NMI SUMMIT 2024

An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, & Healthy Ageing

Friday 11th October

Featuring Professor Nick Lane, Dr. Iain Hargreaves, Dr. Joseph Pizzorno, Dr. Nina Fuller-Shavel, Dr. Deanna Minich and Benjamin Brown

An event by: Nutritional Medicine Institute

Platinum sponsors: regenerus labs powered by ONNOS, pure encapsulations

1

An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, and Healthy Ageing

Benjamin Brown, ND

Brain Bioenergetics: Can Personalised Nutrition Help Overcome Treatment Failures?

2:45-3:30pm

An event by: Nutritional Medicine Institute

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2

Brain Bioenergetics: Can Personalised Nutrition Help Overcome Treatment Failures?

3

Affiliations and disclosures

Affiliations:

Director, the Nutritional Medicine Institute

Editor, the Nutritional Medicine Journal

Disclosures:

I am a consultant for Pure Encapsulations. I have no other relevant conflicts of interest to disclose.

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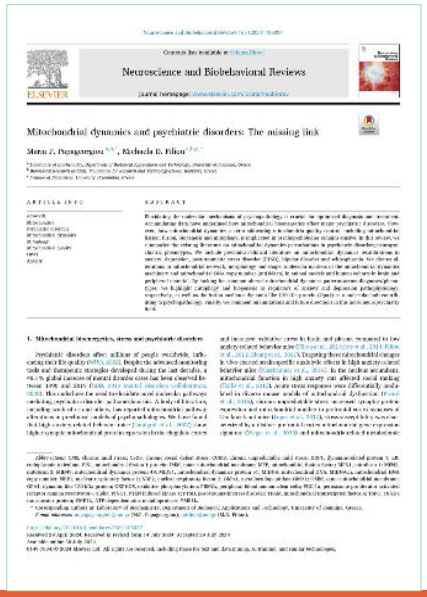
4

The missing link

"Elucidating the molecular mechanisms of psychopathology is crucial for optimized diagnosis and treatment. Accumulating data have underlined how mitochondrial bioenergetics affect major psychiatric disorders."

Biobehav Rev. 2024 Oct;165:105837.


Neuroscience and Biobehavioral Reviews

Mitochondrial dynamics and psychiatric disorders: The missing link

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5

Challenges with current treatment

- **Talking and behavioural therapies** (e.g., cognitive behavioural therapy) significantly alleviate symptoms in only 43–50% of patients with major depressive disorder (MDD).[1]
- **Antidepressant pharmacotherapies** reduce symptoms in 60% of patients vs. 20–40% for placebo treatments.[2]
- Of patients prescribed antidepressants 28% **stop taking their medication** within the first month after prescription, 44% within 3 months, and 73% within 6 months due to side effects.[3]
- **Side effects** include sexual dysfunction (71.8% of patients), weight gain (63.5%), and feeling emotionally numb (64.5%).[4]

1. Lancet Psychiatry. 2016 Feb;3(2):137-44.
2. Lancet. 2018 Apr 7;391(10128):1357-1366.
3. Psychiatry Investig. 2016 Jul;13(4):440-6.
4. Patient Prefer Adherence. 2016 Jul 28;10:1401-7.

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6

Treatment resistance

"**Treatment resistance affects 20–60% of patients with psychiatric disorders**; and is associated with increased healthcare burden and costs up to ten-fold higher relative to patients in general. Whilst there has been a recent increase in the proportion of psychiatric research focussing on treatment resistance, in absolute terms this is less than 1% of the total output and grossly out of proportion to its prevalence and impact."

Mol Psychiatry. 2022 Jan;27(1):58-72.

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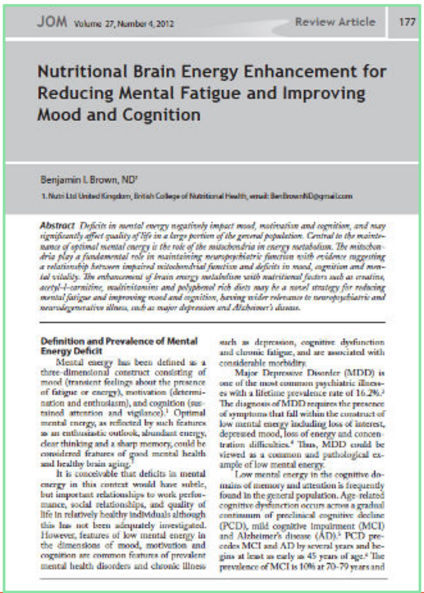
7

A role for mitochondrial nutrition?

"Deficits in mental energy, defined as measures of mood, motivation and cognition, may significantly affect quality of life in a large portion of the general population. Central to the maintenance of optimal mental energy is the role of the mitochondria in energy metabolism in the central nervous system."

JOM. 2012; 27(4): 177-186.



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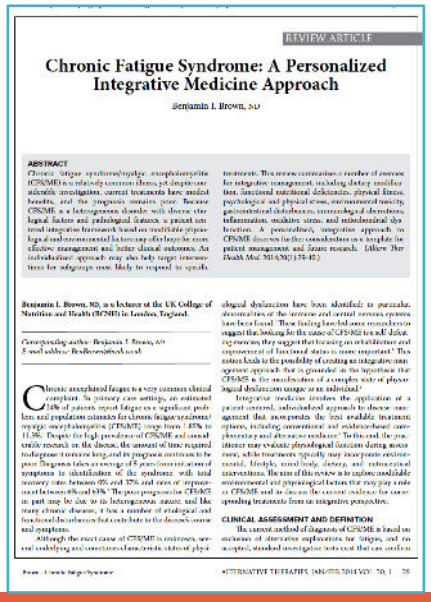
8

Mitochondrial nutrients

"Mitochondrial nutrients have been defined as nutritional compounds that (1) enter the cells and mitochondria following exogenous administration, (2) protect the mitochondria from oxidative damage, and (3) improve mitochondrial function."

Altern Ther Health Med. 2014 Jan-Feb;20(1):29-40.



REVIEW ARTICLE

Chronic Fatigue Syndrome: A Personalized Integrative Medicine Approach

Benjamin I. Brown, ND

ABSTRACT

Benjamin I. Brown, ND, is a lecturer at the UK College of Nutrition and Health (UKCNH) in London, England.

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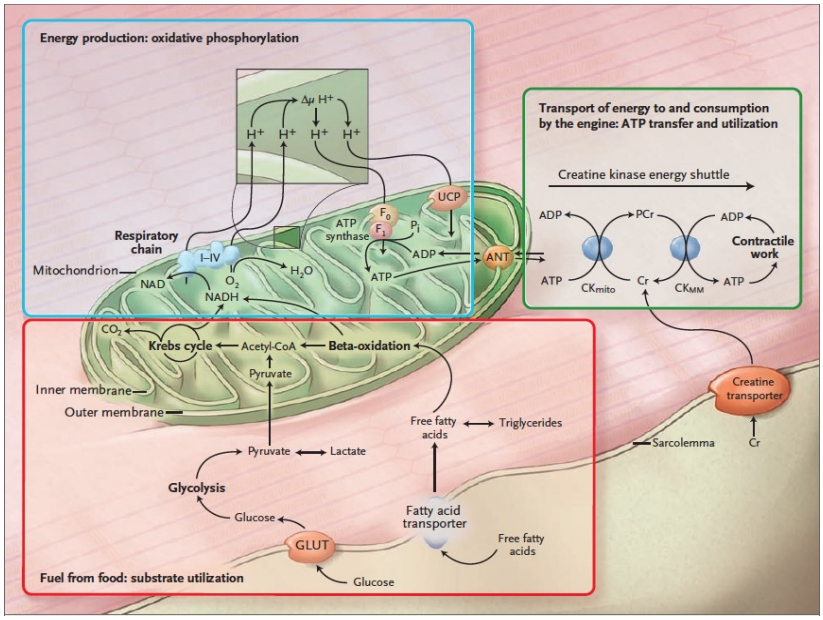
9



