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# Stem cell therapy for end stage COPD: a cautionary tale of direct-to-consumer advertising


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# Stem cell therapy for end stage COPD: a cautionary tale of direct-to-consumer advertising

## **Cover Page Footnote**

This manuscript was prepared during a summer externship sponsored by the Michigan Academy of Family Physicians.

# Stem cell therapy for end stage COPD: a cautionary tale of direct-to- consumer advertising

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**ABSTRACT** A critical appraisal and clinical application of Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. *Chest*. 2013;143(6):1590-1598. doi: [10.1378/chest.12-2094](https://doi.org/10.1378/chest.12-2094)

**Keywords:** *Stem cell therapy, COPD, direct-to-consumer advertising*

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## Clinical Context

A 72 year-old man presented to the clinic for ongoing management of Stage IV chronic obstructive pulmonary disease. He quit smoking two years ago after an 80 pack-year history of prior smoking. This patient is on 2 liters per minute oxygen and maximal medical therapy including fluticasone with salmeterol-tiotropium inhaler. He complains of worsening dyspnea, wheezing, and mucus production. He experiences these symptoms walking more than 45 feet and during performance of his activities of daily living. In past visits, he has expressed frustration and emotional difficulty in dealing with his declining functional status. He frequently asks if there are any experimental protocols in which he can participate. At this visit, the patient brought a packet of information he retrieved from the internet detailing a "Lung Institute" that provides stem cell therapy for the treatment of advanced COPD and other lung diseases. He asked if this treatment could improve his functional ability.

## Clinical Question

Does stem cell treatment improve functional ability in patients with stage IV COPD?

## Research Article

Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. *Chest*. 2013;143(6):1590-1598. doi: [10.1378/chest.12-2094](https://doi.org/10.1378/chest.12-2094).

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## Related Literature

The information that the patient gave us was a brochure from a website claiming to include a pilot study formatted with an introduction, methods, results, analysis, conclusion and references.<sup>1</sup> This had the appearance of a published research article; however, this study was neither peer reviewed nor published in a registered journal. The website the patient identified made a disclaimer that “all claims regarding efficacy... are based solely on anecdotal support” and “the treatments, claims, and other information contained on this page... have not been evaluated or approved by the FDA.”<sup>1</sup>

Two of the 19 references in the brochure mentioned stem cells. Each of these two references were in PubMed and found to be not clinically useful. A PubMed search was conducted using the terms “stem[tiab] AND cell[tiab] AND (COPD[tiab] OR (obstructive[tiab] AND pulmonary[tiab]))”. The search resulted in only two clinical trials with human subjects, the Ribeiro-Paes paper and the Weiss paper.<sup>2,3</sup> There was also a recent systematic review in *PLoS ONE* that identified these same two trials as the only two clinical trials of stem cells in COPD patients.<sup>4</sup> Therefore, a review of these two articles evaluates the sum total of the knowledge on this subject.

The Ribeiro-Paes paper is a case series of four patients that claimed benefit; however, parameters on pulmonary function tests were unchanged at 12 months. Also, there was no comparison group to determine if this was an actual improvement, the natural history of the disease process, or placebo effect. The Ribeiro-Paes paper used autologous stem cells, which matched the therapy presented by the patient, but with only four cases, it lacked reliability. This evidence was considered too weak to use clinically.

The Weiss paper was a placebo-controlled, double-blinded, randomized trial of 62 patients. This study used allogenic stem cells, which express low levels of HLA. Subjects in this trial did not require immunosuppressive therapy or donor-recipient HLA matching, indicating that allogenic stem cells have similar safety when compared to autologous stem cells. The study methodology of the Weiss paper was stronger because it purported to be double blinded, randomized, and had a comparator group. Thus we chose this paper for critical appraisal to evaluate whether stem cells will improve functional status in our patient.

## Critical Appraisal

This article describes a randomized, double-blinded, placebo controlled trial. Because this was a Phase II trial, it is inappropriate to assign a level of evidence. The primary goal of the investigators was to determine safety of stem cell administration for COPD patients; the secondary goal was to assess efficacy of stem cell treatment for Stage II and Stage III COPD designated by the GOLD Criteria (<http://www.goldcopd.org>). Because efficacy is not the primary goal, this obviously detracts from the ability of this study to answer our clinical question.

The investigators of this paper recruited 62 patients that were randomized into placebo (control) and stem cell (experimental) groups. This study is not powered to determine efficacy. Inclusion criteria included a diagnosis of Stage II or III COPD based on the GOLD Criteria, patient age between 40 and 80 years old, a history of smoking over 10 pack-years, and certain post-bronchodilator FEV1 and FVC values. Exclusion criteria included other clinically relevant lung diseases, current infection, and other appropriate criteria delineated in the study. The authors tried to improve the strength of the study by removing any potential subjects that could have confounding factors. Our patient had more advanced disease, but was otherwise represented in the study participant groups.

