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Ketogenic Diet in Bipolar Disorder

Investigation of unsolicited online patient reports suggests that following a ketogenic diet may have mood stabilizing benefits in patients with bipolar disorder.

Background: Research has suggested that mitochondrial dysfunction may have an underlying role in bipolar disorder. Based on the substantial mitochondrial effects of ketosis and 2 reported cases of patients who experienced mood stabilization for 2–3 years while in a ketotic state, the present observational study was undertaken to clarify the effects of ketosis on mood symptoms in patients with bipolar disorder.

Methods: Using text-mining techniques, the authors conducted an analytic observational study of free-text comments collected from 10 online bipolar disorder forums with the largest memberships. A script developed for the study identified posts across the forums that mentioned bipolar disorder or manic depression in combination with ketogenic diet or several synonyms. In addition, to form a control group of other dietary interventions, a similar script was used to identify comments that included bipolar disorder and variations of omega 3 or vegetarian. The collected posts were then classified by independent raters into 6 response categories: remission of symptoms and/or discontinuation of bipolar disorder medications with stable mood; substantial improvement; some improvement; no difference in mood; some deterioration/ destabilization; significant deterioration/destabilization; and hospital admission or care-seeking for mood deterioration.

Results: Information from 165 posts relating to a ketogenic diet and 94 related to omega-3 supplementation or a vegetarian diet were analyzed. Significantly more patients in the ketogenic diet group reported remission of symptoms (12.1% vs 1.1%; p=0.002) and substantial improvement (56% vs 15%; p< 0.0001). Specifically, patients following a ketogenic diet reported improved mood stability; fewer episodes of depression and mania; reduced anxiety/panic attacks; increased energy; and improvements in clarity of thought and speech, sleep, control of actions, and memory. Mood deterioration was reported much less frequently (5–9%) and the rate did not differ between the groups.

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Discussion: These observations provide preliminary evidence supporting ketogenic diets in patients with bipolar disorder. However, because the study is based on self-reports, neither bipolar disorder diagnosis nor mood response could be clinically confirmed. Nevertheless, the ketogenic diet could affect mood symptoms via changes in mitochondrial function or alterations of neuronal intracellular sodium and calcium, and additional study appears to be warranted.

Campbell I, Campbell H: Ketosis and bipolar disorder: controlled analytic study of online reports. *British Journal of Psychiatry Open* 2019; doi 10.1192/bjo.2019.49. From the University of Edinburgh, U.K. **The authors declared no competing interests.**

Guideline Update: Suicide Assessment & Management

A revised guideline for assessing and managing patients at risk for suicide has been published by the U.S. Department of Veterans Affairs (VA) and the Department of Defense (DoD). The guideline is based on a review of literature published since the previous 2011 version.

Assessment. Recommendations for suicide-risk screening in the general public are not included in other current guidelines. The VA/DoD guideline recommends assessing suicide risk in all patients. The evaluation should include suicide risk factors including: prior attempts; current suicidal ideation; recent stressors; availability of firearms; prior psychiatric hospitalization; and psychiatric conditions or symptoms. Despite concerns that screening might increase an individual's risk of suicide, no studies have identified risks or harms of screening. However, current screening tools tend to falsely identify persons as at-risk and have low accuracy in identifying true cases. The Patient Health Questionnaire (PHQ-9), particularly responses to item 9 which asks about the desire for death or about self-harm, appears to be an accurate predictor of increased suicide risk. The guideline recommends use of multiple methods, such as self-reported measures and clinical interviews, to assess suicide risk.

Pharmacotherapy. Few medications have been found to be helpful in patients at risk for suicide. However, some individuals with major depression and suicidal ideation may benefit from ketamine infusions, which work rapidly but have short-lived effects. Some evidence suggests lithium may prevent suicide attempts in patients with unipolar depression or bipolar disorder. Clozapine may reduce suicidal behavior in patients with schizophrenia, but the effects may be related to the frequent monitoring required by the Clozapine Risk Evaluation and Mitigation Strategy (REMS) program.

Nonpharmacological Treatments. Evidence supports several nonpharmacological treatment strategies to reduce suicidal behavior, some in subgroups of patients only. CBT-based interventions are recommended for patients with a recent history of self-directed violence. Several studies have shown CBT reduces suicidal ideation or repeated suicide attempts by half. A crisis response plan, including collaborative identification of signs of crisis, steps to take if stressed, social supports, and other resources, has also been shown to reduce suicide attempts. Periodic caring communication is effective if repeated multiple times for ≥1 year. Lethal means safety, which includes restricting access to weapons and poisons and counseling about firearms safety, has also been effective. Dialectical behavior therapy (DBT), which combines techniques from CBT, skills training, and mindfulness techniques, is also supported for patients with borderline personality disorder. Problem-solving therapy was found to be effective in patients with traumatic brain injury. Despite the recent growth of community-based intervention programs for suicide prevention, evidence for these interventions is lacking, and technology-based methods for delivering therapy have not been well studied.

