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Does Tadalafil Improve Exercise Capacitance in Patients over 12 Years Old with Pulmonary Hypertension?

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Abstract

Objective: The objective of this systematic review is to determine whether or not the oral Phosphodiesterase inhibitor Tadalafil improves exercise capacitance in those over 12 years with pulmonary hypertension.

Study Design: Review of three primary research materials published in English language in 2009.

Data Sources: Randomized, controlled, double blind clinical trials found using PubMed, OVID and COCHRANE databases.

Outcome measured: Trials measured 6-minute walking distance and health related quality of life measurements which included: SF-36 (a measure of self reported health status), and the EQ-5D (a patient reported health related quality of life measure), WHO functional class, clinical worsening, and hemodynamic measurements.

Results: Two of the randomized controlled trials included in this review showed that tadalafil is effective at improving exercise capacitance in patients with pulmonary hypertension. The trials showed patients had an improvement in their 6-minute walking distance, self reported health status and quality of life, and improvement in time to clinical worsening. The trial conducted by Fischler et al showed that tadalafil was not effective at improving exercise capacitance in patients with high altitude pulmonary edema in comparison with dexamethasone.

Conclusions: Tadalafil 40 mg is an effective monotherapy for increasing exercise capacitance and improving health related quality of life in patients with pulmonary hypertension. In the Galie et al and Pepke-Zaba et al studies, tadalafil was found to improve exercise capacitance and quality of life in patients with pulmonary arterial hypertension. However, in the Fischler et al study, dexamethasone, not tadalafil improved exercise capacity in patients with high al2titude pulmonary edema.

Key Words: Tadalafil, pulmonary hypertension

Introduction:

Pulmonary arterial hypertension (PAH) is a chronic and progressive disorder where the pulmonary arterial pressure is persistently elevated, eventually leading to right sided heart failure and death.[2] This disorder can be grouped into two main categories: primary and secondary PAH. Primary pulmonary hypertension is considered to be idiopathic because it arises without a family history or any underlying condition. Whereas, secondary PAH is due to some sort of underlying disease such as: collagen vascular disease, HIV infection, congenital heart disease, left-sided heart failure, pulmonary embolism, portal hypertension, or sarcoidosis. It is estimated that idiopathic PAH effects about 0.1-0.2% of the population with the mean age at diagnosis being 50 years old; furthermore, more women are affected by PAH than men, with a ratio of 2:1.[4] Moreover, it is estimated that 2-4% of patients with chronic liver disease, 0.5% of patients with HIV and about 23-25% of patients with mixed connective tissue diseases have secondary PAH. However, of the people who are diagnosed yearly with pulmonary hypertension, it is estimated that only about 15,000 to 25,000 are diagnosed and treated appropriately.[4]

The exact cause and pathogenesis of this disease is unknown; however, it is thought that several different factors play a role in the vasoconstriction and narrowing of the pulmonary vasculature. More specifically, some sources of PAH include: vascular cell proliferation and apoptosis, influx of cellular inflammation, excess vasoconstriction, and in situ thrombosis.[2,3] Normal pulmonary arterial pressure is 12-16 mmHg; however, this disease is considered pathologic when the mean arterial pressure exceeds 25 mmHg at rest over an extended period of time.[4]

Patients who have PAH usually will present with non-specific symptoms such as chest pain, dyspnea, fatigue, peripheral edema, cyanosis and syncope[2,3] The World Health Organization has come up with its own classification of PAH which includes: Class I: Patients with PAH but without resulting limitation of physical activity. Ordinary physical activity does not cause any limitation. Class II: Patients with PAH resulting in slight limitation of physical activity. They are comfortable at rest, but ordinary physical activity causes limitative symptoms such as: dyspnea, fatigue, chest pain, or near syncope. Class III: Patients with PAH resulting in marked limitation of physical activity. They are comfortable at rest; however, less than ordinary activity causes limitation symptoms. Class IV: Patients with PAH who are unable to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure and have limitative at rest which are increased with physical activity.[4]