N Engl J Med. 2007 Mar 15;356(11):1140-51

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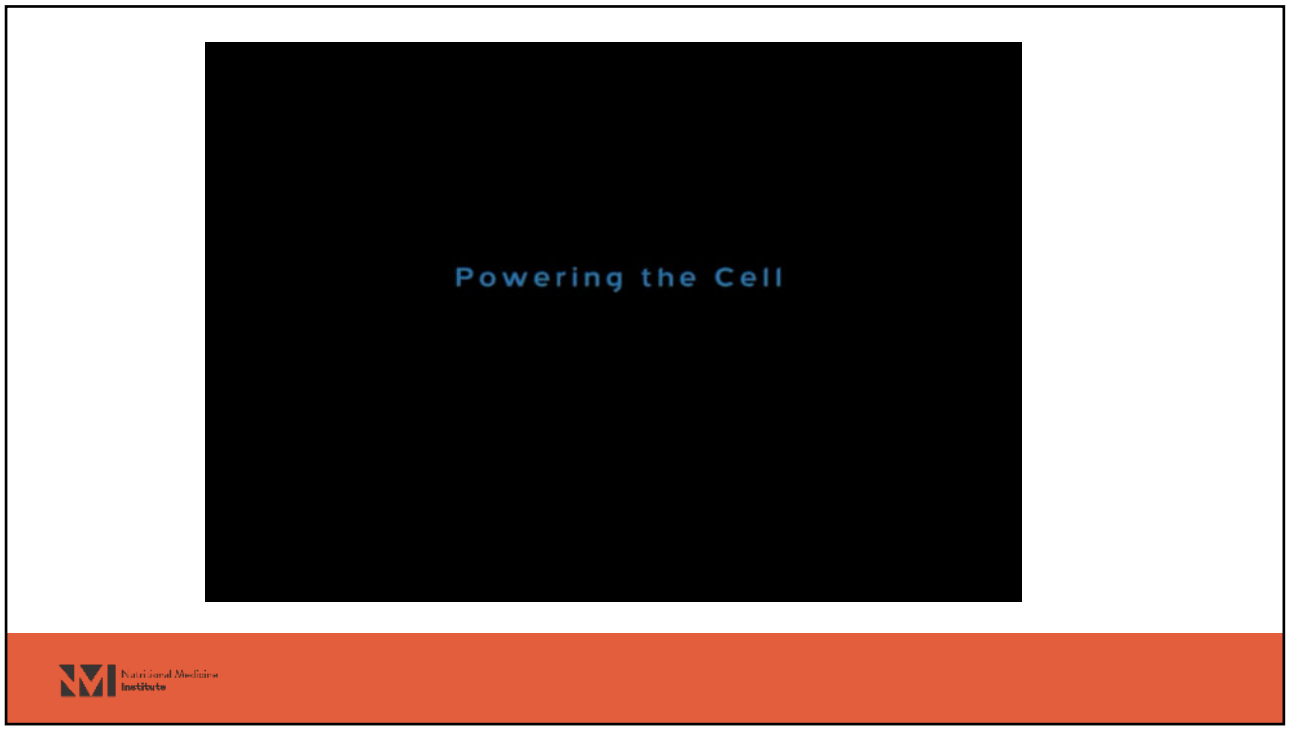
10



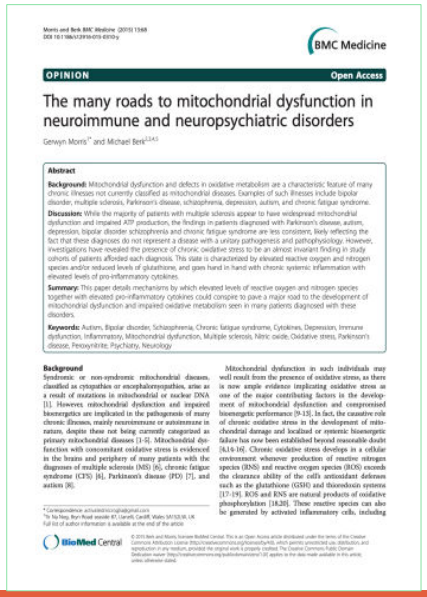
11

12

Neuropsychiatric disorders

"Mitochondrial dysfunction and defects in oxidative metabolism are a characteristic feature of many chronic illnesses **not currently classified as mitochondrial diseases.** Examples of such illnesses include **bipolar disorder, multiple sclerosis, Parkinson's disease, schizophrenia, depression, autism, and chronic fatigue syndrome."**

BMC Med. 2015 Apr 1;13:68.



BMC Medicine

OPINION Open Access

The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders

Genwyn Morris* and Michael Berk[2,3,4,5]

Abstract

Background: Mitochondrial dysfunction and defects in oxidative metabolism are a characteristic feature of many chronic illnesses not currently classified as mitochondrial diseases. Examples of such illnesses include bipolar disorder, multiple sclerosis, Parkinson's disease, schizophrenia, depression, autism, and chronic fatigue syndrome.

Discussion: While the majority of patients with multiple sclerosis appear to have widespread mitochondrial dysfunction and impaired ATP production, the findings in patients diagnosed with Parkinson's disease, autism, depression, bipolar disorder schizophrenia and chronic fatigue syndrome are less consistent, likely reflecting the fact that these diagnoses do not represent a disease with a unitary pathogenesis and pathophysiology. However, investigations have revealed the presence of chronic oxidative stress to be an almost invariant finding in study cohorts of patients afforded each diagnosis. This state is characterized by elevated reactive oxygen and nitrogen species and/or reduced levels of glutathione, and goes hand in hand with chronic systemic inflammation with elevated levels of pro-inflammatory cytokines.

Summary: This paper details mechanisms by which elevated levels of reactive oxygen and nitrogen species together with elevated pro-inflammatory cytokines could conspire to pave a major road to the development of mitochondrial dysfunction and impaired oxidative metabolism seen in many patients diagnosed with these disorders.

Keywords: Autism, Bipolar disorder, Schizophrenia, Chronic fatigue syndrome, Cytokines, Depression, Immune dysfunction, Inflammatory, Mitochondrial dysfunction, Multiple sclerosis, Nitric oxide, Oxidative stress, Parkinson's disease, Peroxynitrite, Psychiatry, Neurology

Background

Syndromic or non-syndromic mitochondrial diseases, classified as cytopathies or encephalomyopathies, arise as a result of mutations in mitochondrial or nuclear DNA [1]. However, mitochondrial dysfunction and impaired bioenergetics are implicated in the pathogenesis of many chronic illnesses, mainly neuroimmune or autoimmune in nature, despite these not being currently categorized as primary mitochondrial diseases [1-5]. Mitochondrial dysfunction with concomitant oxidative stress is evidenced in the brains and periphery of many patients with the diagnoses of multiple sclerosis (MS) [6], chronic fatigue syndrome (CFS) [6], Parkinson's disease (PD) [7], and autism [8].

Mitochondrial dysfunction in such individuals may well result from the presence of oxidative stress, as there is now ample evidence implicating oxidative stress as one of the major contributing factors in the development of mitochondrial dysfunction and compromised bioenergetic performance [9-13]. In fact, the causative role of chronic oxidative stress in the development of mitochondrial damage and localized or systemic bioenergetic failure has now been established beyond reasonable doubt [6,14-16]. Chronic oxidative stress develops in a cellular environment whenever production of reactive nitrogen species (RNS) and reactive oxygen species (ROS) exceeds the clearance ability of the cell's antioxidant defenses such as the glutathione (GSH) and thioredoxin systems [17-19]. ROS and RNS are natural products of oxidative phosphorylation [18,20]. These reactive species can also be generated by activated inflammatory cells, including

BioMed Central

An energetic view of stress

"…**mitochondria are endocrine organelles that provide both the energy and signals that enable and direct stress adaptation.** Neural circuits regulating social behaviour - as well as psychopathological processes - are also influenced by mitochondrial energetics."

Front Neuroendocrinol. 2018 Apr;49:72-85

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review article

An energetic view of stress: Focus on mitochondria

Martin Picard[1,2,3,*], Bruce S McEwen[4], Elissa S Epel[5], Carmen Sandi[6]

ARTICLE INFO

ABSTRACT

"Without the vital force the material organism is unable to feel, or act, or maintain itself (…). Without the vital force the body dies."
Samuel Hahnemann (1833)

1. Introduction

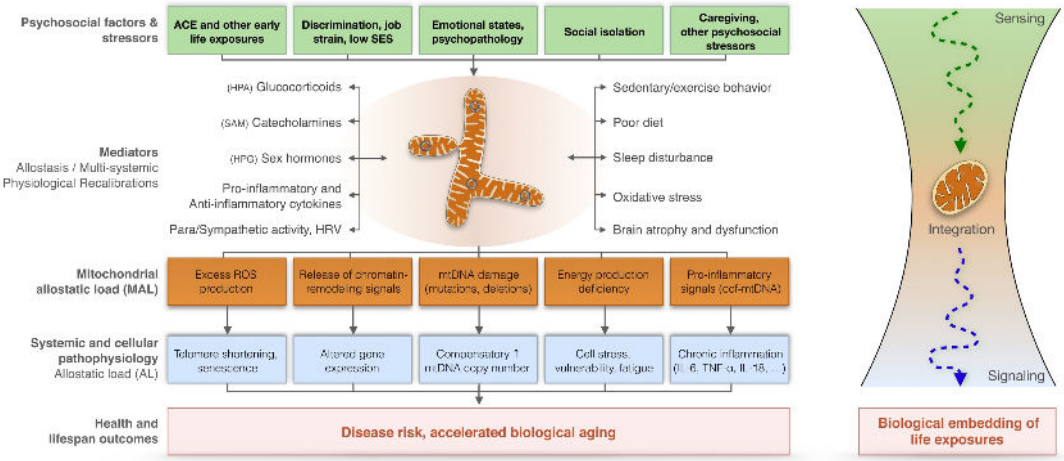
Life emerges when biological structures are animated by energy. Energy is defined as a fundamental entity of nature that is transferred between parts of a system in the production of physical change within the system, and usually regarded as the capacity for doing work (Morowitz Webster, 2017). Without energy, there is no life – molecules alone do not interact in meaningful ways, and complex structures do not assemble nor replicate. A crucial factor that distinguishes the breathing living organism from the inanimate body (i.e., cadaver) is the flow of energy. There are no intrinsic differences in the molecular composition of dead and living organisms. But it is a required quality of living organisms to experience a constant flow of energy through and between their different parts. This flow of energy sustains the movement, chemical reactions, and dynamic changes in the position and organization of molecules that is required to think, feel, move, and execute every element of the stress response. Without energy, stress adaptation is not possible, and the body dies.

