Call for Retraction (preprint): Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients with Moderate to Severe COVID-19 *JAMA* 2021

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Citation, summary, and implications

- **Citation**: Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients with Moderate to Severe COVID-19: Randomized Clinical Trial. *JAMA—Journal of the American Medical Association* February 17, 2021
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- **doi**: 10.1001/jama.2020.26848
- **Purported conclusions**: Via their inappropriate (bolus) and unprofessional (failure of competent literature review) use of the intervention and more than 11 days of delay between the onset of symptoms and the implementation of treatment, the authors inappropriately conclude that vitamin D is ineffective in the management of COVID-19 infections.
- **Implications**: Their publication misrepresents appropriate clinical management of this condition and directly leads to confusion among medical physicians, the general public and political policymakers. This unreliable research will adversely affect medical treatment and international healthcare policy for hundreds of millions of patients.
- **Reviewer's expert summary**: For the reasons outlined in the following sections, this unprofessional and unethical research should have never been published and should now be withdrawn immediately.
- **Preprint (20 Feb 2021)**: academia.edu/45159442 *Note that this manuscript will be continuously updated until accepted for peer-reviewed publication; refresh/review the hyperlink provided above for the most recent version/updates*
- **Original spontaneous video review (18 Feb 2021)**:
  ❶ rumble.com/vdze3h-jama-2021-effect-of-single-high-dose-vitamin-d3-on-hospital-length-stay-in-.html
  ❷ youtube.com/watch?v=_sfGV_xz0_Q
  ❸ brighteon.com/11397575-a1bf-4afc-86df-26f6c6efa299

Criteria for withdrawal of biomedical publications— widely accepted professional standards

Editors of biomedical journals are expected to perform within certain parameters of professionalism and competence. Documents accepted for publication should reflect current science and clinical practice rather than recycling/republishing outdated/refuted ideas and practices that are inconsistent with quality healthcare and expectations in the practice of medicine. Guidelines for the retraction/withdrawal of published research have been published by Committee on Publication Ethics (COPE)[1] and include the following:

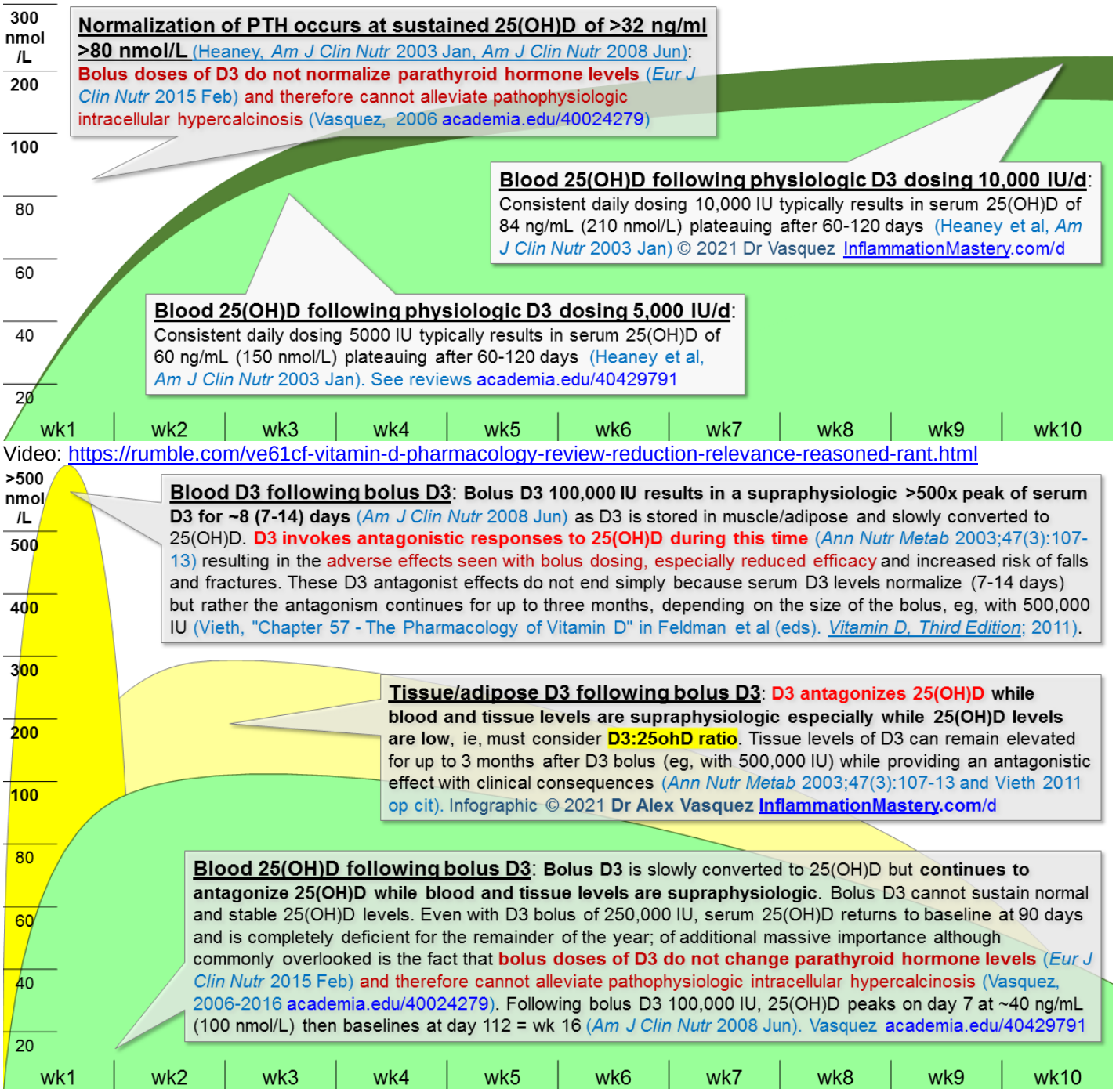
1. **Findings are unreliable as a result of major error, fabrication or falsification**
2. Plagiarism
3. Redundant/duplicated publication
4. Unauthorized use of private data
5. Copyright infringement, libel, privacy violation
6. **Unethically conducted research**
7. Compromised or manipulated peer review process
8. "The author(s) failed to disclose a major competing interest (a.k.a. conflict of interest) that, in the view of the editor, would have unduly affected interpretations of the work or recommendations by editors and peer reviewers."

On the basis of these independent and broadly accepted criteria, the article in question should be withdrawn because the findings are unreliable as a result of major error and because the research was not conducted ethically—the investigators knowingly **1) delayed treatment** in a manner that had consequences for the patients/subjects involved in the study and which negatively affected the conclusions in a way that is misleading to the readers— physicians, doctors, researchers, patients, politicians, policymakers, and the investigators **2) inappropriately administered the treatment in the form of bolus doses** by failing to administer smaller doses over the course of treatment, and the investigators knowingly **3) performed laboratory testing at the end of hospital discharge rather than at the beginning of treatment**, thereby creating a false picture that their treatment was efficacious (e.g., that appropriate serum levels were met early in the course of the illness and its treatment) when it could not have possibly been efficacious based on the known/published pharmacology of the intervention; furthermore, the authors acknowledge that **4) their treatment completely failed to reach therapeutic serum levels in more than 13% of patients**.

Inventory of errors and problems in this publication

Problems in study design, performance, randomization, review/acceptance of this article include but are not limited to the following:

1. **Unethical treatment, inappropriate delivery of treatment**: Bolus dosing (the unphysiologic administration of large doses on a single occasion rather than smaller doses on a daily/weekly basis) of vitamin D3 was already proven to be less effective or ineffective against respiratory infections in a major meta-analysis published in the *British Medical Journal* in 2017 ("**Treatment with large boluses of vitamin D has been associated with reduced efficacy** for non-classic effects, and in some cases an **increased risk of adverse outcomes**.")[2]; thus, this current study was designed to fail before it was even started. The authors were obviously aware of the aforementioned publication (their citation number 9) and the evidence that their intervention would be less efficacious when administered as a bolus dose than if it had been administered in small physiologic doses. **The administration of any treatment in an ineffective manner is unethical, and on this basis alone the article should be withdrawn.** To make this point more clear: such a research study would never be accepted in the treatment of serious disease with pharmaceutical drugs; for example the inappropriate administration of an antibiotic in patients suffering from any acute infection would never be accepted as reasonable or ethical treatment. This hypocrisy of allowing unethical research to be published misrepresents the appropriate use of therapeutics in general and nutrition in particular.



Video: https://rumble.com/ve61cf-vitamin-d-pharmacology-review-reduction-relevance-reasoned-rant.html

Infographics: D3 dose size determines clinical effect: Modest physiologic doses (top image) follow first-order pharmacokinetics characterized by a dose-response relationship that is predictable and also which does not result in significant accumulation of D3 relative to 25(OH)D; in contrast, unnatural bolus dosing of D3 follows unpredictable zero-order kinetics resulting in >500x non-physiologic elevations of D3 relative to deficient 25(OH)D with antagonistic

biochemical/physiological effects leading to negative clinical consequences (Heaney *Am J Clin Nutr* 2008 Jun; Vieth, "Chapter 57: Pharmacology of Vitamin D" in *Vitamin D, 3rd Ed.*, Academic Press, 2011).