Unfortunately, at the present time there is no cure for PAH. However, there are currently three classes of drugs which have been approved for the treatment of PAH in the United States which include: prostanoids (epoprostenol, treprostinil,iloprost), endothelin receptor antagonists (bosentan, ambristan, sitaxsentan), and phosphodiesterase type 5 inhibitors (sildenafil and tadalafil).[3,7] Other conventional therapies such as calcium channel blockers, digoxin, warfarin, oxygen and diuretics may also be used to aide in the treatment of PAH; but, the only definitive treatment of PAH is lung transplantation at this time.[3,7] An exact number for the total healthcare cost of PAH has not been indentified; however, the annual drug costs for Sildenafil, Bosentan, Ambrisentan, and Iloprost is $12,761, $55,890, $56,736, and $92,146, respectively.[5] Furthermore, an estimate of patients hospitalized with PAH was not available within the past few years, but between 2000 and 2002, 807,000 patients were hospitalized with PAH and in 2002 PAH led to 260,000 hospital visits in the United States[6]

Objective:

The objective of this systematic review is to determine whether or not the Phosphodiesterase inhibitor Tadalafil improves exercise capacitance in those over 12 years old with pulmonary hypertension.

Methods:

The studies used for this review were selected based on the following criteria. The patient population included those who were over 12 years of age with symptomatic pulmonary arterial hypertension. The diagnosis of PAH included: a resting mean pulmonary artery pressure ≥ 25 mmHg, pulmonary wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance ≥ 3 Wood units. The intervention used was oral tadalafil. The treatment groups were compared to placebo groups who received a visually matched placebo. The outcomes measured were exercise capacitance with measurement of the 6-minute walk distance (6-MWD), health related quality of life measures (measured by the SF-36 and ED-50), WHO functional class, Borg dyspnea score, and hemodynamic measurements, all of which can qualify as patient oriented evidence that matters (POEMs). Furthermore, all three studies were randomized double blind, placebo controlled clinical trials.

In research conducted by Fischler et al, 23 patients aged age 44 ± 10 years with a body mass index of 24.5 ± 3.0 kg/m^2 and a history of high altitude pulmonary edema (HAPE) were enrolled into the trial. The patients were randomized in a double blind fashion and were given either 10 mg of tadalafil twice a day, 8 mg of dexamethasone twice a day, or placebo twice a day the morning before their ascent to high altitude. On day one of the ascent cycle ergometer cardiopulmonary exercise test (CPET) was performed and on day two an echocardiograph

examination was performed which both allowed for hemodynamic measurements to be taken. Patients were excluded from the study if they spent more than four nights above 2,500 meters within 30 days before study entry.

Four hundred and five patients over the age of 12 years old with PAH that was idiopathic/heritable or related to anorexigen use, connective tissue disease, HIV infection, congenital systemic-to-pulmonary shunts were part of the Galie et al study. The patients were either treatment naïve or on background therapy with bosentan, an endothelin receptor antagonist. Furthermore, patients were continued on bosentan throughout the study if they were on a maximum stable dose of 125 mg twice daily for a minimum of 12 weeks at the time of screening. The majority of the patients had symptoms in WHO functional class II or III and about 53% of the patients were on background bosentan therapy. The patients were randomized into placebo and treatment groups, those in the treatment group received either tadalafil 2.5, 10, 20, or 40 mg orally once daily. Outcomes included: the change from baseline in the 6-MWD, changes in the WHO functional class, Borg dyspnea score, time to clinical worsening, and health related quality of life measurements, via the SF-36 and EQ-5D. Patients were excluded from this study if the patient had a 6-minute walk distance (6-MWD) of <150 m or >450 m or if they were previously treated with intravenous epoprostenol, intravenous or inhaled iloprost, or subcutaneous treprostinil.