Both experimental and control groups received the same volume of infusion under the same conditions. The experimental group received infusions containing allogenic mesenchymal stem cells (MSC) produced by Osiris Therapeutics, Inc. The control group received the same solution but without stem cells. All patients received a monthly infusion for a total of 4 months, which all 62 patients completed. Patients were followed for 2 years and evaluated for adverse effects as well as efficacy measures. Twenty six percent (N=16) of the participants were lost to follow-up. Measures of efficacy included FEV1 and FVC values, total lung capacity, 6-minute walk test, oxygen saturation during the walk test, multiple quality of life (QOL) questionnaires, number of COPD exacerbations, and levels of circulating markers of inflammation. The 6-minute walk test, the two QOL scales, and the time to exacerbation of COPD were the only patient oriented outcomes.

Patients were analyzed in the groups to which they were randomized and the two groups were found to be reasonably similar, except that the experimental group was slightly older (68 years vs. 64 years) and contained fewer current smokers (17% vs. 38%). Both groups had similar COPD medication regimens. While the two groups are relatively similar, there still exists a difference



between them. The authors disclosed that 63% of the experimental group and 84% of the control group completed the full 2 year protocol. This drop out rate makes it more difficult to extract relevant conclusions from the efficacy data.

The investigators report that no adverse events occurred during administration of the infusions. All instances of adverse events (AE) were recorded over the 2 years. It is quite disappointing that this Phase II trial's primary outcome was safety, but the reporting of adverse events is inconsistent in multiple locations in the paper. Table 4 and Table 5 do not match. The textual description is confusing. There is no definition or methodology to describe "Probable," "Possible," or "Unlikely" even though AE were reported with those categories. Despite the flaws in the manuscript, it seemed as though there was no difference between groups. It is notable that 90% in the MSC group experienced an AE and 87.5% in the placebo group experienced an AE.

Efficacy measures reported no statistically significant differences in FEV1, FVC, total lung capacity, 6 minute walk test, oxygen saturation during the test, quality of life questionnaires, and number of COPD exacerbations. The only significant difference was in the levels of one of the circulating inflammation markers, C-reactive protein (CRP), which was lower in the experimental group. Although, CRP may suggest some underlying mechanism of decreased inflammation, this statistically significant finding has no clinical significance for the patient. In addition, the ClinicalTrials.gov application listed that efficacy was to be measured at one year, but the publication reported that efficacy was measured at two years. This may reflect wishful thinking by the authors (sponsor) that extending the study might demonstrate benefit.

Another pitfall of the study is that the patients' use of rescue medications was not recorded, which is a confounding factor. It should also be noted that the company that produces the stem cells used in the experiment funded this study. Employees of the funding agency contributed to study conception, design, data interpretation, drafting and revising the article, and final approval of the article.

Despite the flaws of this study, it is the most appropriate to answer our clinical question. Stem cell therapy did not show a statistically significant improvement in functional ability in patients with COPD.

## Clinical Application

Based on the current evidence in the scientific literature, stem cell therapy is not recommended for this patient. There is no evidence for its efficacy and, according to a representative of the company, the therapy would cost up to \$12,000. Also, it cannot be ruled out that stem cell therapy may potentially harm this patient. A recent *New York Times* article described the story of a man who underwent stem cell therapies in various foreign countries and ended up with a large mass of stem cells growing uncontrollably in his spinal column.<sup>5</sup> The FDA is in the process of considering stricter regulation of stem cell clinics in America.<sup>6</sup> A statement from the FDA warns consumers that it "is concerned that the hope that patients have for cures not yet available may leave them vulnerable to unscrupulous providers of stem cell treatments that are illegal and potentially harmful," and they vow to "pursue perpetrators who expose the American public to the dangers of unapproved stem cells."<sup>2</sup>

There is not enough evidence to determine if stem cell therapy is safe in humans.

Our patient poses a novel therapy retrieved from surfing the Internet, a situation that happens often. Patients frequently bring in information or ask about novel treatments, and they look to the physician to investigate it for them. The responsibility we feel to take care of patients is counterbalanced by the time we have to research novel treatments. In this instance, a quick literature search yielded a clinically worthwhile answer for the patient's sake and they received that answer from someone they trust. Once an appropriate brief review is done, the process of shared decision-making can take place between doctor and patient. Risks and benefits must be discussed, along with the strength of the scientific evidence behind the potential risks and benefits.

While this patient continues desperately searching for experimental therapies, we were able to tell him we recommended against the stem cell treatment from the brochure. We had a conversation about the course of his COPD, which is a chronic, progressive, and debilitating disease. It is important that the patient internalizes and develops a realistic view of the morbidity and mortality associated with that disease. While physicians do not want to dash a patient's hope, the potential harms, both financial and medical, must factor into the decision. Most



patients want to know that every option has been considered, and only then are they accepting of the fact that a certain treatment option would probably not benefit them. It is the physician's utmost privilege to help the patient come to a decision about how to move forward and enjoy the best quality of life that can be achieved.

#### Take-home points

- 1.) At this time, there is no evidence that stem cell therapy benefits patients with COPD.
- 2.) Critically appraising current scientific literature can save patients from seeking therapies that can be financially or medically harmful.
- 3.) Patients often ask about medical information, and it is the physician's duty and privilege to give them the best answer possible to aid in their shared decision-making.

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