2. **Inexcusable and unprecedented delay in treatment**: Treatment/intervention with vitamin D was delayed for more than 10 days from the onset of symptoms and this delay is medically and ethically inappropriate. Such practice does not reflect legitimate clinical nutrition practice which would have implemented treatment immediately, nor does it reflect "unprofessional" personal self-care because most laypeople in the general public would not delay a potentially effective treatment by 10 days (if they were properly informed about such treatment). The authors of this original publication completely fail to acknowledge this **structural lag time** in the title of the article as well as the abstract of the article which are the only parts of the article that are read by the majority of physicians and journalists. "**The mean (SD) time from the onset of symptoms to randomization was 10.3 (4.3) days and from hospitalization to randomization was 1.4 (0.9) days" thus a total of 11.7 days passed from the onset of symptoms to the initiation of vitamin D supplementation, with a range of variance as long as 14.6 days and 2.3 days, respectively, for a total of 16.9 days from the onset of symptoms to the initiation of treatment**. **This is medically and ethically inappropriate, both in clinical care and the publication of research.** Any properly educated medical student or pharmacology student would know that treatments have an expected "window of opportunity" in which to function and delaying treatment for 2-2½ weeks for an acute infection is clearly beyond the window of opportunity for the majority of interventions. As I have said before in previous research reviews, the unprofessional behavior that is tolerated in nutrition research when performed by the medical world would never be tolerated by that same community if it were the study of drugs and infectious disease, for example. No legitimate excuses provided for this treatment delay, and at least the article should be retitled to reflect the fact that intervention was delayed in a manner that is clearly out of any standard of care—the authors and journal editors should have used a more accurate title for this publication: **Two-week delayed administration of inactive vitamin D3 in a single ineffective bolus dose to obese comorbid polypharmacy patients does not alleviate COVID-19**. Furthermore, certain antiviral drugs (eg, oseltamivir/Tamiflu) are known to require administration within a very defined and limited timeframe following the onset of symptoms (within 48 hours of symptoms) so the **hypocrisy and failure to follow a reasonable standard of care** in the publication of this article appears to be quite political. This research was not ethically conducted. This research inappropriately models unethical behavior for clinicians. Because research serves as an example of what is acceptable and within standards of care, this article misleads healthcare providers into thinking that such delays in treatment are somehow justified. **Any clinician who knowingly delays effective antimicrobial treatment for two weeks after the onset of acute infectious disease would probably be liable for malpractice for any resulting complications, injuries or deaths—so how could these authors and editors have possibly modeled such behavior in this publication?**
3. **Failure of adequate literature review and appropriate planning**: The authors knew that bolus dosing was ineffective (or at least less effective than smaller frequent dosing), and they also ignored the pharmacokinetics of vitamin D3. **Following administration of supraphysiologic bolus dosing of vitamin D3, serum levels peak and remain elevated far into the supraphysiologic range for up to 14 days** ("In the acute study, subjects receiving a single 100000-IU dose of vitamin D3 had a rise in serum cholecalciferol to a mean of 521 nmol/L at 1 d and then a fall to near-baseline values by 7–14 d.").[3] During this time, vitamin D3 has antagonistic effects which have been described in previous literature, and the authors should have been well aware of these facts before using this treatment especially in the setting of acute infectious disease. **Conversion of vitamin D3 to the active form 25 hydroxy vitamin D3 requires approximately two weeks** which these acutely sick patients could ill afford; adding this two-week physiologic lag time atop the **structural lag time in the implementation of treatment which was reported by the authors to be at least 11 days** makes the **total lag time 25 days from the onset of symptoms to the receipt of active unantagonized vitamin D therapy**. The pharmacology of vitamin D has been well described and is accessible to all researchers; in fact, one could simply access the article by Vieth titled "the pharmacology of vitamin D"[4] to learn about the pharmacology of vitamin D as the authors of the study question should have performed. If they had read this expertly written article titled *the pharmacology of vitamin D* then they would have learned how and why bolus dosing is inappropriate, less efficacious, and occasionally harmful for up to three months following administration.
4. **Intentional or accidental failure of randomization**: The experimental (vitamin D) group was significantly sicker than the placebo group. Table 1 provides evidence that the vitamin D group was significantly more sick than the placebo group with more or more severe obesity, cough, fever, sore throat, joint pain, hypertension, diabetes, rheumatic disease, chronic obstructive pulmonary disease, chronic kidney disease, anticoagulant drug use, corticosteroid drug use, antihypertensive drug use.
5. **Clear underperformance of authors and journal editors**: The authors and reviewers and editors involved with this article clearly underperformed for their level of responsibility and education/training. The authors claim graduate/doctorate-level credentials with 19 diplomas at the graduate degree level or higher, and yet not a single one of them appears to have adequately reviewed the literature nor even studied the pharmacology of the intervention being used. For any high-profile medical journal, we could reasonably expect at least 2 to 3 reviewers at the doctorate level plus the review from an associate editor and the chief editor for an additional four-five graduate/doctorate level diplomas in charge of the review and acceptance of this manuscript for publication. Thus, for approximately 25 graduate/doctorate level diplomas, not a single one of them functioned to produce a competent document.
6. **Insufficient treatment dose**: Administration of vitamin D3 as 200,000 international units (IU) over the course of 10 days is only 20,000 units per day which is equal to less than half an hour of midday equatorial/tropical sunbathing and certainly not any heroic or skillful intervention by any standard whatsoever, especially for patients who are acutely ill, obese, polymedicated, and sick with other diseases. Importantly, the authors claim that they justify this dose based on what is within the range of appropriate dosing for healthy people but apparently they selectively overlook the fact that their patient population was obese, acutely ill with

an infectious disease, and sick with various comorbidities and affected by polypharmacy. Corticosteroid drugs are known to result in the destruction of vitamin D—this has been known since at least 2009 via publication by the American Academy of Family Physicians in their journal *American Family Physician* ("A common cause of [vitamin D] deficiency is medication use, such as anticonvulsants or glucocorticoids, which can increase catabolism and actively destroy vitamin D.").[5] So what appears to be justification is actually completely stupid in the real world. Furthermore, the authors could have easily provided the same 200,000 units *bolus* as 20,000 units *daily* over the course of 10 days and this would have been much more physiologic and would have been more likely to result in clinical benefit.