The Pepke-Zaba et al study lasted for 16 weeks and included 405 patients over the age of 12 years old with symptomatic PAH. The majority of the patients included in this study had PAH that was idiopathic/familial, a WHO functional class of II or III, and were mostly female. Furthermore, patients who were already on background bosentan therapy of a dose of 125 mg twice daily for 12 weeks were able to continue that along with the study medication. Patients

were randomized into placebo and experimental groups, with experimental group having received either tadalafil 2.5, 10, 20, or 40 mg once daily. The main outcome of this study was measuring the mean change from baseline in the 6-MWD in order to evaluate exercise capacitance, along with patient reported health related quality of life measurements, through the SF-36 and EQ-5D. These outcomes were measured at baseline and then weeks 8 and 16. If patients had a 6-MWD <150 and >450 meters or were treated previously with epoprostenol, iloprost, treprostinil, sitaxsentan, ambrisentan, and sildenafil they were excluded from the study.

Key words used in searches were Pulmonary Hypertension, Tadalafil. All articles were published in the English language and in peer-reviewed journals. This author personally did the article search in PubMed, OVID and Cochrane database. Inclusion criteria were: patients over the age of 12, randomized controlled trials, articles that were not previously published in a meta-analysis or systematic review, had POEM outcomes, and articles that were published between 1996 and the present. Exclusion criteria were studies with patients under 12 years old, articles previously used in a meta-analysis or systematic review and studies published before 1996. Of the three papers, they all reported p-values of statistical significance; however, the Fischler et al study was the only one to report a RRR, ARR, and NNT.

Table 1. Characteristics of Studies for systematic review of Tadalafil on exercise capacitance with PAH

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Fischler[1] (2009)	Double blind RCT	29	44 ± 10 years	age 44 ± 10 years with a body mass index of 24.5 ± 3.0 kg/m^2; a history of HAPE	spending more than four nights above 2,500 meters within 30 days before study entry	6	Regimen of Tadalafil 10 mg bid, dexamethasone 8 mg bid, or placebo starting the day before ascent
Galie[2] (2009)	Double blind RCT	405	>12 years old	Patients were at least 12 years of age and had symptomatic pulmonary arterial hypertension	Patients with a 6-minute walk distance (6-MWD) of <150 m or >450 m, treatment with intravenous epoprostenol, intravenous or inhaled iloprost, or subcutaneous treprostinil was prohibited	3	Regimen of Tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg or placebo orally once daily
Pepke-Zaba[3] (2009)	Double blind RCT	405	>12 years old	Patients were at least 12 years of age and had symptomatic pulmonary arterial hypertension	6-MWD test distance <150 and >450 meters, treatment with epoprostenol, iloprost, treprostinil, sitaxsentan, ambrisentan, and sildenafil	0	Regimen of Tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg or placebo orally once daily

Outcomes Measured:

The Fischler et al study measured exercise capacitance by performing Cycle Ergometer Cardiopulmonary exercise test (CPET) and an echocardiography and calculating hemodynamic measurements at low and high altitudes. The CPET was performed on Day 1 about 4 to 6 hours after the patients' arrival at 4, 559 m and an echocardiography was performed on the second day. The CPET measured O2-uptake kinetics, oxygen saturation, heart rate and blood pressure; whereas the echocardiogram measured the pulmonary artery pressure. Furthermore, assessment of HAPE (high altitude pulmonary edema) was defined as previously reported and the development of AMS (acute mountain sickness) via the Lake Louise consensus scoring system.

The Galie et al study measured exercise capacitance via the change from baseline in the 6-MWD, changes in the WHO functional class, and the Borg dyspnea score. Health related quality of life was measured using the SF-36 and the EQ-5D. The SF-36 consists of 36 items which represent one of the following topics: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health. The EQ-5D has two parts, which include 5 questions that assess mobility, self care, usual activity, pain/discomfort and anxiety/depression. The 6-MWD, WHO functional class, and Borg dyspnea score were all measured at baseline and at weeks 4, 8, 12, and 16. Furthermore, Pepke-Zaba et al measured exercise capacitance by using the 6-minute walk test and also measured self-reported health status and quality of life measures via the SF-36 and EQ-5D which were all measured at baseline and then again at weeks 8 and 16.

