Ozone therapy is gaining credence and is being used by an increasing number of clinicians to treat ever more diverse types of patients. Previous reviews have highlighted potential mechanisms-of-action arising out of clinical experience as well as theoretical bases of this therapy in various diseases [1]. However, ozone therapy is still viewed with skepticism in mainstream medicine, especially since there has been scant evidence from stringent clinical trials.

In this issue of the Journal of Experimental and Integrative Medicine, Re et al. [2] review the basic mechanisms underlying ozone therapy, and the barriers that need to be overcome if this therapy is to establish its place within orthodox medicine. Re et al. describe why ozone cannot be considered a drug, i.e. it doesn't act on specific receptors; it doesn't follow pharmaco-dynamic or pharmaco-kinetic models; and optimum schedules/doses for administration cannot be established based on any calculated “half-life”. Additionally, ozone has many non-linear effects, as described by the authors according to the concept of "hormesis" (i.e. a cellular adaptive response to specific stimuli). So, it is crucial to achieve an appropriate ozone-concentration sufficient to induce a calculated oxidative stress while avoiding toxic levels (which are different for different tissues)[3]. Ozone "only acts" as a modulator or pro-drug and, by inducing secondary messengers, will enhance the subsequent adaptive responses. These actions are better achieved by the recent theoretical concepts regarding administration "start at low ozone concentration and increase slowly". According to this concept, the best final concentration and dose will depend on different diseases, on the route of administration, and the patient's characteristics (such as basal pro/anti-oxidant status)[1]. The advantage is that ozone can be used in a "personalized medicine" approach. However, this can also be a considerable limitation in the progress of ozone therapy since, with this personalized approach, it is more difficult to establish standard protocols and to evaluate outcomes such as in a clinical trial. The existing clinical experiences with ozone therapy have been obtained using different protocols, different ozone concentrations and gas-volumes, as well as range of administration schedules. All these preclude a systematic evaluation and comparison of studies to help clinical decision making. However, major efforts have been made over recent years to merge ozone therapy procedures. The most relevant are:

(1) The "Madrid Declaration on Ozone therapy" in June 2010 [4]. This represents the first consensus document on ozone therapy. It was developed by the relevant specialists, initially from 11 countries (with subsequent addition of more countries). The consensus document, which will be updated regularly, was translated into 10 different languages and supported by 24 international Ozonetherapy Associations.

(2) The foundation of the International Scientific Committee of Ozonetherapy in October 2010. Presided over by the eminent Prof. Velio Bocci, this is an independent International Scientific Board whose objectives include standardization of clinical practice in the use of ozone, together with harmonization and unification of criteria among different scientific societies [5].

The advent of this preliminary consensus, and the setting-up of the International Scientific Board, will take ozone therapy to the next level in clinical practice, with more homogeneous and rigorous criteria.

The review by Re et al. [2] also describes a major handicap in conducting clinical trials with ozone therapy, i.e. the lack of interest by the pharmaceutical industry. Ozone is inexpensive and, unlike conventional medications, it is not patentable and it cannot be conveniently packaged and marketed. Ozone needs to be generated and administered in situ [3]. We need to remind ourselves that, nowadays, most biomedical research depends on funding from the pharmaceutical industry. The administrative procedures to initiate a clinical trial or for obtaining approval from the national regulatory agencies are complex and
expensive. Occasionally, trials supported and conducted by the pharmaceutical industry have a risk of methodological bias. Nevertheless, “rules are rules” and these regulatory procedures were created to protect patients from unethical research practices, whether from industry or from individual researchers. Currently it is increasingly difficult to conduct research without the support of pharmaceutical companies. This places constraints on funding for research units, or even contracting of external specialized companies, who accept the responsibility for the conduct and budgeting for the numerous administrative procedures necessary in setting-up and performing a clinical trial.

Currently, few clinical trials with ozone therapy have been registered. For example, in the database of the U.S. National Institutes of Health in May 2012 they constitute only 6 clinical trials [6]. This situation is difficult to solve, even more so if drug companies see ozone therapy as the “enemy”.

However, all is not lost. While awaiting more specific clinical evidence, it would be better to reinforce the concept that ozone could be useful as an adjuvant treatment in several diseases, in close collaboration with “official” medicine. The main role of ozone therapy is not to replace pharmacotherapies but to improve the clinical results that they can offer in several diseases. In the United States, over one hundred thousand people die each year from adverse effects of medications that are unrelated to clinical error [7]. We should highlight the potential role of ozone to prevent, decrease or ameliorate toxicity induced by several drugs such as cisplatin [8], methotrexate [9] or procedures such as surgery or radiation therapy [10, 11]. These collaborative efforts should be of interest to the pharmaceutical industry rather than being seen as a threat, i.e. the consequence of these efforts could improve the outcomes of standard drug therapy and even increase indications for several drugs or medical interventions. For example, many articles have described the effect of ozone preconditioning in the protection against damage mediated by free radicals or ischemia-reperfusion; these effects would be very relevant for organ transplantation. A final field to explore could be the use of ozone therapy in the management of symptoms, with a focus on quality-of-life improvement [10, 11].

Needless to say, options for ozone therapy will depend on evidence from well-addressed clinical trials. If ozone is presented as a potential partner (rather than a threat) would ozone therapy receive support from the pharmaceutical industry, at least in setting-up clinical trials teams? Perhaps not; and, as such, other ways to continue ozone-research need to be explored. Following the steps taken in other fields of “official” medicine, perhaps scientific associations that support ozone therapy and/or collaboration among the ozone-device manufacturers (which are usually small start-up companies with very limited budgets) should play more important roles in supporting short, relatively inexpensive, well-designed, clinical trials.

We agree with Re et al [3] in that the medical use of ozone is now ready for a rigorous scientific evaluation. But are we, the practitioners, sufficiently geared-up to meet the challenge?

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References

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Correspondence:
B. Clavo
Department of Radiation Oncology, Chronic Pain Unit and Research Unit
Dr. Negrin University Hospital,
C/ Barranco la Ballena s/n,
35010 Las Palmas (Canary Islands), Spain.
bernardinoclavo@gmail.com, bernardinoclavo@terra.es

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