This review discusses the concept of stress as an energy-dependent and coordinated process, with an emphasis on the key role that mitochondria plays in these processes. With a broad view of energy, we take a multi-level approach exploring the role of mitochondria in glucocorticoid and catecholamine metabolism, and the effects of stress hormones on energy substrate distribution within the body. We also consider the reciprocal action of steroid hormones on mitochondria. The influence of stress on food/energy-seeking behavior and emerging evidence regarding the influence of mitochondrial functions on mental health, social behaviors, and physiological stress reactivity are also discussed. An energetic view of stress adaptation and pathophysiology opens new possibilities to rationalize and investigate the integrated adaptive and maladaptive effects of stress on the brain and body.

2. Mitochondria transform energy

In human/mammalian cells, a substantial fraction of energy flow occurs through a specific endosymbiotic organelle, the mitochondrion. Mitochondria are the only organelles that contain their own genome –

Mitochondrial stress transduction



Picard and McEwen. Psychosom Med. 2018 Feb/Mar;80(2):126-140.

15

Psychological state and mitochondrial health

A functional index of mitochondrial health (MHI) for human leukocytes has been developed that can distinguish between mitochondrial content per cell (quantity), or in mitochondrial functional capacity (quality). The MHI outperformed individual mitochondrial function measures. **Daily mood and chronic caregiving stress are associated with mitochondrial functional capacity.**

Biol Psychiatry. 2018 Jul 1;84(1):9-17.

Priority Communication

A Mitochondrial Health Index Sensitive to Mood and Caregiving Stress

Martin Picard, Aric A. Prather, Eli Puterman, Alexandre Dufferier, Michael Cocolia, Kirstin Aschbacher, Yan Burelle, and Elissa S. Epel

ABSTRACT

16

Biomarker-led treatable subtypes

"Abnormalities were identified in 67 of 141 treatment refractory depression participants. The CSF abnormalities included: low cerebral folate (*n* = 20), low tetrahydrobiopterin intermediates (*n* = 11), and borderline low-tetrahydrobiopterin intermediates (*n* = 20). Serum abnormalities included abnormal acylcarnitine profile (*n* = 12) and abnormal serum amino acids (*n* = 20). Eighteen patients presented with two or more abnormal metabolic findings. Sixteen patients with cerebral folate deficiency and seven with low tetrahydrobiopterin intermediates in CSF showed improvement in depression symptom inventories after treatment with folinic acid and sapropterin, respectively. No healthy controls had a metabolite abnormality."

Psychol Med. 2023 Oct;53(13):6046-6054.

Metabolomic disorders: confirmed presence of potentially treatable abnormalities in patients with treatment refractory depression and suicidal behavior

Original Article

CAMBRIDGE UNIVERSITY PRESS

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17

Acetyl-l-carnitine

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18

Carnitine deficiency

"Secondary exploratory analyses showed that the degree of acetyl-L-carnitine (ALC) deficiency reflected both the severity and age of onset of MDD. Moreover, these analyses showed that the **decrease in ALC was larger in patients with a history of treatment-resistant depression** (TRD), among whom **childhood trauma** and, specifically, a history of **emotional neglect** and **being female**, predicted the decreased ALC."

Proc Natl Acad Sci U S A. 2018 Aug 21;115(34):8627-8632

Acetyl-L-carnitine deficiency in patients with major depressive disorder

Carla Nasca[a,1], Benedetta Bigio[a,b], Francis S. Lee[c,d], Sarah P. Young[e,f], Marin M. Kautz[g], Ashly Albright[g], James Beasley[f], David S. Millington[e,f], Aleksander A. Mathé[h], James H. Kocsis[i], James W. Murrough[g], Bruce S. McEwen[a,1], and Natalie Rasgon[a,j]

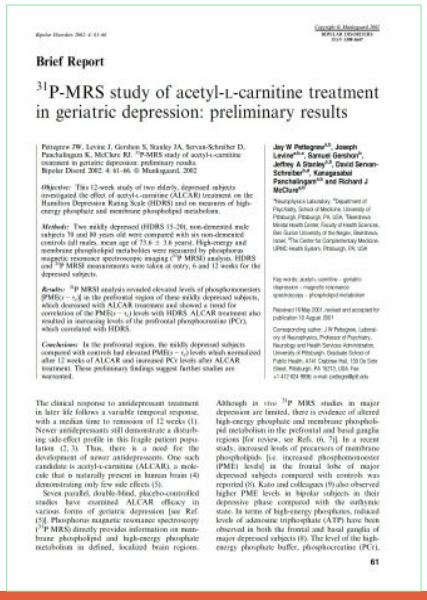
PNAS

19

Can carnitine improve brain energy?

Two mildly depressed, non-demented male subjects 70 and 80 years old were treated with acetyl-L-carnitine at a dose of 3 g daily for 12 weeks. **Acetyl-L-carnitine increased brain prefrontal phosphocreatine levels** which **directly correlated with an improvement in depressive symptoms.**

Bipolar Disord. 2002 Feb;4(1):61-6.



Brief Report

^{31}P-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results

20

Can carnitine improve brain energy?

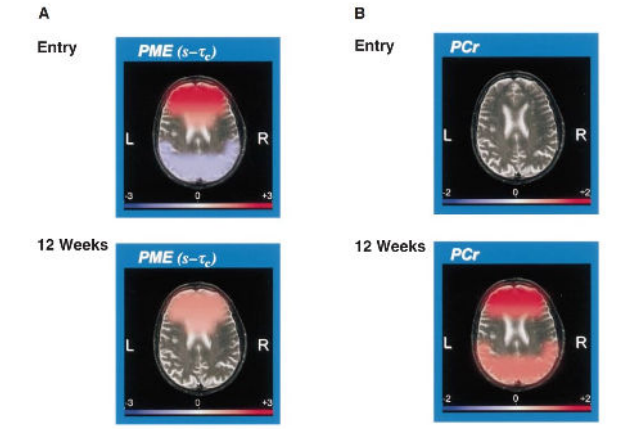


Fig. 3. Z-scores indicated by a color scale of the two mildly depressed subjects compared with controls at entry and 12 weeks for (A) PME($s-\tau_c$) and (B) PCr metabolite levels for those regions with Z-scores greater than 1. The intensity of the colour is scaled to the z-score (mean difference/SD) given on the scale below the image. Z-scores for PME($s-\tau_c$) and PCr levels in the frontal region exceed 3.0 and 2.0, respectively.

Bipolar Disord. 2002 Feb;4(1):61-6.

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21

Acetyl-L-carnitine for depression

"Twelve RCTs (11 of which were ALC monotherapy) with a total of 791 participants were included. Pooled data across nine RCTs (231 treated with ALC versus 216 treated with placebo and 20 no intervention) showed that **ALC significantly reduced depressive symptoms.** In three RCTs comparing ALC versus antidepressants (162 for each group), **ALC demonstrated similar effectiveness compared with established antidepressants** in reducing depressive symptoms. In these latter RCTs, **the incidence of adverse effects was significantly lower in the ALC group** than in the antidepressant group. Subgroup analyses suggested that **ALC was most efficacious in older adults.**"

Psychosom Med. 2018 Feb/Mar;80(2):154-159.

SYSTEMATIC REVIEW/META-ANALYSIS

Acetyl-L-Carnitine Supplementation and the Treatment of Depressive Symptoms: A Systematic Review and Meta-Analysis

Nicola Veronese, MD, Brendon Stubbs, PhD, Marco Solmi, MD, Olesya Ajnakina, PhD, Andre F. Carvalho, MD, and Stefania Maggi, MD

ABSTRACT

INTRODUCTION

Psychosomatic Medicine, V 80 • 154-159 154 February/March 2018

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22

Clinical use of acetyl-l-carnitine

People who may be more likely to respond:

- Symptoms of pain (e.g., neuropathy, fibromyalgia, migraine).
- Symptoms of fatigue (e.g., age-related fatigue, chronic fatigue syndrome).
- Older age.
- Low serum acetyl-L-carnitine.
- Elevated inflammatory biomarkers.
- Insulin resistance.