Results:

All three of the articles were presented as double blind, randomized control trials. The Fischler et al study presented their results as dichotomous data; whereas, the Galie et al and

Pepke-Zaba et al studies presented their results as continuous data. Fischler et al conducted research with 23 participants, three women and twenty men, in order to evaluate the tadalafil and improving exercise capacitance in patients who developed HAPE. Six people within this study had to be excluded because of technical problems with the equipment. The Galie et al study conducted research on a total of 405 patients with only 341 patients completing the entire 16 week study. Three patients died during the study; one patient died in the placebo group due to PAH progression, another in the 10 mg tadalafil group died suddenly and the third death was in the tadalfil 20 mg group which was due to histiocytosis hematophagic syndrome. Lastly, the Pepke-Zaba study contained a total of 405 patients; however, there was no definite information presented within the study as to how many patients did not finish the study.

The Fischler et al study evaluated the effects of dexamethasone, tadalafil and placebo on improving exercise capacitance at high altitude. This study found that dexamethasone improves exercise capacity and partially limits hypoxia-induced pulmonary hypertension at 4,559 meters in HAPE susceptible individuals. Whereas, tadalafil did not significantly improve exercise capacitance and did not significantly limit instances of hypoxia-induced pulmonary hypertension. Dexamethasone significantly improved maximum oxygen uptake and oxygen kinetics compared with placebo ($P<0.05$); however, peak oxygen saturation did not differ significantly between the three treatment groups. Blood pressure did not change among the three groups, but there was a significant increase in heart rate among all three groups, which was significantly lower in the dexamethasone group than the other two groups ($p < 0.01$). Furthermore, echocardiography showed that dexamethasone revealed lower pulmonary artery pressures in comparison to placebo. Acute mountain sickness scores did not differ between the three groups on day 1; however, on day 2 the dexamethasone group had statistically significant

lower scores with a p value of <0.01. The RRR was calculated as -84% and the ARR was -74%. The NNT was determined as -1.4 with a p-value of 0.001. The negative value of NNT indicates that if two people were treated with tadalafil, one less person in the tadalafil treatment group will have increased exercise capacitance compared to those people in the dexamethasone treatment group.

Table 2. Treatment effects of Tadalafil on exercise capacitance in PAH

Study	Relative risk reduction	Absolute risk reduction	Number needed to treat	p-value
Fischler et al, 2009[1]	-84%	-74%	-1.4	0.001

Galie et al researched the efficacy of tadalafil on improving exercise capacitance and quality of life in patients with PAH. In this study, exercise capacitance was measured using the 6- MWD through comparing the mean change from baseline between the experimental and placebo groups. Tadalafil 10, 20, and 40, not the 2.5 mg group, notably improved the 6-MWD in comparison to the placebo group. However, only the tadalafil 40 mg group achieved statistical significance with a p-value < 0.01. Furthermore, in the 40 mg tadalafil treatment group, the mean change in the 6-MWD was 44 m in treatment naïve individuals (CI 95%, P<0.01) and 23 m in individuals on background bosentan therapy (CI 95%, P=0.09). There was no statistically significant difference amongst the experimental and placebo groups with improvement or worsening in WHO functional class. Moreover, time to clinical worsening was significantly improved in the tadalafil 40 mg group (P=0.041) when compared with placebo and the overall incidence of clinical worsening was reduced in the tadalfil 40 mg group.

Furthermore, there was no difference in changes in the Borg dyspnea score between treatment and placebo groups. However, statistically significant improvements in quality of life

were seen in 6 out of the 8 domains in the SF-36 ($P<0.01$) and all sections of the EQ-5D in the tadalafil 40 mg group ($P<0.02$). Throughout this 16 week study, the most common adverse events seen with taking tadalafil were: headache, myalgia, and flushing.

