders, schizophrenia, and neurodegenerative conditions, such as Alzheimer's and Parkinson's diseases can benefit from the KD. While the treatment of choice for those conditions, like antipsychotic drugs and antidepressants, may be effective for some patients [4,5], around 75% of patients experience side effects [6,7]. There is a variety of those side effects [8] and they can negatively impact quality of life and functioning [9], contribute to higher morbidity and mortality rates [10], lead to stigmatization [11], and cause poor medication adherence, increasing the risk of relapse in psychiatric conditions [12]. Thus, it is important to search for alternative ways to help manage these disorders. Unfortunately, despite encouraging results from early studies, the evidence remains limited, and the underlying mechanisms of this diet are not fully understood yet. This paper reviews the current literature on the ketogenic diet in psychiatric treatment and provides insights into its clinical potential and limitations.

Methods:

A comprehensive literature search was conducted using the PubMed database to identify studies exploring the use of the ketogenic diet in psychiatric conditions. The keywords used were ketogenic diet searched alone or in combination with mental health, psychiatry, mood disorders, bipolar disorder, depression, neurodegenerative diseases, Alzheimer's disease or Parkinson's disease. Relevant articles published in the last 18 years were included in the review. Articles of various types were analysed. Only publications in

English were used. Articles cited in the publication were selected by 6 independent researchers.

Results:

1. Mood Disorders

The ketogenic diet has been analysed in several studies in terms of its influence on mood disorders, particularly bipolar disorder and depression.

A pilot trial by Sethi et al. (2024) showed results of the KD in patients suffering from bipolar disorder, consisting of an improvement in life satisfaction, an improvement in social, occupational, and psychological functioning, and an improvement in quality of sleep. Besides the positive psychiatric outcomes, there was also a positive impact on overall health parameters, such as reduction in weight, BMI, fat mass index, waist circumference, and systolic blood pressure. Various metabolic biomarkers, such as triglycerides, visceral adipose tissue, and HbA1c, also decreased. This study implies that there is a correlation between higher ketone levels and a higher degree of an individual's improvement [2].

In a case report conducted by Chmiel (2022) on a patient with bipolar disorder, the introduction of the ketogenic diet allowed doses reduction, and even discontinuation of most of the subject's psychiatric medication. The KD also improved cognitive functions and energy levels. The patient achieved full remission – he did not show any symptoms of depression and hypomania [13].

In a case study conducted by Calabrese et al. (2024) in case number 1, a man with previously moderately severe depression achieved a complete remission of depressive symptoms within five weeks of consistent therapeutic nutritional ketosis. He also improved his blood pressure, lost weight, and lowered his body fat. Similarly, in case number 2 and number 3 – the subjects' depression remitted, and metabolic parameters have improved [14].

2. Schizophrenia

Schizophrenia is another psychiatric disease where the ketogenic diet might be found useful, and used as an alternative to the traditional treatment.

A case report by Kraft et al. (2009) shows that the KD has made the patient's auditory or visual hallucinations completely subside, although the prescribed medications have not been changed. Additionally, the subject has lost weight and has observed an increased level of

energy. Even temporary slip-ups in diet did not cause a reappearance of her hallucinations over the course of twelve months [15].

Another case study by Palmer et al. (2019) examines two female patients suffering from schizophrenia that has been treated with the ketogenic diet. The first case is a 82 years old woman. She spotted an improvement of her psychotic symptoms after two weeks of following the KD. Later during the treatment, she noticed an enhancement of mood and lack of suicidal thoughts. She has even discontinued all of her medications. The second case is a 32 years old female, severely psychiatrically burdened, on extensive psychiatric drug treatment in the past. After a month of being on the ketogenic diet, she reported that her psychotic symptoms have subsided completely. She also was able to discontinue all of her medications [16].

3. Neurodegenerative Diseases

The ketogenic diet has also been studied for its neuroprotective effects in neurodegenerative diseases, like Alzheimer's and Parkinson's.