Dose and duration:

- 3 grams daily, in divided doses, for at least 8-weeks (onset of action has been reported in as little as 1-week).

23

Clinical use of acetyl-l-carnitine

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1. Di Stefano G, Di Lionardo A, Galosi E, Truini A, Cruccu G. Acetyl-L-carnitine in painful peripheral neuropathy: a systematic review. J Pain Res. 2019 Apr 26;12:1341-1351.
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3. Bersani G, Meco G, Denaro A, Liberati D, Colletti C, Nicolai R, Bersani FS, Koverech A. L-Acetylcarnitine in dysthymic disorder in elderly patients: a double-blind, multicenter, controlled randomized study vs. fluoxetine. Eur Neuropsychopharmacol. 2013 Oct;23(10):1219-25.
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24

Creatine

25

Creatine deficiency

- Lower creatine levels in the prefrontal cortex are associated with **low mood/increased depression**,[1] and a history of **geriatric depression**.[2]
- Creatine levels are lower in white matter of patients with **generalized anxiety disorder** (GAD) related to early trauma.[3]
- Creatine levels in the hippocampal region of the brain are lower in patients with **post-traumatic stress disorder** (PTSD).[4,5]
- Several brain regions have reduced creatine in patients with **bipolar disorder**, however, evidence is conflicting.[6]

1. J Psychopharmacol. 2021 Dec;35(12):1464-1472.
2. Psychiatry Res. 2009 Apr 30;172(1):49-54.
3. Psychiatry Res. 2006 Jun 30;147(1):27-39.
4. Psychiatry Res. 2008 Feb 28;162(2):147-57.
5. Can J Psychiatry. 2002 Sep;47(7):666-70.
6. Mol Psychiatry. 2005 Oct;10(10):900-19.

26

Can creatine improve brain energy?

Consumption of 20 g creatine-monohydrate a day for 4 weeks resulted in **a statistically significant in brain creatine levels** measured by ^{1}H MRS by, on average, 4.7% in grey matter and 11.5% in cerebral white matter.

Am J Physiol. 1999 Sep;277(3):R698-704.


Increase of total creatine in human brain after oral supplementation of creatine-monohydrate

P. DECHENT, P. J. W. POUWELS, B. WILKEN, F. HANEFELD AND J. FRAHM

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27

Clinical trials of creatine for depression

Study	Population (n)	Design	Creatine Dose	Duration	Effect	Significant Adverse Effects Related to Creatine
Roitman 2007 [186]	MDD-D (n = 8); BD-D (n = 2)	Open-label, adjunctive	3–5 g/day	4 weeks	Average HAM-D scores declined from 23.1 at baseline to 12.6 at week 4	Both bipolar subjects developed hypomania/mania
Kondo 2011 [133]	Adolescent girls with MDD-D (n = 5)	Open-label, adjunctive	4 g/day	8 weeks	The mean CDRS-R score fell by 56.6%	None
Kondo 2016 [170]	Adolescent and young-adult women with MDD-D (n = 34)	Open-label, adjunctive, dose-ranging	2 g, 4 g, or 10 g/day	8 weeks	Creatine increased frontal cortical phosphocreatine levels in a fashion associated with lower depression ratings	None
Lyoo 2012 [188]	Women with MDD-D (n = 52)	Randomized, double-blind, placebo-controlled, adjunctive	3 g/day × 1 week then 5 g/day × 7 weeks	8 weeks	HAM-D scores in the creatine group fell by 79.7% by week 8, compared to 62.5% in the placebo group	None
Nemets 2013 [189]	MDD-D (n = 18)	Randomized, double-blind, placebo-controlled, adjunctive	5 g/day or 10 g/day	4 weeks	No significant difference between creatine and placebo in HAM-D scores	None
Hellem 2015 [193]	Methamphetamine dependence with depression (n = 14)	Open-label, monotherapy	5 g/day	8 weeks	Mean HAM-D scores fell to 10.4 by week 2, representing response	Gastrointestinal symptoms (n = 5) and muscle cramps (n = 2)
Kious 2017 [190]	Women with MDD-D (n = 15)	Open-label, adjunctive	5 g/day (with 5-HTP 200 mg twice daily)	8 weeks	HAM-D scores improved by ~60% by week 8	None
Toniolo 2017 [191]	BD-D (n = 18)	Randomized, double-blind, placebo-controlled, adjunctive	6 g/day	6 weeks	Significant improvement in verbal fluency but no significant changes in other measures reported	None
Toniolo 2018 [192]	BD-D (n = 53)	Randomized, double-blind, placebo-controlled, adjunctive	6 g/day	6 weeks	No significant difference in MADRS scores between groups, but MADRS remission rate was significantly greater in creatine group (52.9% vs. 11.1%)	Two participants in creatine group developed hypomania/mania

Biomolecules. 2019 Aug 23;9(9):406.

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28

A novel pilot study

Patients with treatment-resistant depression (8 unipolar and 2 bipolar) received 3-5 g of creatine monohydrate for four weeks. Both bipolar patients developed hypomania/mania and withdrew. One patient with unipolar depression improved considerably after one week and withdrew. For the remaining seven patients, **all depression scores significantly improved** (51% had a reduction in HAM-D scores of greater than 50%).

Bipolar Disord. 2007 Nov;9(7):754-8.


Brief Report

Creatine monohydrate in resistant depression: a preliminary study

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29

Adolescent major depression

Treatment resistant adolescent females with major depressive disorder received creatine at a dose of 4 grams daily for 8-weeks. After the creatine intervention **the Children's Depression Rating Scale-Revised (CDRS-R) decreased by 56%**. Brain scans, by (31)P MRS, revealed a significant increase in brain phosphocreatine (PCr) concentration when compared to healthy controls.

J Affect Disord. 2011 Dec;135(1-3):354-61.


Journal of Affective Disorders

Preliminary communication

Open-label adjunctive creatine for female adolescents with SSRI-resistant major depressive disorder: A 31-phosphorus magnetic resonance spectroscopy study

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30

Adult depression

Adult women (n=15) with major depressive disorder who were currently taking but **had failed to respond to selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) monotherapy** received 5-HTP (200 mg daily) and creatine (5 g daily) for 8-weeks. **Mean HAM-D scores declined from 18.9 at pretreatment visits to 7.5 (P < 0.00001), a decrease of 60%.** Participants did not experience any serious treatment-related adverse events.

J Clin Psychopharmacol. 2017 Oct;37(5):578-583.


ORIGINAL CONTRIBUTION

An Open-Label Pilot Study of Combined Augmentation With Creatine Monohydrate and 5-Hydroxytryptophan for Selective Serotonin Reuptake Inhibitor– or Serotonin-Norepinephrine Reuptake Inhibitor–Resistant Depression in Adult Women

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31

Clinical use of creatine

People who may be more likely to respond:

- Symptoms of poor cognition, poor memory, mental fatigue.
- Poor muscle strength, physical fatigue.
- Vegetarian or vegan diet.

Dose and duration:

- 3-6 grams, once daily, for at least 4-8 weeks.
- A loading phase of 20 g/day (4 x 5 g) for 5 days and a maintenance dose of 3 to 5 g/day is sometimes recommended. However, similar (intramuscular) phosphocreatine levels can be accomplished by taking 3 g/ day over 30 days. After 2 days of loading, maximal accumulation of (intramuscular) creatine occurs and therefore amounts of 20 g/day are unnecessary and will minimise GI side-effects associated with 20 g doses.

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32

Clinical use of creatine

References:

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4. Persky AM, Brazeau GA, Hochhaus G. Pharmacokinetics of the dietary supplement creatine. Clin Pharmacokinet. 2003;42(6):557-74.

33

CoQ10

34

CoQ10 deficiency

"We found that plasma CoQ10 was significantly (p=0.0002) lower in depressed patients than in normal controls. **51.4% of the depressed patients had plasma CoQ10 values that were lower** than the lowest plasma CoQ10 value detected in the controls. **Plasma CoQ10 was significantly lower in** patients with **treatment resistant depression** and with **chronic fatigue syndrome** than in the other depressed patients. There were no significant correlations between plasma CoQ10 and the HDRS."

Neuro Endocrinol Lett. 2009;30(4):462-9.

Neuroendocrinology Letters Volume 30 No 4 2009

Lower plasma Coenzyme Q10 in depression: a marker for treatment resistance and chronic fatigue in depression and a risk factor to cardiovascular disorder in that illness

ORIGINAL ARTICLE

Abstract

There is now evidence that major depression is accompanied by an induction of inflammatory and oxidative and nitrosative stress (IO&NS) pathways and by a lowered antioxidant status. Coenzyme Q10 (CoQ10) is a strong antioxidant that has anti-inflammatory effects.

