



## Letter to the Editor

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### **Who decides what a pseudo-therapy is? Evidence vs hasty opinions on ozone**

### **¿Quién decide qué es una pseudoterapia? Evidencia vs opiniones precipitadas en torno al ozono**

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**More detailed CVs of the authors at the end of the Letter to the Editor.**

## Conflict of interests

None of the undersigned have any conflict of interest due to being linked to the application, research or sale of ozone.

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*The controversy generated by the compassionate use of ozone therapy in COVID-19 patients opens the debate about who is entitled to decide what is a pseudo therapy and based on what criteria.*

During the summer of 2021, a strong controversy was generated [in Spain] regarding the possibility of using an experimental treatment with ozone as a last resort in COVID-19 patients. In August 13<sup>th</sup>, a court in the Valencian Community forced the [public] Hospital de La Plana [Vila-Real, Castellón] to allow the entry of doctors who are experts in ozone therapy to treat a critical patient. This fact initiated a series of reactions and statements by various professional groups and associations, who were against of a hypothetical judicial interference in medical matters. For this they argue that ozone therapy does not have "[scientific evidence](#)" and that it is a "[pseudo-therapy](#)", despite not being part of the list of pseudo-therapies of the Ministry of Health, and despite the fact that the patient [recovered](#) after treatment. Faced with this situation, the undersigned have taken the time to review the scientific literature on ozone therapy, which is what allows us to determine its degree of "scientific evidence" or its possible consideration as "pseudo-therapy".

First, we have observed that there is considerable published evidence on the efficacy and safety of ozone therapy for various pathologies, especially lumbar hernias and knee arthritis. Note that a simple [search in PubMed with the words "ozone therapy"](#) results in 3,966 articles indexed on this platform, which performs a filter to avoid fraudulent or predatory medical journals. This figure is by no means small, especially for a non-patentable molecule and therefore not attractive for research by pharmaceutical companies.

It would be impossible to summarize here all the relevant clinical trials studying the safety and efficacy of ozone. We limit ourselves to mentioning one of the meta-analysis published in this regard. Meta-analysis are studies that bring together and analyze the data from the most relevant trials, and their results are considered stronger than those of any other study alone. And they are, of course, much more relevant than any communication from a professional association or college, which are not subject to a peer review process, lack clear authorship and do not specify their conflicts of interest, all basic rules of any study of serious review.

This [meta-analysis](#), published in [JVIR, a high impact journal \(Q1\)](#), includes 12 clinical trials with a total sample of 8000 patients with herniated discs, concluding that “oxygen/ozone treatment of herniated discs is an effective and extremely safe procedure.” It also adds that “the estimated improvement in pain and function is impressive in view of the broad inclusion criteria, which included patients ranging in age from 13 to 94 years with all types of disc herniations. The rest of the meta-analysis located for the use of ozone in herniated discs and knee arthritis offer results that also point to moderate to strong evidence of safety and efficacy. None of them claim that the therapy lacks “scientific endorsement” or anything similar.

Many of the studies on ozone therapy are also published in high impact journals such as [PloS One](#), [Pain Physician](#) or [JVIR](#), all in the upper quartile of their discipline. We do not understand, therefore, how the Association to Protect the Sick from Pseudoscientific Therapies [can state](#) that ozone studies are “low impact”, something that can be refuted with a simple *click* on the impact level of the mentioned journals. In the same way, it is also incomprehensible the claim by this association that all the ozone studies are of “low quality, with a small number of patients and without statistical significance”, something directly false.

Perhaps this situation may be influenced by the fact that the association has [commissioned](#) a disseminator with a degree in Biological Sciences and a master's degree in molecular approaches to health sciences to evaluate the effectiveness of ozone, without a doctorate or hardly any research background. That is, a person who is far from being able to prove that he is an expert in biostatistics or medical research methodology.

Biostatistics is a discipline that is barely received once in the first year of the degree, which has little resemblance to the rest of the subjects and which is difficult to remember. Magazines such as [Nature](#) or the [New England Journal of Medicine](#) have placed great emphasis on the problem of the lack of biostatistical knowledge, showing how widespread certain [wrong commonplaces](#) are in the medical community, such as, for example, privileging the number of patients in the evaluation of a study over the P-value that measures the relevance of their results (and that includes the number of patients itself in its formula). Being aware of this general lack, the signatories of this article have turned to several experts in this field, such as Luis Prieto Valiente, professor and professor of biostatistics and research methodology at the Complutense University [of Madrid] for 25 years, currently at UCAM [San Antonio de Murcia Catholic University]<sup>1</sup>.

Once the question of whether or not ozone is a pseudo-therapy has been addressed, it is worth asking whether it has potential for the treatment of COVID-19, based on the possible anti-inflammatory and tissue oxygenating [effect](#) that expert researchers are betting on in its use. In this sense, the bibliography is much more modest, as is obvious since it is a much more recent disease than a herniated disc or diabetic foot. Having analyzed 11 publications, mostly observational studies or series of clinical cases, we can conclude that, on the one hand, no adverse effects are observed in any of them, and that certain positive effects appear that still need to be accurately quantified through randomized controlled clinical trials.

That is, for the treatment of COVID-19, ozone cannot be considered an already proven therapy, but one more experimental treatment, like so many others that have been administered during the pandemic with few specific studies behind it, considering that its mechanism of action in other pathologies can be useful in coronavirus. This is common in a new disease for which there is no known treatment, and especially when the patient is in a situation with little chance of survival. The paucity of studies on a safe treatment with reasonable evidence of efficacy should encourage further research until it can be known whether it works or not. In this sense, the *Clinical Trials* website shows [9 studies](#) with ozone for COVID-19 in different stages of development. Let us remember that confusing scarcity of evidence with no evidence is a serious epistemological error.

To lightly disqualify a whole line of research under the concept of "pseudo-therapy", without thoroughly reviewing and entering into debate with the studies published on the matter, is an irresponsibility that can condemn countless present and future patients. Not to mention the fact that the work of thousands of doctors and researchers behind the published articles is being accused of fraudulent, which could be considered slander.

Ultimately, this situation raises the discussion of who are these "guards" of the good or bad use of a treatment, what training and experience they have—often less than that of the investigators who they attack—and who controls or protects their performance. Entrusting this difficult (and necessary) task to graduates in health careers without extensive training in biostatistics and research methodology, or even to disseminators without a research career, is reckless and produces serious errors such as the one discussed here. Let us not forget that it is not up to the professional associations to settle the truth or scientific evidence, but to the universities and research centers through academic publications.

**Note:** None of the undersigned have any conflict of interest due to being linked to the application, research or sale of ozone.

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