7. **Inappropriate dose selection for ill, comorbid, and obese patients**: The authors state that they chose their interventional dose based on what was appropriate for healthy persons but the subjects/patients in the study were clearly not healthy and were noted to have several comorbidities; all the subjects were obese in addition to having an acute infection. Therefore and obviously, utilizing a dose that is deemed appropriate for lean/normal-weight healthy unmedicated people is completely inappropriate for an 1) obese 2) acutely infected 3) comorbid 4) polymedicated group. Furthermore these authors repeatedly ignore the physiologic time lag in the conversion of vitamin D3 to the active form 25-hydroxy-vitamin D; this physiologic lag time is characterized by a **supraphysiologic spike of inactive or antagonistic vitamin D3 which requires 7 to 14 days to normalize** while 25-hydroxy-vitamin-D levels increase over the course of approximately 10 days but obviously do not reach full physiologic benefit for several weeks or months. Numerous studies have shown that tissue saturation requires 20-60 days following administration of vitamin D supplementation.[6]
8. **Inappropriate form of treatment for an acute illness**: The form of vitamin D used in this study is inappropriate for any type of rapid response for acute illness, and this data is well known on pharmacologic basis as well as previous clinical studies. Bolus doses of vitamin D3 require approximately 7-14 days to normalize after administration, and during those first 7-14 days vitamin D3 is unquestionably functioning in an antagonistic role against normal vitamin D metabolism. Furthermore and as previously documented, the authors note that treatment was delayed until at least 11 days following the onset of symptoms.
9. **The entire patient/subject population was obese with an average BMI of ~31.5**: The patient population was obviously obese, and serves as a reasonable surrogate marker for other nutritional deficiencies, gastrointestinal dysbiosis, and consumption of a pro-inflammatory diet pattern characterized by ultra-processed foods (UPF), which represent approximately 60% of Western diets.
10. **Documented failure of treatment to achieve therapeutic serum levels**: 14% of patients in the vitamin D group did not respond to supplementation and were still deficient throughout the study. The hypocrisy of the publication of this study is astounding because in an analogous study of antibiotic therapy for infectious disease or antiseizure therapy in the treatment of epilepsy, no competent journal would publish a study in which such a large percentage of patients did not achieve therapeutic serum levels of the antibiotic or antiseizure medication, respectively.
11. **Serum levels of 25-hydroxyvitamin D were unknown during the treatment period and only normalized at the end of treatment**: Measuring serum levels of 25-hydroxyvitamin D at the end of the study was completely inaccurate and inappropriate because the researchers should have sought to normalize these levels at the start of therapy not at the end of hospital discharge. Patients/subjects in the study were almost certainly deficient in vitamin D for the majority of time they were under the care of these clinicians/investigators—this does not represent competent research or clinical care but clearly the opposite.
12. **Inaccurate and unphysiologic definition of vitamin D sufficiency**: The authors defined vitamin D sufficiency as 30 ng/mL and this is not physiologically ideal and is less than the minimum of 32 ng/mL at which parathyroid hormone levels begin to normalize.
13. **Inappropriate and delayed administration did not provide time for expected physiologic effects and benefits**: The authors appear to have zero awareness that vitamin D is necessary for the transcription of 3000 different gene/DNA docking sites as well as regulation of the gut microbiota. All of these can have an impact on outcomes and under no circumstances whatsoever could all of these be expected to normalize with a vitamin D level that was minimally normalized on the last possible day of hospitalization, but only in approximately 85% of subjects
14. **Impressively high exclusion rate; questionable representativeness of real-world sample**: 1240 patients were assessed for eligibility and 1000 of these were excluded (including two that died); thus, more than 80% of potential patients were excluded from the study. Roughly 10% of the initial group received placebo and the other 10% received vitamin D, albeit in ineffective bolus dosing and more than a week-and-a-half after the onset of symptoms. Although we appreciate the importance of gaining "clean" investigative data, we also need data that reflects the real-world experience of clinicians and patients. Avoiding a physiologic intervention when we know that the global population shows 60-90% deficiency of vitamin D is illogical.

Conclusions

This document is still in process, but the conclusions are included in the points above. This document is not to be considered in its final form until it is presented in its final edited peer-reviewed form as stated within the PDF document itself .

