Sildenafil for idiopathic pulmonary fibrosis: A systematic review and meta-analysis

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Abstract

**Background:** Patients with idiopathic pulmonary fibrosis have a poor overall prognosis and there are few evidence based drug therapies that reduce mortality.

**Objective:** This systematic review and meta-analysis aims to assess whether sildenafil reduces mortality, reduces disease progression and the adverse side effects associated with it.

**Methods:** In this review, randomized controlled studies (RCTs) were retrieved from MEDLINE, Cochrane, and EMBASE. The primary outcome was mortality. The secondary outcomes included change in FVC, acute exacerbations and hospitalizations and adverse drug effects leading to discontinuation. We used an inverse variance random effects meta-analysis method to calculate pooled odds ratio (OR) and standardized mean difference (SMD).

**Results:** A total of 4 studies were included. Sildenafil probably reduces mortality when compared to placebo or to standard care, [OR 0.63 (0.38,1.03), I²=0%]. Pooled results showed sildenafil does not alter the rate of change of FVC [SMD 0.02 (-0.14,0.18)], or DLCO [SMR -0.01 (-0.18,0.17)], [I²=0]. Pooled results showed sildenafil may not reduce the number of hospitalizations or acute exacerbations, [OR 1.06 (0.67,1.67)], I²= 0]. There was no significant difference in drug discontinuation due to adverse effects when comparing sildenafil to the control group, [OR 0.79 (0.56, 1.11)], I²=0].

**Conclusion:** Sildenafil probably reduces all-cause mortality in IPF patients. More studies need to be done in order to confirm the magnitude and reliability of the point estimate.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic restrictive pulmonary disease with a poor overall prognosis.¹,² Both pirfenidone and nintedanib have been shown to slow the progression of the disease and have the highest likelihood of conferring mortality benefit.² Sildenafil is a phosphodiesterase-5 inhibitor and a selective pulmonary-selective vasodilator used to treat group 1 pulmonary hypertension.³ A potential benefit for sildenafil has been suggested in IPF and its use has been evaluated in patients with and without group 3 pulmonary hypertension.

A recent network meta-analysis (NMA) that analyzed IPF medical therapies found that pirfenidone, nintedanib, and sildenafil had the highest probability when compared to other treatments to confer an overall mortality benefit.² The results of the few trials that have tested the efficacy of sildenafil in these populations, however, are generally limited by short follow up, small sample size, and variable patient populations.

The current evidence-based international treatment guidelines for IPF provide a conditional recommendation against the use of sildenafil.⁴

The objective of this review is to provide an update of the evidence on whether sildenafil provides mortality benefit, improves overall lung function, reduces exacerbations and hospitalization and adverse events leading to drug discontinuation.

Methods

We registered a protocol for this review at Open Science Framework (OSF) (osf.io/wkg7p). This review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations.⁵

Search strategy

We searched MEDLINE, EMBASE, CENTRAL, and Clinicaltrials.gov from inception to May 2021 (Supplementary 1). We did not include unpublished trials.
Eligibility criteria and screening

We included randomized controlled trials (RCTs) that reported on patients 18 years of age or older, diagnosed with IPF, and compared standalone PDE-5 inhibitors versus placebo or PDE-5 inhibitors with standard IPF care with either nintedanib or pirfenidone.

Data management & selection process

We used COVIDENCE to screen search records. Reviewers, working independently and in duplicate, screened titles and abstracts of search records and subsequently the full-texts of records deemed potentially eligible at the title and abstract screening stage. Reviewers resolved discrepancies by discussion, and if necessary, by third party adjudication.

Data collection process & data outcomes

We extracted data using a pilot-tested data extraction form. The form was piloted using a sample of the included primary studies.

We collected data on trial and baseline patient characteristics (e.g., country, age, sex) and outcomes of interest, including all-cause mortality, forced vital capacity (FVC), diffusing capacity of carbon monoxide (DLCO), hospitalizations, and exacerbations, as well as adverse events leading to drug discontinuation.

Risk of bias

For each included trial, pairs of reviewers, working independently and in duplicate, used a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0) to assess risk of bias across five domains: bias arising from the randomisation process; bias due to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Supplementary 2 reports criteria for risk of bias assessments. Reviewers resolved discrepancies by discussion and, when not necessary, with adjudication by a third party reviewer.