The objective of the Pepke-Zaba study was to study the effect of tadalafil on health related quality of life measures in patients with PAH. The mean change in the 6-MWD was greater for all patients that were treated with tadalafil in comparison with the placebo group; however, the mean change was greatest in the tadalafil 40 mg group. The pre-specified value of statistical significance ($p < 0.01$) was only achieved in the tadalafil 40 mg group. Furthermore, only the tadalafil 40 mg group showed improvement over placebo in six out of the eight domains of the SF-36 along with a significant change from baseline to week 16 on the EQ-5D score. The most common adverse events encountered during this study were headache, myalgia, and flushing, which were described as mild to moderate in severity.

Discussion:

Tadalafil is the second phospodiesterase inhibitor to be used for the treatment of PAH and is currently FDA approved in the United States for treatment of erectile dysfunction under the trade name Cialis. However, for the treatment of PAH, it is marketed as Adcirca. The most common adverse effects which have been experienced while taking tadalafil include: flushing, headache, dyspepsia, myalgia, extremity pain, upper respiratory infection, and nasopharyngitis. Also, some contraindications to using tadalafil include: hypersensitivity reaction to tadalafil and concomitant use with other organ nitrates.[8] In the Galie et al and Pepke-Zaba et al studies, tadalafil 40 mg showed statistically significant improvement in the outcomes measured. Tadalafil 40 mg improved the 6-MWD, quality of life measurements, including both the SF-36 and the

EQ-5D, and reduced time to clinical worsening. However, within the Fischler et al study, tadalafil did not significantly improve exercise capacitance at a high altitude and did not significantly limit instances of hypoxia-induced pulmonary hypertension or acute mountain sickness.

A limitation of these three trials was the length of studies. The patients were not followed for longer than 16 weeks; therefore, long term efficacy and safety were not able to be properly assessed. Another limitation within the Galie et al and Pepke-Zaba studies include patients that were on background bosentan therapy while in the trials because this may have altered the results. A final limitation of this review on tadalafil is that two of the studies were performed at sea level and the Fischler et al study was conducted at a high altitude; therefore, an equivalent comparison of tadalafil could not be evaluated.

Conclusion:

Even though tadalafil was not effective in increasing exercise capacitance in patients who experience high altitude pulmonary edema, the other two studies demonstrated that tadalafil 40 mg is an efficient monotherapy for increasing exercise capacitance in patients older than 12 years old with pulmonary hypertension. Tadalafil was effective at improving the 6-minute walk distance, quality of life measurements, including both the SF-36 and the EQ-5D, and reducing time to clinical worsening. In order to fully examine the long term benefits and outcomes of tadalafil, a larger subset of patients who are followed for a longer period of time is needed. Further research would include targeting the diseases in which patients develop secondary PAH and formulating disease specific therapies. Another research opportunity would be to find a cure for PAH since this is a chronic and progressive condition.

References

1. Fischler M, Maggiorini M, Dorschner L, et al. Dexamethasone but not tadalafil improves exercise capacity in adults prone to high-altitude pulmonary edema. *Am J Respir Crit Care Med*. 2009;180(4):346-352.
2. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119(22):2894-2903.
3. Pepke-Zaba J, Beardsworth A, Chan M, Angalakuditi M. Tadalafil therapy and health-related quality of life in pulmonary arterial hypertension. Curr Med Res Opin. 2009 Oct;25(10):2479-85
4. Barst RJ, Rubin LJ. Chapter 71. Pulmonary Hypertension. In: Fuster V, Walsh RA, Harrington RA, eds. *Hurst's The Heart*. 13th ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=7824908. Accessed October 1, 2011.
5. Abraham, Teena, Wu, Gary, Vastey, Fabienne, et al. Combination Therapy in the Treatment of Pulmonary Arterial Hypertension: Cost of Therapy. *Pharmacotherapy*. 2010;30(4):390-404.
6. Pulmonary Hypertension Fact Sheet. Centers for disease control and prevention website. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5405a1.htm. Accessed September 28, 2011
7. Treatment options for PAH. Pulmonary Hypertension Association Website. http://www.phassociation.org/Page.aspx?pid=977. Accessed September 25, 2011.
8. Tadalafil. PubMed Health website. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000252/. Accessed November 14, 2001.