The full guideline, which includes evidence-based clinical practice algorithms for assessment and treatment, the latter stratified according to whether suicide risk is low, intermediate, or high, is available at www.healthquality.va.gov.

Sall J, Brenner L, Bell A, Colston M: Assessment and management of patients at risk for suicide: synopsis of the 2019 US department of veterans affairs and department of defense clinical guidelines. *Annals of Internal Medicine* 2019;171 (September 3):343–353. doi 10.7326/M19-0687. From the Veterans Administration, Washington, D.C.; and other institutions. **Funded by the VA. The authors declared no competing interests.**

Common Drug Trade Names*: clozapine—*Clozaril*; ketamine—*Ketalar

ECT and Gray Matter Volume

Sequential MRI scans in patients with major depression showed increases in gray matter volume, widely distributed throughout the brain, following electroconvulsive therapy. However, the changes were not associated with clinical outcome and are not feasible markers of response.

Background: Earlier MRI studies in patients receiving ECT have shown increases in gray matter volume or density. The location and extent of these changes have varied considerably between studies, probably as a result of differences in populations, treatments, and methods of image acquisition and analysis. Most studies have focused on a few regions of interest. Initial reports that some of these changes were associated with clinical response have not been replicated in larger studies.

Methods: The present study included 328 patients (mean age, 55 years; 61% women) who underwent MRI scans before and immediately after completing a course of ECT for depression. A total of 95 healthy controls were also scanned on 2 occasions. ECT practice differed among the study's 14 sites with regard to electrode placement, electrical charge, and pulse width. At most centers, patients' psychotropic medication was continued during ECT. Volume changes were measured for 66 cortical gray matter regions (33 left and 33 right), for left and right cerebellar gray matter, and for 16 (8 left and 8 right) subcortical gray matter regions. Volume changes were also calculated for 4 main tissue compartments: cortical gray matter, subcortical gray matter, white matter, and total ventricle volume.

Results: Montgomery-Asberg Depression Rating Scale (MADRS) scores decreased from a baseline mean of 34.0 to 14.4 following ECT ($p<0.001$); 63% of patients were classified as responders, with a ≥50% decrease in MADRS score, and 47% had achieved remission, with a MADRS score <10. Following ECT, patients showed enlargement in the cortical and subcortical gray matter, but not cerebellar gray matter or white matter. The gray matter changes were broadly distributed across cortical and subcortical compartments and were statistically significant for 79 of 84 gray matter regions of interest. Although the gray matter expansion was general, changes were largest in regions closest to the temporal electrodes, which are subjected to the highest electrical stimulation. No changes were observed in the healthy controls.

Gray matter volumetric increases were analyzed as a possible predictor of clinical response, testing each region of interest individually and in a model that combined all regions. The grey matter changes were not associated with changes in MADRS score and did not differ based on response or remission status. However, future studies should investigate if microstructural or molecular changes, as opposed to the macrostructural changes investigated in the present study, are related to clinical outcomes.

Ousdal O, Argyelan M, Narr K, Abbott C, et al: Brain changes induced by electroconvulsive therapy are broadly distributed. *Biological Psychiatry* 2019; doi: 10.1016/biopsych.2019.p07.010. From Haukeland University Hospital, Norway; and other institutions. **Funded by the Western Norway Regional Health Authority; and other sources. One of 34 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Environmental Risk Score for Psychosis

Presymptomatic risk prediction is routinely used in medicine, and models have been developed for a range of conditions including cardiovascular disease and diabetes. Despite extensive evidence suggesting that early intervention can improve outcomes and delay or prevent the onset of psychotic disorders, presymptomatic risk prediction is not common in psychiatry. Algorithms that do exist are typically based on single demographic or genetic factors that individually have little predictive power. However, polygenic risk scores (PRS), which aggregate multiple genetic polymorphisms, have been promising in psychiatric risk prediction. A number of environmental exposures have also been identified that, individually, are associated with an increased risk of psychosis. As with PRS, an environmental risk score (ERS), as an estimate of the cumulative load of established environmental risk factors, could give a more accurate estimate of risk. The proposed Maudsley Environmental Risk Score for Psychosis was developed to combine multiple environmental factors into a single risk score.

A comprehensive literature search was undertaken to select candidate environmental risk factors for psychosis. The search identified 6 individual environmental risk factors: minority ethnic group; urbanicity; high paternal age; obstetric complications; cannabis use; and childhood adversity. Odds ratios* for development of psychosis were collected from systematic reviews and meta-analyses, and a weighted sum of environmental exposures, similar to the Framingham Risk Score for cardiovascular disease, was generated. The ERS was estimated by summing the risk ratios for individual factors; scores can range from 4.5 (lowest risk) and 16 (maximum risk).

