Irresponsible use of hormones, poorly-structured research, and misrepresentation of functional medicine: critique of Cutshall, Bergstrom, Kalish's "Evaluation of a functional medicine approach to treating fatigue, stress, and digestive issues in women" in *Complement Ther Clin Pract*. 2016 May

- Reviewer: Alex Vasquez DC ND DO FACN
- Citation: Cutshall SM, Bergstrom LR, Kalish DJ. Evaluation of a functional medicine approach to treating fatigue, stress, and digestive issues in women. *Complement Ther Clin Pract*. 2016 May;23:75-81
- Date of review: June 10, 2016 with a few post-press changes/edits highlighted with blue.
- Summary of study from the authors' abstract: The authors report a "28-week pilot study to assess the efficacy of a functional medicine approach to improving stress, energy, fatigue, digestive issues, and quality of life in middle-aged women. Findings showed significant improvements in many stress, fatigue, and quality-of-life measures. The treatment program increased mean salivary dehydroepiandrosterone levels and the cortisol-dehydroepiandrosterone ratio. Stool sample analyses suggested that these treatments reduced Helicobacter pylori infections. This study suggests that functional medicine may be an effective approach to managing stress and gastrointestinal symptoms."
- Interventions: The authors state that treatments were "personalized" but provide no data on how the treatment was allocated and selected, other than to divide patients into two groups "low cortisol" and "high cortisol" for the "adrenal protocols" which are poorly described other than administration of "DHEA drops" and "pregnenolone drops." The authors fail to provide the dosages of either of these steroid hormones; such a failure to describe the dosage is scientifically irresponsible as it makes replication and validation of the study impossible, and it is also ethically irresponsible as it suggests to the public that such hormones could be taken in any undefined range with impunity. Nowhere in the report are the doses or product descriptions provided for either of these neurotropic steroid hormones; the authors make no mention of risk:benefit considerations. The authors did not measure for changes in serum hormones such as testosterone and estradiol; such testing would have been reasonable to evaluate for effectiveness, conversion of pregnenolone and DHEA into the more active hormones that potentially have the ability to promote cancer growth. A common error in articles of this sort is the statement that treatments were "personalized" by which the authors justify their failure to disclose and describe how treatments were administered; however, because the treatments are *personalized* in the *deployment* of the study does not mean that the results have to be *secretive* in the *reporting* of the study.
- Errors in this study's design and report; negative findings:
    1. The authors define functional medicine as "The functional medicine model is focused on restoring optimal functioning of 3 body systems: hormonal, digestive, and detoxification." This is an inaccurate definition and inappropriately limits an otherwise wide clinical approach; the definition of functional medicine provided by these authors is discordant with descriptions published by other groups such as the Institute for Functional Medicine[1] and International College of Human Nutrition and Functional Medicine.[2]
    2. The sweeping statement "Restoring these 3 body systems has positive effects on stress, energy, fatigue, digestive issues, and quality of life" has no citations. Such a statement might appear intuitively reasonable for casual conversations, but in scientific publications such statements require substantiation.
    3. The authors misrepresent the intervention in the introductory text of the article by stating "The approach included lifestyle factors coupled with specific nutritional supplement protocols to treat HPA axis dysregulation and gastrointestinal infections." To the contrary, the treatment protocol included the administration of two steroid hormones that are known to have neurotropic and antidepressant effects. Taking undefined doses of steroid hormones is neither "lifestyle factors" nor "nutritional supplementation." Further, administration of steroid hormones requires careful patient selection and laboratory surveillance; the standard in medical practice is serum analysis—not saliva analysis via undisclosed methods. One of the hormones used in this study—DHEA—is known to convert androgens and estrogens[3]—to estradiol[4]—and can thereby promote the development of cancers, specifically breast cancer in women.[5] While many clinicians agree that DHEA is safe for clinical use, the implementation of DHEA administration as described in this study is at variance with clinical practice.
    4. The authors describe the time of year of their study as "September 2014 through April 2015" but they failed to control for vitamin D levels, leaving the reader to wonder if the patients felt better to extraneous factors such as sunshine, sunlight exposure, and increased vitamin D levels—all of which are known to improve mood and cognition.[6,7] Further, vitamin D also has a systemic antiinflammatory effect which would result in reduced symptomaticity.[8] The lack of a control group, plus the change in seasons allows the conclusions to read, "The passage of time and the change of seasons toward more sunshine and warmer weather (in northern California) over six-months' time is associated with alleviation of stress and improvement of gastrointestinal complaints regardless of treatment."
    5. The "Lifestyle and nutritional counseling" included a 1-hour in person coaching session at the start of the study, followed by various telephone contacts and "online group sessions" including "nutrition coaching and follow-up with diet compliance." This obviously results in the possibility that the patients felt better simply as a result of social contact and conversation with an interested educated health professional rather than as a result of any biomedical/nutritional intervention; the patients were located in the United States, a country notorious for its social isolation and lack of social networks.[9]

