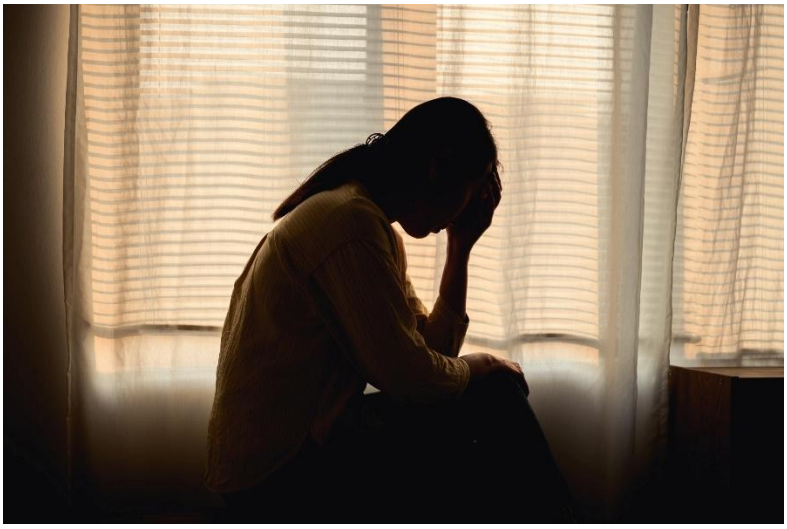
Linked to PTSD Early Studies Hint Ketones may Affect Pathways

Researchers evaluated the potential of ketogenic therapy as a treatment for post-traumatic stress disorder (PTSD), including evidence concerning efficacy, mechanisms, safety, and feasibility.



Study

The authors conducted an integrative review to synthesize evidence from multiple study designs, following the principles described by Whittemore and Knafl. They also drew on selected recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) without seeking to meet all criteria for a systematic review.

Searches were conducted from January 9 to January 14, 2025, in PubMed, Scopus, PsycArticles, PsycINFO, PSYNDEX, and MEDLINE, and the International Clinical Trials Registry Platform, European Union (EU) Clinical Trials Register, and ClinicalTrials.gov. Search terms combined ketogenic therapy terms, including ketogenic, ketosis, ketones, medium-chain triglycerides (MCT), Atkins diet, and low-carbohydrate terms with PTSD terms.

Duplicates were identified with Rayyan and manually removed after confirmation. Two reviewers independently screened records and assessed full-text eligibility.

Eligible publications were preclinical, clinical, mechanistic, observational, or review articles reporting biological mechanisms, clinical outcomes, participant experiences, biological changes, safety, or feasibility relevant to both ketogenic therapy and PTSD.

Study quality was assessed using evidence hierarchies and the Critical Appraisal Tool (CAT) on a three-point scale; disagreements in quality ratings were resolved by a third reviewer.

The authors organized preliminary efficacy, feasibility, and safety data in tables and combined the mechanistic findings in a conceptual model.

An updated search on May 4, 2026, identified 32 potentially relevant records, of which five met the eligibility criteria and were included in the review.

Findings

Sixteen eligible publications published during 2020–2026 were included: Three pilot trials, one cross-sectional quasi-case-control study, three preclinical studies, five human case reports, one mechanistic study, and three mechanistic narrative reviews.

Interventions included ketogenic diets, ketone injection, ketone salts, acetate supplementation, and combined approaches. The quality assessment rated all studies as at least moderate. Two randomized controlled pilot reports were ranked as high-level evidence by study design, though the reviewers noted that they may have derived from the same participant cohort.

Five human studies provided data relevant to the safety assessment. In a six-week randomized placebo-controlled pilot involving 21 patients, researchers found no significant group differences in systolic or diastolic blood pressure, mean arterial pressure, resting heart rate, complete blood count, or comprehensive metabolic panel.

A four-week uncontrolled pilot involving three patients following a ketogenic diet with ketone salt supplementation reported no cases of serious adverse reactions or events.

Transient increases in liver enzymes, C-reactive protein (CRP), and low-density lipoprotein cholesterol (LDL-C) were observed in a subset of patients during the first two weeks.

One case report observed increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and LDL-C, but the review authors cautioned against crediting these changes solely to the ketogenic diet.

Another case reported reduced carnitine. The review identified no PTSD-specific safety signals.

Feasibility findings were favorable but limited. In the four-week pilot, 40% of intended participants were identified, 75% of those identified were recruited, and 67% of participants who began the study completed it.

Treatment acceptance was 100%. All participants achieved nutritional ketosis, which was maintained on 87% of intervention days. Dietary logs were completed on 93% to 100% of occasions, while ketone and glucose measurements were submitted on 89% of occasions in the pilot and 91% in the case report.

Participants reported different levels of burden. One dropout was attributed to meal preparation, combined with study measurements and record-keeping.

Mechanistic findings suggested possible roles for brain energy metabolism and mitochondrial function, inflammation, oxidative stress, neuroprotection, BDNF, and neurotransmitter regulation.

Three narrative reviews proposed that ketogenic therapy may shift energy production toward ketone-driven adenosine triphosphate (ATP) synthesis. Ketone signaling was linked to several inflammatory and oxidative-stress pathways, including NF-κB, PPARγ, NLRP3, HCA2, and Nrf2.

The review linked these pathways to inflammatory cytokines, reactive oxygen species, neuronal damage, and BDNF regulation. Regulation of gamma-aminobutyric acid (GABA) and glutamate was also proposed.

The authors described the mechanistic model as conceptual and hypothesis-generating; it does not establish causal mechanisms.

Preclinical studies showed reduced anxiety-like or avoidance behaviors after β-hydroxybutyrate, MCT oil, or acetate interventions in rodent models. The six human records reported numerical reductions in Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) scores. The randomized pilot found no significant between-group difference.

These data provide early signals of efficacy; clinical efficacy is still unproven.

Conclusion

The review concluded that ketogenic therapy warrants further study for PTSD, but current evidence is too limited for firm conclusions.

Preclinical evidence indicated reductions in anxiety, avoidance, and stress behaviors, while human studies provided preliminary signals of reduced PTSD symptoms.

Short-term exogenous ketone supplementation appeared safe in the small controlled study. Biochemical changes were observed during ketogenic diet use.

Proposed mechanisms include altered brain energy metabolism, increased ATP, reduced inflammation and oxidative stress, BDNF-related mechanisms, and altered GABA and glutamate signaling. Human evidence comes from very small cohorts, including case reports and pilot studies.

Larger, adequately powered randomized controlled trials are needed to establish efficacy and characterize safety and feasibility and to test ketogenic therapy alone or together with established trauma-focused psychotherapy.

Source:

https://www.news-medical.net/news/20260911/Early-studies-hint-that-ketones-may-affect-pathways-linked-to-PTSD.aspx