Mitochondrial Medicine

Treating Chronic Fatigue with Mitochondrial Support





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Disclosure Statement

- Jon Kaiser, MD is the Chief Medical Officer of K-PAX Pharmaceuticals, Inc.
- K-PAX Pharmaceuticals is an integrative medicine pharmaceutical company developing treatments to strengthen immune function and support energy metabolism.
- This educational activity has been reviewed by the California Naturopathic Doctors Association and contains no commercially biased information
- Therapeutic use of all prescription medications discussed is off-label.

Diseases Linked to Mitochondrial Dysfunction

Neurodegenerative Diseases

(Dementia, Fatigue, Peripheral neuropathy ALS, Alzheimer's, & Parkinson's Dz.)

Immune Diseases

(Chronic Fatigue Syndrome, Fibromyalgia Recurrent infections, Chronic inflammation & Cancer)

Hepatic & Metabolic Diseases

(Multiple Chemical Sensitivities, Nonalcoholic Hepatitis, Type II Diabetes)

Diseases Linked to Mitochondrial Dysfunction

25%	Neurodegenerative Diseases
2070	(Dementia, Fatigue, Peripheral neuropathy
<u>Energy</u>	ALS, Alzheimer's, & Parkinson's Dz.)
10-50%	Immune Diseases
	(Chronic Fatigue Syndrome, Fibromyalgia
<u>Usage</u>	Recurrent infections, Chronic inflammation & Cancer)
30%	Hepatic & Metabolic Diseases
	(Multiple Chemical Sensitivities, Nonalcoholic Hepatitis, Type II Diabetes)

Alzheimer's Disease

Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology.

Moreira, PI, et al. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1802(1), 2-10, 2010.

Reducing mitochondrial decay with mitochondrial nutrients to delay and treat cognitive dysfunction, Alzheimer's disease, and Parkinson's disease. Liu, J, et al. Nutritional neuroscience, 8(2), 67-89, 2005.

Deconstructing mitochondrial dysfunction in Alzheimer disease.

García-Escudero, V, et al. Oxidative Medicine and Cellular Longevity, 2013.

Parkinson's Disease

Mitochondria: A Therapeutic Target for Parkinson's Disease?

Luo, Y, et al. International journal of molecular sciences, 16(9), 20704-20730, 2015.

Mitochondrial dysfunction in Parkinson's disease.

Winklhofer, KF, et al. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1802(1), 29-44, 2010.

Pink1, Parkin, DJ-1 and mitochondrial dysfunction in Parkinson's disease.

Dodson, MW, et al. Current opinion in neurobiology, 17(3), 331-337, 2007.

Type II Diabetes Mellitus

Mitochondrial dysfunction and type 2 diabetes. Lowell, BB, et al. Science, 307(5708), 384-387, 2005.

Role of mitochondrial dysfunction in insulin resistance. Kim, J.A, et al. Circulation research, 102(4), 401-414, 2008.

Oxidative capacity, lipotoxicity, and mitochondrial damage in type 2 diabetes.

Schrauwen, P, et al. Diabetes, 53(6), 1412-1417, 2004.

Prevention of mitochondrial oxidative damage as a therapeutic strategy in diabetes.

Green, K, et al. Diabetes, 53(suppl 1), S110-S118, 2004.

Fibromyalgia

Oxidative stress and mitochondrial dysfunction in fibromyalgia.

Cordero, MD, et al. Neuroendocrinology Letters, 31(2), 2010.

Is inflammation a mitochondrial dysfunction-dependent event in fibromyalgia?

Cordero, MD, et al. Antioxidants & redox signaling, 18(7), 800-807, 2013.

Mitochondrial dysfunction in fibromyalgia and its implication in the pathogenesis of disease.

Cordero, MD, et al. Medicina clinica, 136(6), 252-256, 2011.