6. The authors use unprofessional lay terminology "adrenal and digestive cleanse protocols" without definition, justification, or citation. In a scientific publication, these terms are meaningless without explanation.
7. Unreliable methods with uninterpretable results are reported, for example "A **significant increase was seen in mean salivary DHEA concentration**, with an initial value of 4.7 (4.8) ng/mL and an end-of-study value of 5.7 (15.4) ng/mL (P=0.047). However, **the median DHEA concentration decreased** from baseline to end of study (3.1-2.2 ng/mL), which suggests that the mean value may not accurately reflect the effect of the protocol on DHEA levels. In addition, 1 participant had a **36-fold increase in salivary DHEA level**, which affected the mean." Thus, the same marker was found to increase, decrease, and change inexplicably, leaving these results completely meaningless. The authors fail to detail the laboratory methodology for this saliva testing, although they do prominently mention the laboratory name.
8. The results section "Stool microbial analysis" is uninterpretable with statements such as "Two participants' results for Cryptosporidium antigen changed during the study, 1 positive to negative and 1 negative to positive." Are we to then believe that some patients acquire gastrointestinal pathogens as a result of this protocol? What is the proposed clinical significance of Cryptosporidium, and why was it tested, if the interpretation of positive and negative results is equivocal? Again, the authors fail to detail the laboratory methodology for this microbiologic testing, although they do prominently mention the laboratory name for a second time.
9. Of the 21 patients who completed the study, 2 communicated complaints or intolerance to the treatment protocol; that is nearly 10% of the study population.
10. Table 5 of the results shows that Cortisol/DHEA ratio started at 5.2 and resulted at 12 at the end of the study. Consistently throughout the medical literature, respectively higher levels of cortisol and lower levels of DHEA are consistently and causatively associated with insulin resistance, hippocampal atrophy, and bone loss[10]; to the contrary of the bulk of the peer-reviewed literature, these authors surprisingly represent these results as positive changes.
11. The reduction in H plyori positivity from 9 to 1 subjects is expected with the use of mastic gum as listed in the protocol. According to the footnote describing this product, the authors appear unsure of the company which made the product; also, doses of active ingredients are not listed, making replication of these results in research or clinical practice impossible.
12. The authors correctly state that "There was no control group, so positive outcomes could have been attributed to the placebo effect"; they should have expanded the range of consideration to include 2) effect of time, spontaneous resolution, 3) change in season, perhaps additional sunlight and/or higher vitamin D levels as the group transitioned from fall to spring, and 4) other population-wide economic, political, or social changes.
13. The authors state following the conclusion that they deny conflict of interest and that "The study sponsors had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication." However, the authors completely fail to disclose who are the sponsors—the laboratories? The providers of the nutritional supplements? Speaking fees at conferences where this report will be discussed? Consulting fees? The authors prominently list many companies in the Methods and the product descriptions; presumably these are the sponsors of this article. One of the authors (Kalish) is also a consultant/employee/trainer/speaker for a large distributor of nutritional supplements[11], but the authors fail to describe any aspect of this relationship or even to acknowledge its existence.

- Reviewer's conclusions: This study is of very low quality and is not an accurate representation of the clinical practice of functional medicine. The study design is flawed, the methods are not reproducible, the treatments were not sufficiency described, and the study cannot be either validated or refuted scientifically due to these design flaws. By failing to describe the dose of the steroid hormones used, the authors present to the general public that these hormones can be used wantonly and without regard to dosage; this presents a potential hazard to the public health given the conversion of these neurosteroid hormones into sex hormones such as estrogen which can promote a wide range of cancers. The authors further fail to provide the identity of the study sponsors and the nature of the conflict(s) of interest. The functional medicine approach to healthcare is science-based, eclectic, and effective[12]; however, the field is not benefited by poorly conducted research, especially that which does not accurately reflect the practice, which employs poor methodology, and/or which uses steroid hormones without appropriate risk/benefit considerations.

About the author of this review: Dr Vasquez is Director of the International College of Human Nutrition and Functional Medicine (ICHNFM.ORG), founded in the United States and now also based in Spain. Dr Vasquez has served as a consultant researcher and lecturer for Biotics Research Corporation.

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