This paper examines the plasma concentrations of CoQ10 in 35 depressed patients and 22 normal volunteers and the relationships between plasma CoQ10 and treatment resistant depression (TRD), the severity of illness as measured by means of the Hamilton Depression Rating Scale (HDRS) and the presence of chronic fatigue syndrome (CFS). We found that plasma CoQ10 was significantly (p=0.0002) lower in depressed patients than in normal controls. 51.4% of the depressed patients had plasma CoQ10 values that were lower than the lowest plasma CoQ10 value detected in the controls. Plasma CoQ10 was significantly lower in patients with TRD and with CFS than in the other depressed patients. There were no significant correlations between plasma CoQ10 and the HDRS.

The results show that lower CoQ10 plays a role in the pathophysiology of depression and in particular in TRD and CFS accompanying depression. It is suggested that depressed patients may benefit from CoQ10 supplementation.

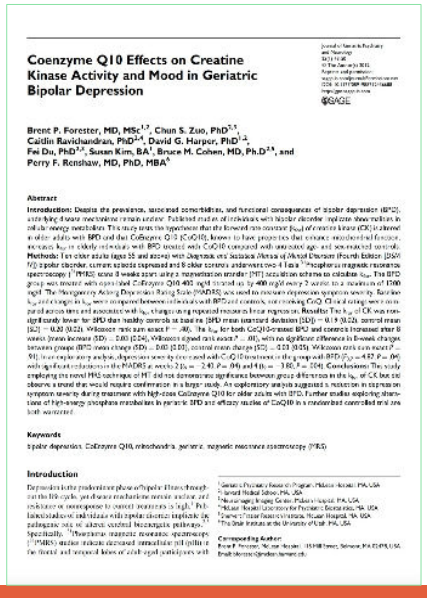
The findings that lower CoQ10 is a risk factor to coronary artery disease and chronic heart failure (CHF) and mortality due to CHF suggest that low CoQ10 is another factor explaining the risk to cardiovascular disorder in depression. Since statins significantly lower plasma CoQ10, depressed patients and in particular those with TRD and CFS represent populations at risk to statin treatment.

35

Can CoQ10 improve brain energy?

Older adults (n=10, aged 55 and above) with bipolar disorder received CoQ10 400 mg daily titrated up by 400 mg daily every 2 weeks to a maximum of 1200 mg daily over 8-weeks and underwent brain scans (31PMRS) to assess energy metabolism as creatine kinase. **Creatine kinase for both groups increased after 8-weeks, with no significant difference between groups.** In an exploratory analysis, depression severity decreased with CoQ10 treatment in the group with bipolar disorder with significant reductions in symptoms scores at weeks 2 and 4.

J Geriatr Psychiatry Neurol. 2012 Mar;25(1):43-50.



Coenzyme Q10 Effects on Creatine Kinase Activity and Mood in Geriatric Bipolar Depression

Brent P. Forester, MD, MSc[1,2], Chun S. Zuo, PhD[3,1], Caitlin Ravichandran, PhD[2,4], David G. Harper, PhD[1,2], Fei Du, PhD[1,2], Susan Kim, BA[1], Bruce M. Cohen, MD, Ph.D[2,5], and Perry F. Renshaw, MD, PhD, MBA[6]

Abstract

Introduction: Despite the prevalence, substantial comorbidities, and functional consequences of bipolar depression (BPD), underlying brain mechanisms remain unclear. Published studies of individuals with bipolar disorder indicate abnormalities in cellular energy metabolism. This study tests the hypothesis that the lowered rate constant $k_{forward}$ of creatine kinase (CK) is altered in older adults with BPD and that Coenzyme Q10 (CoQ10), known to have properties that enhance mitochondrial function, increases $k_{forward}$ in elderly individuals with BPD treated with CoQ10 compared with age- and sex-matched controls.

Methods: Ten older adults (aged 55 and above) with Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM IV) bipolar disorder, current episode depressed and 8 older controls underwent two 4 Tesla ^{31}P-magnetic resonance spectroscopy (^{31}PMRS) scans 8 weeks apart using a magnetization transfer (MT) acquisition scheme to calculate $k_{forward}$. The BPD group was treated with open-label Coenzyme Q10 400 mg/d titrated up by 400 mg/d every 2 weeks to a maximum of 1200 mg/d. The Montgomery Asberg Depression Rating Scale (MADRS) was used to measure depression symptom severity. Baseline $k_{forward}$ and change in $k_{forward}$ were compared between individuals with BPD and controls, and among CoQ10 clinical ratings were compared across time and associated with $k_{forward}$ changes using repeated measures linear regression. Results: The $k_{forward}$ of CK was significantly lower for BPD than healthy controls at baseline (BPD mean (standard deviation [SD]) = 0.19 (0.02), control mean [SD] = 0.28 (0.02)). Wilcoxon rank sum exact $P = .01$). The $k_{forward}$ for both CoQ10-treated BPD and controls increased after 8 weeks (mean increase [SD] = 0.03 [0.04]), Wilcoxon signed rank exact $P = .08$), with no significant difference in 8-week changes between groups (BPD mean change [SD] = 0.03 [0.03], control mean change [SD] = 0.03 [0.05], Wilcoxon rank sum exact $P = .91$). In an exploratory analysis, depression severity decreased with CoQ10 treatment in the group with BPD ($t_{10} = 4.87$, $P = .006$) with significant reductions in the MADRS at weeks 2 ($t_{10} = 2.40$, $P = .04$) and 4 ($t_{10} = 3.82$, $P = .004$). Conclusions: This study employing the novel MRS technique of MT did not demonstrate significant between-group differences in the $k_{forward}$ of CK but did observe a trend that would require confirmation in a larger study. An exploratory analysis suggested a reduction in depression symptom severity during treatment with high-dose Coenzyme Q10 for older adults with BPD. Further studies exploring alterations of high-energy phosphate metabolism in geriatric BPD and efficacy studies of CoQ10 in a randomized controlled trial are both warranted.

Keywords

bipolar depression, CoEnzyme Q10, mitochondria, geriatric, magnetic resonance spectroscopy (MRS)

Introduction

Corresponding Author:

36

Studies examining antidepressant effects of CoQ10

Study	Subjects	Design	Dose	Duration	Outcome
Majmasanaye et al 2024.	Patients with moderate and severe depression (n=69).	Randomized placebo-controlled trial.	200 mg daily.	8-weeks.	Significantly reduced depression and fatigue. Improved quality of life. Reduced nitric oxide decreased, increased total thiol groups.
Karamali et al 2022.	women with polycystic ovary syndrome (n=55).	Randomized placebo-controlled trial.	100 mg daily.	12-weeks.	Reduction in depression and anxiety scores. Reduction in hs-CRP, total testosterone, DHEAS, hirsutism, SHBG, TAC and MDA levels.
Maguire et al 2021.	Patietns with schizophrenia and schizoaffective disorder (n=72).	Randomized placebo-controlled trial.	300 mg daily.	6-months.	No beneficial for cognitive, psychological or health-related outcomes.
Jahangard et al 2019.	Bipolar disorder patients (n=69).	Randomized placebo-controlled trial.	200 mg daily.	8-weeks.	Reduced inflammation and oxidative stress during depressive episode.
Mehrpooya et al 2018.	Patients with bipolar disorder with a current depressive episode (n=69) .	Randomized placebo-controlled trial.	200 mg daily.	8-weeks.	Significantly improved symptoms of depression. Higher number of treatment responders.
Sanoobar et al 2016.	Multiple sclerosis patients (n=48).	Randomized placebo-controlled trial.	400 mg daily.	12-weeks.	Significant reduction in depression and fatigue.
Forester et al 2015.	Older adults with bipolar depression (n=19).	Open label.	800 mg daily.	4-weeks.	Significant reduction in total depression score.
Alcocer-Gómez et al 2014.	Fibromyalgia patients (n=20).	Randomized placebo-controlled trial.	300 mg daily.	40-days .	Reduced depressive symptoms, restoration of platelet serotonin and CoQ10.
Lesser et al 2013.	Breast cancer patients (n=236).	Randomized placebo-controlled trial.	300 mg daily.	24-weeks.	No significant effect on stress, depression or fatigue scores.