About the author and presenter: Alex Kennerly Vasquez DO ND DC (USA), Fellow of the American College of Nutrition (FACN), Overseas Fellow of the Royal Society of Medicine: An award-winning clinician-scholar and founding Program Director of the world's first fully-accredited university-based graduate program in Human Nutrition and Functional Medicine, Dr Alex Vasquez is recognized internationally for his high intellectual and academic standards and for his expertise spanning and interconnecting many topics in medicine and nutrition. Dr Vasquez holds three doctoral degrees as a graduate of University of Western States (Doctor of Chiropractic, 1996), Bastyr University (Doctor of Naturopathic Medicine, 1999), and University of North Texas Health Science Center, Texas College of Osteopathic

Medicine (Doctor of Osteopathic Medicine, 2010). Dr Vasquez has completed hundreds of hours of post-graduate and continuing education in subjects including Obstetrics, Pediatrics, Basic and Advanced Disaster Life Support, Nutrition and Functional Medicine; while in the final year of medical school, Dr Vasquez completed a Pre-Doctoral Research Fellowship in Complementary and Alternative Medicine Research hosted by the US National Institutes of Health (NIH). Dr Vasquez is the author of many textbooks, including Integrative Orthopedics (2004, 2007 2012), Functional Medicine Rheumatology (Third Edition, 2014), Musculoskeletal Pain: Expanded Clinical Strategies (commissioned and published by Institute for Functional Medicine, 2008), Chiropractic and Naturopathic Mastery of Common Clinical Disorders (2009), Integrative Medicine and Functional Medicine for Chronic Hypertension (2011), Brain Inflammation in Migraine and Fibromyalgia (2016), Mitochondrial Nutrition and Endoplasmic Reticulum Stress in Primary Care, 2nd Edition (2014), Antiviral Strategies and Immune Nutrition (2014), Mastering mTOR (2015), Autism, Dysbiosis, and the Gut-Brain Axis (2017) and **the 1200-page Inflammation Mastery 4th Edition (2016) also published as the two-volume set Textbook of Clinical Nutrition and Functional Medicine**. "DrV" has also written approximately 100 letters and articles for professional magazines and medical journals such as *TheLancet.com*, *British Medical Journal* (BMJ), *Annals of Pharmacotherapy*, *Nutritional Perspectives*, *Journal of Manipulative and Physiological Therapeutics* (JMPT), *Journal of the American Medical Association* (JAMA), *Original Internist*, *Integrative Medicine*, *Holistic Primary Care*, *Alternative Therapies in Health and Medicine*, *Journal of the American Osteopathic Association* (JAOA), *Dynamic Chiropractic*, *Journal of Clinical Endocrinology and Metabolism*, *Current Asthma and Allergy Reports*, *Complementary Therapies in Clinical Practice*, *Nature Reviews Rheumatology, Annals of the New York Academy of Sciences,* and *Arthritis & Rheumatism*, the Official Journal of the American College of Rheumatology. Dr Vasquez lectures internationally to healthcare professionals and has a consulting practice and service for doctors and patients. DrV has served as a consultant, product designer, writer and lecturer for Biotics Research Corporation since 2004. Having served on the Review Boards for *Journal of Pain Research, Autoimmune Diseases, PLOS One, Alternative Therapies in Health and Medicine, Neuropeptides*, *International Journal of Clinical Medicine, Journal of Inflammation Research, BMC Complementary and Alternative Medicine* (all PubMed/Medline indexed), and *Journal of Naturopathic Medicine* and as the founding Editor of *Naturopathy Digest*, Dr Vasquez is currently the Editor (2013-) of *International Journal of Human Nutrition and Functional Medicine* and Former Editor (2018-2019) of *Journal of Orthomolecular Medicine*, published for more than 50 consecutive years by the International Society for Orthomolecular Medicine.

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[1] Committee on Publication Ethics. https://publicationethics.org/retraction-guidelines

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