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# The Emergence of Oral Sildenafil for Pulmonary Hypertension Management

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In November 2002, I came across a letter to the *New England Journal of Medicine* editor that would prove groundbreaking [1]. The letter from Dr Michael A. Gatzoulis's team at Brompton Hospital in London described a desperate patient, which caught my attention (see Exhibit 1).

## 1 | The Desperate Case

The letter detailed a patient suffering from severe primary pulmonary hypertension (PPH) who had deteriorated to the point of being unable to walk even 100 m. Traditional treatments, such as epoprostenol infusion or transplantation, were rejected by the patient at that time. With limited options, Dr. Gatzoulis's team administered sildenafil at a daily maintenance dose of 500 mg (100 mg five times daily). This decision was based on observational reports of its use as a nitric oxide enhancer in children from London and Boston. The patient tolerated the treatment well and made significant improvements.

## 2 | Early Discussions and Trials

I had begun discussing the potential use of sildenafil as early as 1997 when I was a scientific advisor for Pfizer. I engaged with various specialists, particularly Dr. Zapol's group, Dr. Wessels in Boston, Dr. Abrams and Dr. Schulze-Neick from Great Ormond Street Hospital in London. They were interested in using sildenafil as a nitric oxide enhancer. These discussions led to the publication of observations regarding using sildenafil in children [2, 3]. In 1999, I convinced Pfizer to start a multicenter trial of intravenous sildenafil in patients with PPH during cardiac catheterization sessions. The study showed that sildenafil positively impacted pulmonary pressure and vascular resistance, even at lower doses. I shall write a follow-up vignette on the first sildenafil intravenous trial in patients with PPH.

## 3 | Adjusting the Treatment

The higher doses Dr. Gatzoulis's team used prompted me to contact him. We discussed the unpublished initial results of sildenafil, emphasizing the potential for lower doses. Consequently, Dr. Gatzoulis lowered the sildenafil dose. Although there was no follow-up publication on the patient's outcome, Dr. Gatzoulis assured me that the patient thrived and eventually graduated from college several years later.

## 4 | Widespread Off-Label Use

In early 1999, Dr. Tim Higginbottom from Sheffield, United Kingdom, one of the investigators of the intravenous observational study, began off-label use of sildenafil for some of his patients. This, along with the response to the letter to the editor and a few observational publications, sparked discussions among physicians about the potential to be used for the treatment of pulmonary arterial hypertension (PAH). I remember Dr. Gerald Simonneau from France mentioning the treatment in a scientific session on PAH at the November 2000 AHA annual meeting, attended by less than 30 participants. Interest in sildenafil as a treatment for PAH surged, and interest and widespread off-label use of sildenafil to treat PH became common, especially in Europe, the United States, India, and Africa, where conventional treatments were either absent or expensive. The media also took an interest in the use of sildenafil (a lifestyle drug) for treating severe PH, particularly in children.

Spiritual issues and conflict between religious beliefs and recommended treatments are complex and time-consuming matters, and they require the attention of a professional caregiver.[1]

The letter from Castro et al. permits us to make our point. In reporting that 70 percent of the patients in their study wanted their physicians to pray with or for them, do Castro et al. imply that the physicians were ready to do so, possessed sufficient information about the patients to do so knowingly, and were sufficiently religious or spiritual to pray sincerely? Are they concerned about the great and increasing likelihood that physician and patient may be from different religious traditions? Are they arguing that these considerations are irrelevant?

Finally, both Hite and Hall believe that the chaplains seek to protect their professional territory. Who can better address these issues than professionals with training and clinical experience in the area of religion and spirituality in the lives of patients?

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## Sildenafil in Primary Pulmonary Hypertension

*To the Editor:* A 21-year-old man presented with a three-year history of worsening dyspnea and a four-month history of being unable to walk more than 100 yards (90 m) without resting. Physical examination revealed signs of pulmonary hypertension. A chest radiograph showed the typical changes associated with primary pulmonary hypertension. An echocardiogram obtained at the time of admission showed marked right ventricular dilatation; the estimated pulmonary-artery systolic pressure was 120 mm Hg (resulting from tricuspid regurgitation identified on Doppler ultrasonography). Left ventricular systolic function was preserved.

Pulmonary-function tests showed only mild airflow limitation. A computed tomographic scan of the thorax showed massive dilatation of proximal and segmental pulmonary arteries. Cardiac catheterization showed a pulmonary-artery pressure of 128/81 mm Hg (mean, 97) and an aortic pressure of 126/90 mm Hg (mean, 103); there was no increase in oxygen saturation. The myocardial oxygen consumption was 15.2 ml per kilogram per minute (predicted value, 42.9) after seven minutes of exercise. No causes of secondary pulmonary hypertension were identified.

The patient declined treatment with a continuous infusion of epoprostenol and lung transplantation. Subsequently, treatment with sildenafil was begun at a dose of 50 mg once a day and was well tolerated. The dose was then adjusted until a maintenance dose of 100 mg five times per day was reached, and no side effects have been reported. The patient's only other medication was the anticoagulant warfarin.

On follow-up at three months, the patient's condition had improved dramatically, and he was able to perform one hour of regular aerobic exercise. The echocardiogram showed an estimated pulmonary-artery systolic pressure of 90 mm Hg. The myocardial oxygen consumption was 20.3 ml per kilogram per minute after 12 minutes of exercise. An assay of cyclic guanosine monophosphate (cGMP) showed a level of 183 nmol per millimole of creatinine (normal level, less than 51)[1] before treatment and a level of 33.5 nmol per millimole of creatinine at follow-up during treatment.

We propose that oral sildenafil may be beneficial as a selective pulmonary vasodilator in patients with primary pulmonary hypertension. A recent study in children suggested a potential role for sildenafil in the management of pulmonary hypertension.[2,3] Sildenafil may preferentially inhibit cGMP-specific phosphodiesterase, which is abundant in lung tissue[4]; this possibility needs to be evaluated prospectively.

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**EXHIBIT 1** | Letter to the editor of the first published adult patient with primary pulmonary hypertension with oral sildenafil. Prasad et al. [1].

## 5 | A Pivotal Moment in the History of Oral Sildenafil Development

Pfizer initiated their Phase III trial of sildenafil for the treatment of PAH (SUPER study), which later led to the publication of the results [4] and the approval of sildenafil (20 mg, three times a day) in 2006 for the management of PAH. This period marked a pivotal moment in the medical history of treating PAH. I witnessed firsthand how this development transformed the landscape of treatment options for patients suffering from this severe condition.

### Author Contributions

The author takes full responsibility for this article.

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The author has nothing to report.

## Disclosure

Guarantor: N/A.

## Ethics Statement

The author has nothing to report.

## Conflicts of Interest

The author declares no conflicts of interest.

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