Proposed Maudsley Environmental Risk Scores

Risk Factor	Subcategory	Weighted ERS Value
Ethnic Minority	Native	-0.5
	Black	5.5
	White	2
	Other	2.5
Urbanicity	Low	-1.5
	Medium	0
	High	1
Paternal Age	<40 years	0
	40–50 years	0.5
	>50 years	2
Obstetric Complications	Birth weight 5.5 lbs	0
	Birth weight <5.5 lbs	2
Cannabis Use	No exposure	-1
	Little/moderate exposure	0
	High exposure	3
Childhood Adversity	No exposure	-1.5
	Any Exposure	2.5

Additional factors likely to be associated with psychosis risk identified in the meta-analyses included traumatic brain injury, *Toxoplasma gondii* infection, and cigarette smoking. These factors were not included in the ERS either due to insufficient evidence, difficulty establishing exposure in a clinical interview, or potential overlap with other included risk factors. In addition, stressful life events have been implicated in the onset of psychosis, but were also not included in the ERS because they are time-dependent and could not be incorporated in the same model as other risk factors. Family history was also not included in the ERS because of the genetic component.

The authors acknowledge that the clinical utility of the proposed Maudsley Environmental Risk Score for Psychosis is limited. The score is based on the assumption that the risk factors are independent, but environmental risk factors are often correlated. In addition, environmental factors act synergistically and/or interact with genetic risks. While the ERS cannot predict absolute risk for psychosis, it may be useful in determining whether patients are at low, moderate, or high risk for psychosis.

Vassos E, Sham P, Kempton M, Trotta A, et al: The Maudsley environmental risk score for psychosis. *Psychological Medicine* 2019; doi 10.1017/S0033291719002319. From King's College London, U.K.; and other institutions. **Funded by the National Institute for Health Research (NIHR) Biomedical Research Centre; and other sources. One of 10 study authors disclosed a potentially relevant financial relationship.**

***See Reference Guide.**

Magnetic Seizure Therapy for Depression

Results of an open-label, dose-ranging study suggest that high-frequency magnetic seizure therapy (MST) significantly reduces symptoms of depression without producing the adverse cognitive effects that commonly occur with electroconvulsive therapy (ECT).

Background: ECT is effective in major depressive disorder, but its negative effects on memory limit its widespread use. Because MST requires a lower total electrical charge to induce seizure, it may be less likely to cause adverse neurocognitive effects. Early research suggested MST is effective, safe, and well-tolerated, but study samples were small and treatment durations short.

Methods: Study subjects were adults with major depression referred for ECT at a single institution. Eligible patients, aged 18–85 years, were experiencing a major depressive episode with or without psychotic features and had a Hamilton Rating Scale for Depression score of >21. Patients receiving medication for the current depressive episode were not excluded, but the regimen was required to remain unchanged. Participants were consecutively assigned to receive open-label MST applied over the prefrontal cortex 2–3 times per week at 1 of 3 doses: high-frequency (i.e., 100 Hz), medium frequency (i.e., 60 Hz with a reduction to 50 Hz if necessary), or low-frequency (i.e., 25 Hz). The primary outcomes were response (≥50% decrease in HAM-D score) and remission (>60% reduction in HAM-D with a final score of <10) following an adequate course of MST defined as ≥8 sessions. A comprehensive battery of neurocognitive tests was performed at baseline and at the end of the treatment.

Results: A total of 108 patients were randomized; 86 completed an adequate course of MST and were included in the analysis: 24 in the high-frequency group, 26 in the medium frequency group; and 36 in the low-frequency group. Although response rates did not differ significantly between the groups, the percentage was highest with high-frequency MST (42%), followed by low-frequency (33%), then moderate-frequency (27%) treatment. Remission occurred in 33% of the high-frequency group, 19% of the medium-frequency group, and 11% of the low-frequency group. The difference between high- and low-frequency MST was statistically significantly (p=0.04). Response and remission patterns were similar in a separate analysis including only the 47 patients who completed the full MST protocol.

Most cognitive measures were not adversely affected by treatment at any intensity. However, autobiographical memory was significantly reduced in all treatment groups. Postictal reorientation time averaged about 10.5 minutes, but was significantly shorter (4 minutes) following high-frequency treatment ($p<0.01$). Serious adverse effects judged to be at least possibly related to MST included the emergence of mania (n=1), hospitalization related to a fall (n=1), and a superficial burn due to a coil malfunction (n=1).

Discussion: Response and remission rates in this study were comparable to or better than those previously reported with ECT and repetitive transcranial magnetic stimulation (rTMS). However, the lack of a comparison group and sequential rather than random allocation to treatment are important study limitations. To address these concerns, the authors are currently conducting a double-blind, randomized, noninferiority trial comparing MST and ECT in patients with depression.

Daskalakis Z, Dimitrova J, McClintock S, Sun Y, et al: Magnetic seizure therapy (MST) for major depressive disorder. *Neuropsychopharmacology* 2019; doi 10.1038/s41386-019-0515-4. From the University of Toronto, Canada; and other institutions. **Source of funding not stated. Eight of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

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