37

Studies examining antidepressant effects of CoQ10

1. Majmasanaye M, Mehrpooya M, Amiri H, Eshraghi A. Discovering the Potential Value of Coenzyme Q10 as an Adjuvant Treatment in Patients With Depression. J Clin Psychopharmacol. 2024 May-Jun 01;44(3):232-239. doi: 10.1097/JCP.0000000000001845. PMID: 38684047.
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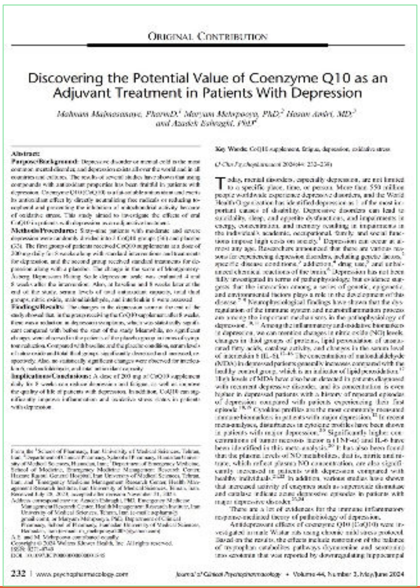
38

CoQ10 for depression

Patients with moderate and severe depression (n=69) received CoQ10 at a dose of 200 mg daily for 8 weeks along with standard interventions and treatments for depression, or placebo. The CoQ10 group experienced a **statistically significant reduction in depression scores,** compared to no change with placebo. Compared with baseline and the placebo condition, **serum levels of nitric oxide decreased, and total thiol groups increased** significantly. No statistically significant changes were observed for interleukin 6, malondialdehyde, and total antioxidant capacity.

J Clin Psychopharmacol. 2024 May-Jun 01;44(3):232-239.


ORIGINAL CONTRIBUTION

Discovering the Potential Value of Coenzyme Q10 as an Adjuvant Treatment in Patients With Depression

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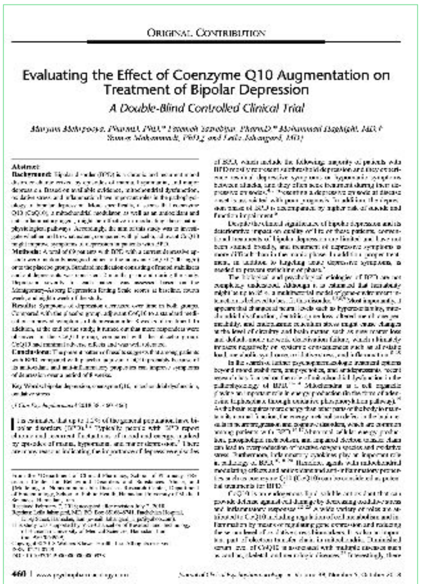
39

CoQ10 for bipolar depression

Patients with bipolar disorder (n=69) with a current depressive episode received adjuvant CoQ10 (200 mg/d), or placebo, for 8-weeks. **CoQ10 treatment significantly improved symptoms of depression**, compared to placebo, with a **higher number of treatment responders** (18% chance vs. placebo of improvement of over 50%). CoQ10 had minimal adverse effects and was well tolerated.

J Clin Psychopharmacol. 2018 Oct;38(5):460-466.


ORIGINAL CONTRIBUTION

Evaluating the Effect of Coenzyme Q10 Augmentation on Treatment of Bipolar Depression

A Double-Blind Controlled Clinical Trial

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40

Clinical use of CoQ10

People who may be more likely to respond:

- Plasma CoQ10 <1µmol/l (may be unreliable).
- Elevated inflammatory biomarkers (CRP, IL-6, TNF-α).
- Elevated oxidative stress (malondialdehyde, total antioxidant capacity, SOD activity).
- Nutrient-drug interactions (statins, beta blockers, propranolol and metoprolol, phenothiazines and tricyclic antidepressants).

Dose and duration:

- 100-300 mg daily, in divided doses, for at least 8-12 weeks.

41

Clinical use of CoQ10

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42

Nutritional ketosis

43

Diet, ketosis and mitochondrial function

"…the **dramatic shift in energy metabolism** and subsequent increase in circulating ketones induced by a ketogenic diet **can enhance mitochondrial function and endogenous antioxidant defence.** The primary mechanism behind these adaptations appears to be the increased demand for fat oxidation resulting from carbohydrate restriction. However, **ketones themselves have important metabolic and signalling effects that enhance mitochondrial function and endogenous antioxidant defence**…"

J Nutr Metab. 2018 Feb 11;2018:5157645.

Hindawi

Review Article

Nutritional Ketosis and Mitohormesis: Potential Implications for Mitochondrial Function and Human Health

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Impaired mitochondrial function often results in excessive production of reactive oxygen species (ROS) and is involved in the etiology of many chronic diseases, including cardiovascular disease, diabetes, neurodegenerative disorders, and cancer. Moderate levels of mitochondrial ROS, however, can protect against chronic disease by inducing upregulation of mitochondrial capacity and endogenous antioxidant defense. This phenomenon, referred to as mitohormesis, is induced through increased reliance on mitochondrial respiration, which can occur through diet or exercise. Nutritional ketosis is a safe and physiological metabolic state induced through a ketogenic diet low in carbohydrate and moderate in protein. Such a diet increases reliance on mitochondrial respiration and may, therefore, induce mitohormesis. Furthermore, the ketone β-hydroxybutyrate (BHB), which is elevated during nutritional ketosis to levels no greater than those resulting from fasting, acts as a signaling molecule in addition to its traditionally known role as an energy substrate. BHB signaling induces adaptations similar to mitohormesis, thereby expanding the potential benefit of nutritional ketosis beyond carbohydrate restriction. This review describes the evidence supporting enhancement of mitochondrial function and endogenous antioxidant defense in response to nutritional ketosis, as well as the potential mechanisms leading to these adaptations.

1. Introduction

All cells of the human body require ATP as the fundamental energy source to support life. Because mitochondria produce the majority of ATP, impaired mitochondrial function is implicated in the majority of today's most concerning chronic and degenerative health conditions including obesity, cardiovascular disease, cancer, diabetes, sarcopenia, and neurodegenerative diseases [1]. Much of this association between mitochondrial function and disease can be attributed to excessive mitochondrial production of reactive oxygen species (ROS) [2].

Although mitochondrial ROS (mtROS) are generally considered harmful, which is certainly the case at high concentrations, modest levels stimulate necessary biological processes such as proliferation, differentiation, and immunity [3]. Adaptations that enhance resistance to oxidative stress are also induced by mtROS [3], possibly decreasing net ROS production during basal metabolism. This adaptive response is called mitohormesis [4–6] and is a promising mechanism through which lifestyle interventions that enhance mitochondrial function may, in turn, enhance resistance to chronic and degenerative diseases.

By dramatically shifting energy metabolism towards ketogenesis and fatty acid oxidation, ketogenic diets are likely to have a profound effect on mitochondrial function. However, despite the rapidly growing amount of research on ketogenic diets and their effects on various disease states, only a small amount of this research has focused on mitochondrial function or oxidative stress. The well-established increase in fat oxidation induced by a ketogenic diet [7, 8] clearly indicates prominent connection with mitochondrial function and, in turn, oxidative stress and mitohormesis [5, 6, 9]. Therefore, the purpose of this review is to describe the current, but limited, understanding of how ketogenic diets may affect mitochondrial function and resistance to oxidative

44

Potential mechanistic effects of a ketogenic diet

Neural Deficit	Neural Symptom	Ketogenic Therapy Effect
Mitochondrial dysfunction	Decrease in energy level production	Induces mitochondrial biogenesis
Oxidative stress and inflammation	Increase in ROS leading to neuronal damage	Decreases ROS levels with ketone bodies; increases HDL cholesterol levels for neuroprotection
Na/K ATPase loss of function	Impaired ATP production via oxidative phosphorylation	Provides alternative energy source via ketosis, replenishes acetyl-CoA
Imbalance in monoaminergic activity	Changes in behaviour and emotion due to imbalance in neurotransmitter concentrations	Regulates neurotransmitter metabolites via ketone bodies and intermediates
GABA/glutamate imbalance	Depressive and mania symptoms, unsustainable energy requirements, and neuronal damage	Increases GABA levels whilst decreasing glutamate levels

J Psychiatr Brain Sci. 2022;7(5):e220009.

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45

Ketogenic diets for mood and anxiety

"**Twelve heterogeneous studies** (stated as ketogenic interventions, albeit with incomplete carbohydrate reporting and measurements of ketosis; diet duration: 2 weeks to 3 years; *n* = 389; age range 19 to 75 years) **were included in the analysis.** This included nine case reports, two cohort studies and one observational study."

"There was **some evidence for efficacy of ketogenic diets in those with bipolar disorder, schizoaffective disorder and possibly unipolar depression/anxiety.** Relapse after discontinuation of the diet was reported in some individuals."

BJPsych Open. 2023 Apr 17;9(3):e70.