Data synthesis

We performed an inverse variance random-effects meta-analysis using a frequentist framework. We reported odds ratios for dichotomous outcomes and, since FVC and DLCO were reported as either change in mL or percent change predicted in primary studies, standardized mean differences for continuous outcomes. For dichotomous outcomes with zero events, we implemented a continuity correction. We quantified heterogeneity by the $I^2$ statistic and considered 25%, 50%, and 75% as low, moderate, and high heterogeneity levels, respectively. We did not assess for publication bias since there were fewer than 10 eligible studies. We performed all analyses in RevMan.

Confidence in evidence

Two reviewers, working independently and in duplicate, assessed the certainty of the evidence using the GRADE approach with a minimally contextualized framework. For judgements related to imprecision, we considered a 2% reduction in mortality, a 10% reduction in hospitalization and acute exacerbation, a 20% reduction in adverse effects leading to drug discontinuation as clinically important. For FVC and DLCO, we considered an SMD of 0.25 as minimally important.

Results

Study selection

Our search strategy identified unique records 295. We reviewed 21 full-texts and identified 4 RCTs. Figure 1 presents additional information related to the selection of eligible trials.
Study characteristics

The age of participants across the four trials ranged from 68.6 to 70.4 and the populations were predominantly male. Baseline pulmonary function was also similar across studies. The range of follow up for all outcomes ranged from 12 to 52 weeks. All trials but one were multicentered and most participants were recruited either from North America or Western Europe. There are differences in the patient population across the studies. Behr 2020 included only World Health Organization (WHO) group 3 pulmonary hypertension patients, whereas the remaining studies included patients with an IPF diagnosis only. Table 1 has details on basic study characteristics.

Risk of bias

All trials were rated low risk of bias across all outcomes.

All cause mortality

Four trials, including 661 patients and 90 deaths, reported on mortality. Pooled results showed that sildenafil probably reduces mortality, [OR 0.63 (0.38,1.03), $I^2=0\%$]. We rated down the certainty of evidence for imprecision in the estimate. Figure 2 and summary of findings table summarizes the results.

Pulmonary function testing

Four trials, including 602 patients reported on FVC and 487 patients reported on DLCO. Pooled results showed sildenafil does not alter the rate of change of FVC [SMD 0.02 (-0.14,0.18)], or DLCO [SMR -0.01 (-0.18,0.17)], $I^2=0\%$. Figure 3, 4 and summary of findings table provide more details.

Acute exacerbations and all-cause hospitalization

Four trials, including 661 patients, reported on all acute exacerbations and hospitalizations. Pooled results showed sildenafil may not reduce the number of hospitalizations or acute exacerbations, [OR 1.06 (0.67,1.67)], $I^2=0\%$. Figure 5 and summary of findings table provide more detail.

Adverse events leading to drug discontinuation

Four trials, including 661 patients, reported on adverse events leading to drug discontinuation. There was no significant difference in drug discontinuation due to adverse effects when comparing sildenafil to the control group, [OR 0.79 (0.56, 1.11)], $I^2=0\%$. Figure 6 and the summary of findings table provides more detail.

Discussion

Main findings

Our review presents the most up-to-date and comprehensive summary of the evidence on sildenafil therapy for IPF patients. We show that sildenafil probably reduces mortality, albeit without meeting statistical significance possibly due to too few patients and events. We did not, however, detect a reduction in disease progression or differences in adverse events.

Relation to previous findings

There have been no systematic reviews or meta-analyses of sildenafil in the treatment of IPF since the publication of the Behr 2020 trial and INSTAGE$^{11,12}$. A network meta-analysis suggested that sildenafil, alongside nintedanib and pirfenidone, showed the highest probability of reducing mortality in IPF.$^{13}$ At that time, there had been no randomized controlled trials that investigated the combination of either pirfenidone or nintedanib to sildenafil, in either standalone IPF patients or in combined IPF and pulmonary hypertension patient populations. Our review showed that sildenafil may reduce mortality in IPF patients, though our results were not statistically significant. The effect size we report needs to be considered in the context of low to
no heterogeneity between studies, which suggests that the result is underpowered and larger RCTs are necessary to produce more precise effect estimates.