Chronic Fatigue Syndrome

Mitochondrial dysfunction and oxidative damage may play a critical role in the pathogenesis of CFS [Fulle, et al. *Free Radical Bio Med.* 2000]

Decreased glutathione and increased lactate in brains of CFS patients [Shungu DC, et al. *NMR Biomed*. 2012;25:1073–1087]

Increased lactate leading to cerebral hypoperfusion promotes a vicious cycle of mitochondrial damage in CFS brains [Biswal B, et al. *J Neurol Sci.* 2011;301: 9–11]

Autoimmune Diseases

Mitochondrial dysfunction plays a key role in progressive axonal loss in multiple sclerosis. Andrews, HE, et al. Medical hypotheses, 64(4), 669-677, 2005.

Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis.

Witte, ME, et al. Trends in molecular medicine, 20(3), 179-187, 2014.

Apoptosis and mitochondrial dysfunction in lymphocytes of patients with systemic lupus erythematosus.

Perl, A, et al. In Autoimmunity (pp. 87-114). Humana Press, 2004.



Mitochondrial Medicine









Oxidation

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Smoke and Ash



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H+

ions

ATP

ATP

HEAT

H+

ions

H+

ions

ATP

CHEMICAL

ENERGY

Electron

transport chain



CELLULAR

WORK



























Smoke and Ash



Mitochondrial Medicine

What stresses the mitochondria?

- 1) Poor nutrition
- 2) Chronic stress
- 3) Sedentary lifestyle
- 1) Chronic inflammation

Mitochondrial Medicine

What stresses the mitochondria?

5) Prescription drugs

- Acetaminophen
- Antidepressants
- Statins
- Antivirals
- Antibiotics
- Chemotherapy

6) Environmental toxins

- Pthalates
- Bisphenol A
- Organophosphates
- Plastics, teflon, etc.



THE WALL STREET JOURNAL.

Toxic Spill Still Haunts Southwest

Six months after EPA accident at gold mine, cnowmelt threatens

BEFORE

long-term monitoring. For instance, they say, there is no federal plan to test about 2,000 private wells in New Mexico that border the Asimer et al. of





Mitochondrial Medicine

What occurs when the mitochondria are stressed?

1) Mild to Moderate Dysfunction →

2) Mitochondrial Toxicity ->

3) Mitochondrial Loss ->

1) Apoptosis (programmed cell death)

When Should You Intervene?

• <u>Immune System</u>	Early effects Frequent infections →	End organ diseases Life threatening infections
• <u>Hepatic System</u>	Chronic inflammation Increased LFT's → Chemical sensitivities	(Pneumonia, MRSA. etc.) NASH, Hepatitis, Cancer
• <u>Nervous System</u>	Decreased cognition → Brain fog, Fatigue	Alzheimers Dz, MS, ALS Parkinsons Dz, CFS

When Should You Intervene?



Mitochondria

Cell

What's the best way to protect and enhance mitochondrial function?

?

?

?

Mitochondria



Cell

Broad-Spectrum Mitochondrial Support

Key Mitochondrial Support Nutrients

Acetyl-L-Carnitine 1,000 mg/day N-acetyl-cysteine 1,200 mg/day Alpha Lipoic Acid 400 mg/day

Additional Supportive Nutrients

Coenzyme Q-10 100 mg/day Methyl Folate 400 mcg/day Methyl B12 1,000 mcg/day Carotenoids 20,000 iu/day Vitamin C 2,000 mg/day Vitamin D 1,000 iu/day Vitamin E 540 iu/day Zinc 30 mg/day

RAPID COMMUNICATION

Micronutrient Supplementation Increases CD4 Count in HIV-Infected Individuals on Highly Active Antiretroviral Therapy: A Prospective, Double-Blinded, Placebo-Controlled Trial

Jon D. Kaiser, MD,* Adriana M. Campa, PhD,† Joseph P. Ondercin, PA-C,‡ Gifford S. Leoung, MD,§ Richard F. Pless, PhD,// and Marianna K. Baum, PhD†