Efficacy of low carbohydrate and ketogenic diets in treating mood and anxiety disorders: systematic review and implications for clinical practice

National Medicine Institute

46

Schizophrenia: case report

A 70-year-old woman with a diagnosis of schizophrenia since the age of seventeen commenced a low-carbohydrate ketogenic diet. **After about 8-days on the diet she reported that her auditory and visual hallucinations had stopped.** After 1-year on the diet she has had no recurrence of her auditory or visual hallucinations, despite 2–3 episodes of dietary non-compliance that lasted several days.

Nutr Metab (Lond). 2009 Feb 26;6:10.

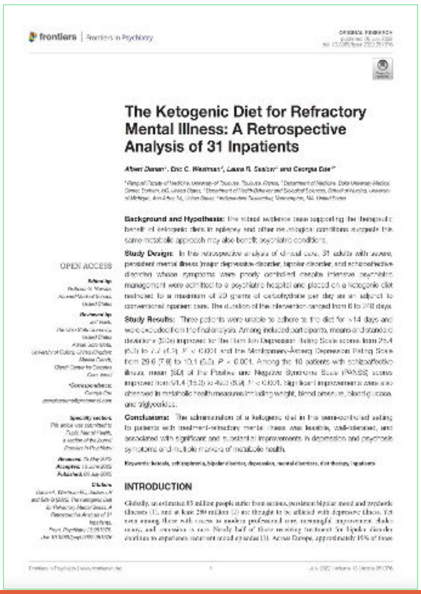
Nutritional Medicine Institute

47

Refractory mental illness

"In this retrospective analysis of clinical care, **31 adults with severe, persistent mental illness (major depressive disorder, bipolar disorder, and schizoaffective disorder)** whose symptoms were **poorly controlled despite intensive psychiatric management** were admitted to a psychiatric hospital and placed on a ketogenic diet restricted to a maximum of 20 grams of carbohydrate per day as an adjunct to conventional inpatient care. The duration of the intervention ranged from 6 to 248 days."

Front Psychiatry. 2022 Jul 6;13:951376.



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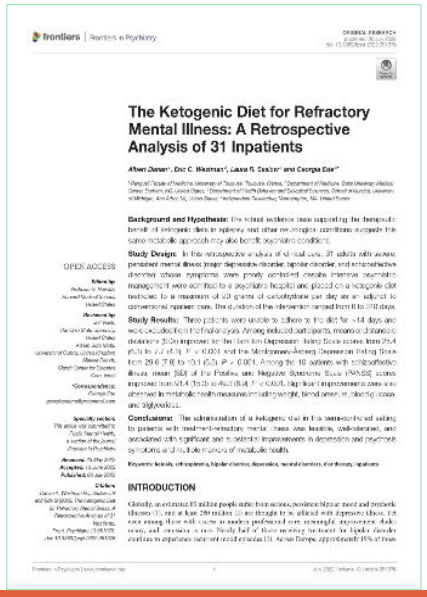
48

Refractory mental illness

"Among included participants, means and standard deviations (SDs) improved for the Hamilton Depression Rating Scale **scores from 25.4 (6.3) to 7.7 (4.2), P < 0.001** and the Montgomery-Åsberg Depression Rating Scale from 29.6 (7.8) to 10.1 (6.5), P < 0.001. Among the 10 patients with schizoaffective illness, mean (SD) of the Positive and Negative Syndrome Scale (PANSS) **scores improved from 91.4 (15.3) to 49.3 (6.9), P < 0.001**. Significant improvements were also observed in metabolic health measures including weight, blood pressure, blood glucose and triglycerides."

Front Psychiatry. 2022 Jul 6;13:951376.



frontiers | Frontiers in Psychiatry

The Ketogenic Diet for Refractory Mental Illness: A Retrospective Analysis of 31 Inpatients

OPEN ACCESS

INTRODUCTION

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49

Schizophrenia or bipolar disorder

A 4–month pilot study to investigating the effects of a ketogenic diet (KD) on individuals with schizophrenia or bipolar disorder (n=23) with existing metabolic abnormalities demonstrated improvements in metabolic health, with no participants meeting metabolic syndrome criteria by study conclusion. **Participants with schizophrenia showed a 32 % reduction in Brief Psychiatric Rating Scale scores. Overall Clinical Global Impression (CGI) severity improved by an average of 31 %,** and the proportion of participants that started with elevated symptomatology improved at least 1–point on CGI (79 %). Psychiatric outcomes across the cohort encompassed increased life satisfaction (17 %) and enhanced sleep quality (19 %).

Psychiatry Res. 2024 May;335:115866.

Psychiatry Research

Ketogenic Diet Intervention on Metabolic and Psychiatric Health in Bipolar and Schizophrenia: A Pilot Trial

ARTICLE INFO

ABSTRACT

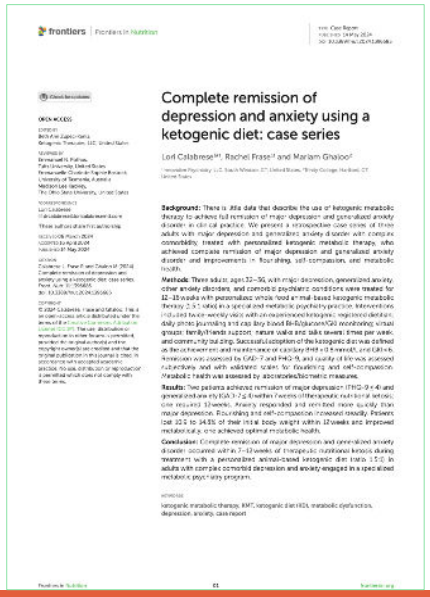
National Medicine Institute

50

Depression and anxiety

"**Two patients achieved remission of major depression (PHQ-9 ≤ 4) and generalized anxiety (GAD-7 ≤ 4) within 7 weeks of therapeutic nutritional ketosis**; one required 12 weeks. Anxiety responded and remitted more quickly than major depression. Flourishing and self-compassion increased steadily. Patients lost 10.9 to 14.8% of their initial body weight within 12 weeks and improved metabolically; one achieved optimal metabolic health."

Front Nutr. 2024 May 14;11:1396685.


frontiers | Frontiers in Nutrition

Complete remission of depression and anxiety using a ketogenic diet: case series

Lori Calabrese[1*], Rachel Frase[2] and Mariam Ghaloo[2]

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51

Clinical indications for a ketogenic diet

People who may be more likely to respond:

- Metabolic dysfunction (e.g., insulin resistance, type-2 diabetes, metabolic syndrome, obesity, antipsychotic medication).

Considerations for clinical implementation:

- Diet personalisation.
- Instruction/monitoring.
- Medication management.
- Adequate fluid and sodium intake.
- Monitoring potential adverse effects.

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52

Clinical indications for a ketogenic diet

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53

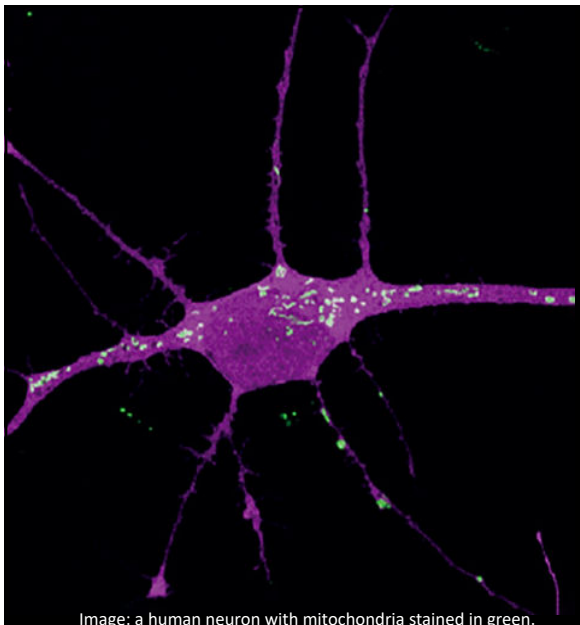

Image: a human neuron with mitochondria stained in green.

"Trying to apply any treatment modality whether psychological, pharmacological, or social, to a brain that cannot function normally because of lack of an essential nutrient is like trying to run a 220-volt electrical appliance on a 120-volt system… No psychiatric patients have fluoxetine or paroxetine deficiencies…. Mental health professionals should be well advised to learn some nutritional biochemistry to keep abreast of this area of scientific development."

– David F. Horrobin, MD, PhD, 2002

54

Nutritional psychiatry

"A growing evidence base suggests that diet and nutrition have a causal role in behavioural health disorders, and dietary interventions may improve outcomes in individuals with these disorders. Accordingly, nutritional medicine should be a focal point in psychiatric practice […]."

Nutr Rev. 2021 Feb 11;79(3):247-260.