The addition of pirfenidone with sildenafil versus pirfenidone alone did not result in a significant reduction in mortality in Behr 2020. In Rochwerg et al 2016, there was no significant difference between sildenafil and pirfenidone in head to head comparisons. The interaction between sildenafil and pirfenidone remains unclear; whether there is a positive or negative effect needs to be studied further. In INSTAGE, the effect of nintedanib combined with sildenafil did not perform better than nintedanib alone but there was a signal towards benefit for FVC. Similarly, there was no significant difference between sildenafil and nintedanib (moderate certainty in evidence) in head to head comparison in Rochwerg et al 2016. Regardless, our analysis does not suggest that combination therapy results in improved overall mortality in patients with IPF.

Our analysis showed that there is no reduction in change of FVC or DLCO in the sildenafil group. In the placebo-controlled Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF), sildenafil treatment was associated with benefits with regard to the DLCO and INSTAGE showed a positive signal towards reducing change in FVC. However, our analysis does not support this across the evidence.

Adverse side effects leading to treatment discontinuation rates were similar in each group, with a non-significant trend towards lower risk overall in the sildenafil group. These findings are consistent with previous analysis that investigated sildenafil in both IPF and Pulmonary hypertension patient populations.

**Strengths and limitations**

The strengths of this review include our comprehensive search strategy, screening and extraction of data in duplicate, rigorous assessment of risk of bias of trials, and the assessment of the certainty of the body of evidence using the GRADE approach.

Our findings are, however, limited by limited follow-up in some trials, which precludes inferences on long-term outcomes. Furthermore, we were unable to identify trials reporting on a number of patient-important outcomes including a 6-minute walk test.

**Conclusion**

Our review presents the most up-to-date and comprehensive summary of the evidence on sildenafil therapy for IPF patients. We found moderate certainty evidence that sildenafil probably reduces all cause mortality without increased risk of drug discontinuation due to adverse effects. However, larger RCTs are needed to confirm this finding. Further randomized controlled trials are required to clarify the role for combination therapy.

**Declarations**

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Data requests can be made to the corresponding author

Competing interests: None

Funding: None

Authors’ contributions: TP is the main author. He designed the study, the collection methods and supervised all aspects of the study. He performed all the analytics and wrote the first draft of the manuscript. JM developed the initial search strategy, helped collect data and supervised data collection. MK, SC, RH, MZ, WH, and JS collected the data, performed the risk of bias
assessment and helped write the manuscript. LB provided consultation in the search strategy and developed the final search. BG and CS helped write the manuscript and provide consultation when needed. DZ and AJ supervised the project and provided statistical consultation.

Acknowledgements: None

References


Tables

Table 1. Basic study characteristics across all outcomes.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Trial registration number</th>
<th>Setting</th>
<th>N</th>
<th>Age</th>
<th>Male (%)</th>
<th>Total</th>
<th>Baseline FVC (%) predicted</th>
<th>Baseline DLCO (%) predicted</th>
<th>Baseline 6MWT (m)</th>
<th>History of smoking %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zisman</td>
<td>USA</td>
<td>NCT00517933</td>
<td>Multicenter</td>
<td>180</td>
<td>68.97</td>
<td>83.3</td>
<td>56.83</td>
<td>26.27</td>
<td>257.43</td>
<td>76.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>USA, Australia, Belgium, Canada, France, Germany, India, Italy, Japan, Republic of Korea, Mexico, Spain, UK</td>
<td>NCT02802345</td>
<td>Multicenter</td>
<td>274</td>
<td>70.15</td>
<td>79.12</td>
<td>67.0</td>
<td>25.7</td>
<td>288.59</td>
<td>0.67</td>
<td>78.02</td>
</tr>
<tr>
<td>INSTAGE</td>
<td>Canada, Belgium, Czech Republic, Germany, Greece, Hungary, Italy, the Netherlands, Spain, and Turkey, Israel, Egypt and South Africa</td>
<td>NCT02951429</td>
<td>Multicenter</td>
<td>177</td>
<td>68.6</td>
<td>75.70%</td>
<td>60.99</td>
<td>25.6</td>
<td>346.78</td>
<td>86.20</td>
<td></td>
</tr>
<tr>
<td>Behr</td>
<td>USA</td>
<td>NCT00359736</td>
<td>Single centre</td>
<td>29</td>
<td>70.4</td>
<td>79.30%</td>
<td>62.46</td>
<td>42</td>
<td>346.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jackson</td>
<td>USA</td>
<td>NCT00359736</td>
<td>Single centre</td>
<td>29</td>
<td>70.4</td>
<td>79.30%</td>
<td>62.46</td>
<td>42</td>
<td>346.78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Summary of findings