J hdq IC+ds kI@HCR 1//5:31'4(9412,417)

"AIDS Drugs Linked To Mitochondrial Toxicity"

Mitochondrial Toxicities of Nucleoside Reverse Transcriptase Inhibitors

Kees Brinkman, MD, PhD Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis (oLVG), Amsterdam

SUMMARY BY TIM HORN EDITED BY MARSHALL GLESBY, MD, PhD, AND THOMAS KAKUDA, PharmD

The PRN Notebook June 2000

% CHANGE IN CD4 COUNT

WEEKS

Chronic Fatigue Syndrome

Myalgic Encephalomyelitis

Advising the nation • Improving health

- IOM reported these findings in 2015:
 - CFS affects between 836,000 to 2.5 million Americans
 - Up to 90% of people with CFS have not yet been diagnosed, meaning the true prevalence is unknown
 - The average age of onset is 33, although CFS has been reported in patients < 10 and > 70 years old
 - At least 1/4 of CFS patients are homebound at some point during their illness

Guidance for Industry Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis: Developing Drug Products for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Dr. Janet W. Maynard at 301-796-2300.

Chronic Fatigue Syndrome Treatment

Mitochondrial Support Nutrients

- ✓ Rapid improvement in energy level
- ✓ Gradual improvement in functional status
- $\checkmark\,$ Rapid improvement in alertness and concentration
- ✓ Improved safety and long term tolerability

Proof of Concept

Prospective, Open-label Trial in

15 Patients with CFS

CFS Symptoms Score

Double-blinded, placebo-controlled

(n=128 patients)

Study Investigators

Jose Montoya, MD (Stanford U.) Lucinda Bateman, MD (Utah) Nancy Klimas, MD (Florida) Susan Levine, MD (NYC)

Completed 2015

CFS Symptoms Score

Excellent Safety Data

Table 3. Low-incidence of Common Methylphenidate Adverse Events (Grade II or greater) in Patients by Treatment Group (safety population)^a

Symptom	K-PAX 002 (n=64)	Placebo (n=67)
Feeling Jittery	4 (6)	4 (6)
Nervousness	0 (0)	0 (0)
Palpitations	1 (2)	3 (5)
Restlessness	0 (0)	1 (2)
Agitation	0 (0)	0 (0)
Irritability	1 (2)	0 (0)
Insomnia	2 (3)	1 (2)

^aValues shown as number (%) of patients.

Direct Mitochondrial Function Assay

Nothings promotes the advancement of knowledge so much as a new instrument

Humphry Davy →	<u>Electric Battery</u> →	Sodium Calcium Potassium Magnesium
Marie Curie →	Radiation Detector →	Radium Polonium

Seahorse XF Mitochondrial Analyzer

Seahorse XF Mitochondrial Analyzer

...bioenergetic status of a cell

© 2016 Agilent Technologies

Seahorse XF Mitochondrial Analyzer

The Bioenergetic Health Index: a new concept in mitochondrial translational research

Balu K. CHACKO^{*}†, Philip A. KRAMER^{*}†, Saranya RAVI^{*}†, Gloria A. BENAVIDES^{*}†, Tanecia MITCHELL^{*}†, Brian P. DRANKA[†], David FERRICK[†], Ashwani K. SINGAL[§], Scott W. BALLINGER^{*}†, Shannon M. BAILEY[†], Robert W. HARDY^{*}†, Jianhua ZHANG^{*}†||, Degui ZHI¶ and Victor M. DARLEY-USMAR^{*}†¹

*Creates a Single Numerical Score That Directly Measures Mitochondrial Health

<u>BHI</u> = $\log \frac{(\text{reserve capacity})^a \times (\text{ATP-linked})^b}{(\text{non-mitochondrial})^c \times (\text{proton leak})^d}$

Victor Darley-Usmar, PhD. University of Alabama, Birmingham

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