Lead Article

Nutrition and behavioral health disorders: depression and anxiety

Penny M. Kris-Etherton*, Kristina S. Petersen, Joseph R. Hibbeln, Daniel Hurley, Valerie Kolick, Seveta Peoples, Nancy Rodriguez, and Gail Woodward-Lopez

Suboptimal nutrition has been implicated in the underlying pathology of behavioral health disorders and may impede treatment and recovery. Thus, optimizing nutritional status should be a treatment for these disorders and is likely important for prevention. The purpose of this narrative review is to describe the global burden and features of depression and anxiety, and summarize recent evidence regarding the role of diet and nutrition in the prevention and management of depression and anxiety. Current evidence suggests that healthy eating patterns that meet food-based dietary recommendations and nutrient requirements may assist in the prevention and treatment of depression and anxiety. Randomized controlled trials are needed to better understand how diet and nutrition-related biological mechanisms affect behavioral health disorders, to assist with the development of effective evidence-based nutrition interventions, to reduce the impact of these disorders, and promote well-being for affected individuals.

INTRODUCTION

Behavioral health refers to the broad spectrum of behaviors and conditions related to mental and emotional well-being that range from coping with daily challenges of life to behavioral health disorders such as depression, anxiety, and other psychiatric conditions.[1] In 2017, more than 46.6 million adults in the United States reported having a mental illness in the previous year.[2] Thus, strategies are needed for the treatment of behavioral health disorders. In addition, prevention of behavioral health disorders is critical.

Nutrition has a role in the prevention and the treatment of behavioral health disorders.[3] Suboptimal nutrition has been implicated in the underlying pathology of behavioral health disorders because of the essential role of nutrients in the neuroendocrine system. Nutrients, including tryptophan, vitamin B_6, vitamin B_{12}, folic acid (folate), phenylalanine, tyrosine, histidine, choline, and glutamic acid are necessary for production of neurotransmitters such as serotonin, dopamine, and norepinephrine, which are involved in the regulation of mood, appetite, and cognition.[4] Marine-derived omega-3 (n-3) fatty acids regulate dopaminergic and serotoner-

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*M.K.-E. and K.S.P. contributed equally to this review.

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Key words: anxiety, behavioral health disorders, depression, diet, nutrition.

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Nutrition Reviews® Vol. 79(3):247–260

55

Lifestyle psychiatry

"For clinical settings, the findings presented [in this meta-review] add to the growing rationale for broad-scale provision of lifestyle interventions within primary and secondary care services for people with mental disorders."

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RESEARCH REPORT

A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders

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There is increasing academic and clinical interest in how "lifestyle factors" traditionally associated with physical health may also relate to mental health and psychological well-being. In response, international and national health bodies are producing guidelines to address health behaviors in the prevention and treatment of mental illness. However, the current evidence for the causal role of lifestyle factors in the onset and prognosis of mental disorders is unclear. We performed a systematic meta-review of the top-tier evidence examining how physical activity, sleep, dietary patterns and tobacco smoking impact on the risk and treatment outcomes across a range of mental disorders. Results from 23 meta-analyses of prospective/cohort studies, 12 Mendelian randomization studies, two meta-reviews, and two meta-analyses of randomized controlled trials were synthesized to generate overviews of the evidence for targeting each of the specific lifestyle factors in the prevention and treatment of depression, anxiety and stress-related disorders, schizophrenia, bipolar disorder, and attention deficit/hyperactivity disorder. Standout findings include a) convergent evidence indicating the use of physical activity in primary prevention and clinical treatment across a spectrum of mental disorders; b) emerging evidence implicating tobacco smoking as a causal factor in onset of both common and severe mental illness; c) the need to clearly establish causal relations between dietary patterns and risk of mental illness, and how diet should be best addressed within mental health care; and d) poor sleep as a risk factor for mental illness, although with further research required to understand the complex, bidirectional relations and the benefits of non-pharmacological sleep-focused interventions. The potentially shared neurobiological pathways between multiple lifestyle factors and mental health are discussed, along with directions for future research, and recommendations for the implementation of these findings at public health and clinical service levels.

Key words: Lifestyle factors, mental disorders, psychological well-being, physical activity, sedentary behavior, tobacco smoking, dietary patterns, sleep, depression, anxiety disorders, bipolar disorder, schizophrenia

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Mental disorders affect almost 30% of individuals across the lifespan[1], and are among the largest contributors to the global burden of disease, accounting for 32% of all years lived with disability, and 13% of disability-adjusted life years[2].

Despite many advances in psychotherapies and pharmacological treatments for a range of psychiatric conditions, there remains a substantial proportion of individuals who do not achieve full remission from standard treatment[3,4]. Additionally, a large portion of the global population do not have access to traditional mental health care, due to the scarcity of psychiatric services available, particularly in many low- and middle-income countries[5,6].

There has also been little improvement in primary prevention of mental illness, with clear gaps in both the evidence and implementation for such interventions[6]. Indeed, rates of common mental disorders (i.e., depression and anxiety) appear to even be increasing among the younger generations[7].

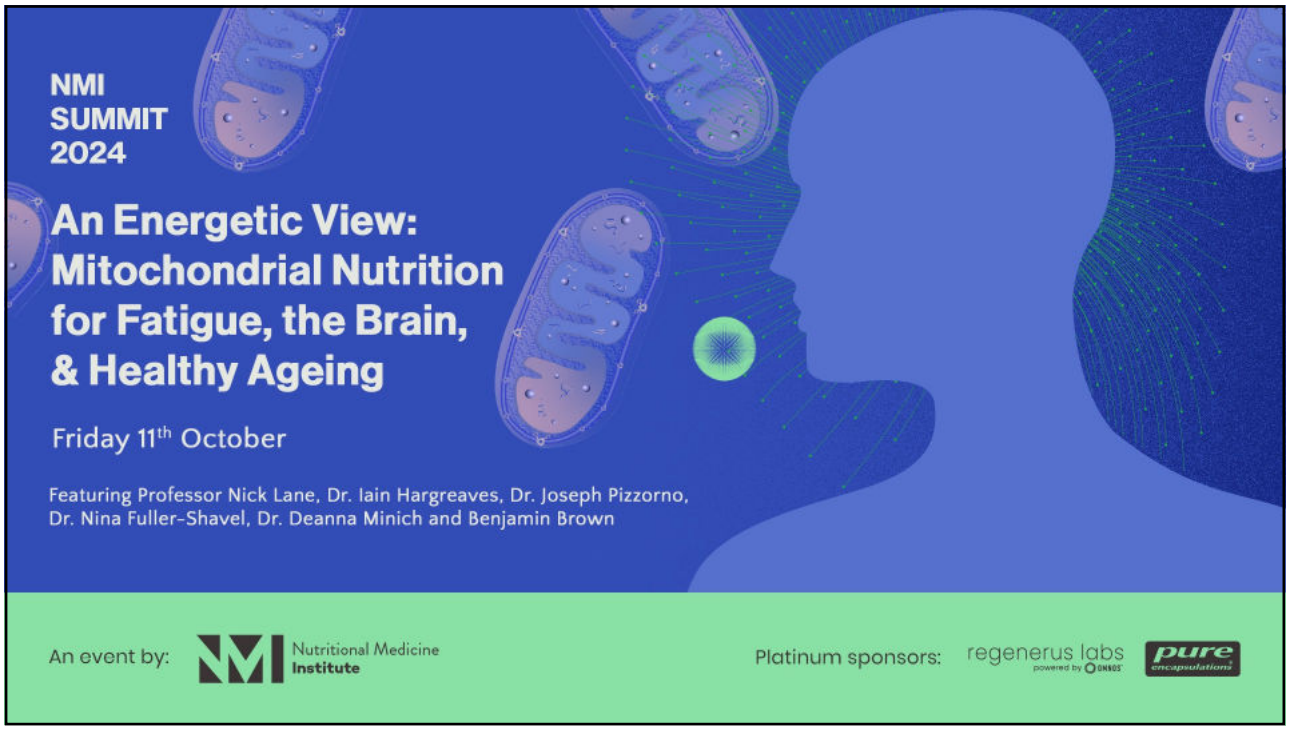
Thus, new approaches towards the prevention and treatment of mental illness, which can be delivered alongside or in the absence of traditional mental health care, are needed to reduce the global and growing burden of these conditions.

An emerging body of research has linked both the onset and symptoms of various mental disorders to "lifestyle factors", a term referring to health behaviors such as physical activity, diet, tobacco smoking and sleep[8].

For instance, a mass of cross-sectional evidence[9] shows that a range of psychiatric conditions (including schizophrenia, bipolar disorder, depression, and anxiety and stress-related disorders) are associated with adverse health behaviors, such as poorer dietary and sleeping patterns, low levels of physical activity, and higher rates of tobacco smoking, compared to healthy controls. Additionally, recent findings from population-scale studies document that the relationships between many of these lifestyle risk factors and mental illness also persist in low- and middle-income countries[10–12].

Although useful, this expansive body of cross-sectional research does not uncover the causality of the observed relation-

56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57