**Sildenafil compared to control group for Idiopathic pulmonary fibrosis**

**Patient or population:** Idiopathic pulmonary fibrosis  
**Intervention:** Sildenafil  
**Comparison:** Control group with placebo, nintedanib or pirfenidone

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>% of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with Placebo</td>
<td>Risk with Sildenafil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>160 per 1,000</td>
<td><strong>107 per 1,000</strong> (67 to 164)</td>
<td>OR <strong>0.63</strong> (0.38 to 1.03)</td>
<td>661 (4 RCTs)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FVC</td>
<td>SMD 0.02 SD higher (0.14 lower to 0.18 higher)</td>
<td>-</td>
<td>602 (4 RCTs)</td>
</tr>
<tr>
<td></td>
<td>DLCO</td>
<td>SMD 0.01 SD lower (0.18 lower to 0.17 higher)</td>
<td>-</td>
<td>487 (4 RCTs)</td>
</tr>
<tr>
<td>Acute exacerbations and hospitalizations</td>
<td>178 per 1,000</td>
<td><strong>186 per 1,000</strong> (126 to 265)</td>
<td>OR <strong>1.06</strong> (0.67 to 1.67)</td>
<td>661 (4 RCTs)</td>
</tr>
<tr>
<td>Adverse effects leading to drug discontinuation</td>
<td>184 per 1,000</td>
<td><strong>144 per 1,000</strong> (99 to 204)</td>
<td>OR <strong>0.75</strong> (0.49 to 1.14)</td>
<td>661 (4 RCTs)</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio; SMD: Standardised mean difference

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**Explanations**

- a. The lower bound of the confidence interval implies a clinically important benefit and the upper bound implies a clinical futility or harm.
- b. The lower bound of the confidence interval implies a clinically important benefit and the upper bound implies significant harm.

**Figures**
Figure 1


Figure 2

Forest plot showing the odds ratio for all-cause mortality
Figure 3

Forest plots for change in FVC

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sildenafil</th>
<th>Control</th>
<th>Std. Mean Difference</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>Behr 2020</td>
<td>-10.4</td>
<td>11.0</td>
<td>80</td>
</tr>
<tr>
<td>Jackson 2010</td>
<td>-8.3</td>
<td>11.3</td>
<td>14</td>
</tr>
<tr>
<td>Kob 2018</td>
<td>-8.3</td>
<td>11.3</td>
<td>10</td>
</tr>
<tr>
<td>Ziment 2010</td>
<td>-8.3</td>
<td>11.3</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>-8.3</td>
<td>11.3</td>
<td>30</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.12, Ch² = 21.0, df = 3 (P = 0.03), P = 6%
Test for overall effect: Z = 2.03 (P = 0.04)

Figure 4

Forest plot showing change in DLCO

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sildenafil</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>M.H., Random, 95% CI</td>
</tr>
<tr>
<td>Behr 2020</td>
<td>58</td>
<td>86</td>
</tr>
<tr>
<td>Jackson 2010</td>
<td>11</td>
<td>10</td>
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<tr>
<td>Kob 2018</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Ziment 2010</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>86</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.20, Ch² = 21.0, df = 3 (P = 0.04), P = 6%
Test for overall effect: Z = 2.03 (P = 0.04)

Figure 5

Acute exacerbations and hospitalizations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sildenafil</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Behr 2020</td>
<td>22</td>
<td>29</td>
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<tr>
<td>Jackson 2010</td>
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<td>18</td>
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<tr>
<td>Kob 2018</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Ziment 2010</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>85</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Ch² = 0.15, df = 3 (P = 0.90), P = 6%
Test for overall effect: Z = 1.16 (P = 0.12)

Figure 6

Forest plot for adverse effects leading to drug discontinuation

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx
- Searchstrategy.docx