A randomized crossover trial by Phillips et al. (2021) investigated the influence of the KD on twenty six patients aged between 50 and 90, suffering from Alzheimer’s disease. The study showed improvements in daily functioning of patients on the ketogenic diet compared to those on a regular diet. It was measured by the ADCS-ADL Scale (The Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale), in which the treatment effect reached 3.13 points, given that a 2-point change is regarded as clinically significant [17]. The observed 3.13 points suggests a level of improvement that is rarely seen with medication use [18].

The participants of this study, which were on the ketogenic diet, have also seen an improvement in the quality of life measured by QOL-AD (Quality of Life in Alzheimer’s Disease), in which they scored 3.37 points higher compared to the results of being on the regular diet.

This observation is considered clinically meaningful, since it was over a 3-point change [19]. Unfortunately, the subjects showed only a non-significant positive change in cognition, measured on the ACE-III scale (Addenbrooke's Cognitive Examination III Scale) [20].

A pilot randomized controlled trial by Phillips et al. (2018) compared a low fat and ketogenic diet in Parkinson’s disease. Forty seven patients aged between 40 to 75 were included in the study. Both the low fat diet group and the ketogenic diet group lost weight and observed BMI decrease. There was no particular difference of magnitude between them. Both

diet groups experienced improvement in motor and nonmotor symptoms, but the ketogenic diet group improvement in nonmotor symptoms was more pronounced. The study was conducted with the help of the MDS-UPDRS (MDS-Unified Parkinson's Disease Rating Scale) which has high internal consistency in measuring motor and nonmotor symptoms [21] to reduce assessment bias. Both groups were taking L-dopa medication alongside with their dietary change [22].

Discussion:

While the ketogenic diet has a promising role in the treatment of psychiatric patients, several limitations exist. Many studies have small sample sizes, short follow-up periods, or short durations of the study. Several trials present selection bias towards participants who are motivated to enrol in studies from an outpatient population. They are lacking international or interracial participants. Some studies examined the influence of the KD on more than one illness at once [2], which may disturb their credibility. Moreover, the diet's high-fat content may raise concerns about its impact on cardiovascular health. Although the study by Sethi et al. (2024) implies that lipid profiles of participants on the KD did not appear to worsen the cardiovascular risk [2]. The exact mechanisms of how the ketogenic diet improves lives of patients with certain psychiatric conditions are not completely understood yet. It is believed that ketosis affects neurotransmitter regulation, mitochondrial function, and neuroinflammation which all play key roles in psychiatric health [2, 14, 23].

It is also important to add that many patients throughout all of the mentioned studies struggled with adherence. The KD is very restrictive, so it can be hard to maintain as a long-term tool in managing diseases. Furthermore, more comprehensive clinical trials are necessary to establish definitive guidelines regarding its efficacy, safety, and the ideal duration usage for specific psychiatric conditions.

Conclusion:

The ketogenic diet is a promising adjunct to treatment, or even a form of therapy alone, in various psychiatric disorders, such as mood disorders, schizophrenia, and neurodegenerative diseases. So far, conducted studies show a bright future for the ketogenic diet in psychiatry. Larger and more rigorous clinical trials are needed to confirm its effectiveness, explore the underlying mechanisms, and evaluate the long-term safety of the diet in psychiatric populations. Clinicians should be full of caution about suggesting the ketogenic diet as a form of treatment, and evaluate the individual needs of each patient.

Disclosure

Authors' Contribution:

Conceptualization, MM, BJ and DM; methodology, MB; software, MF; check, MM, AK and DM; formal analysis, MB; investigation, MM, MF; resources, MM, AK; data curation, MM; writing -rough preparation, MM, BJ; writing -review and editing, MM, DM; visualization, MF; supervision, MM; project administration, MM;

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data availability: Not applicable.

Acknowledgments: None.

Conflicts of interests: Authors declare that there is no conflict of interest.

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