Drugs for Pulmonary Arterial Hypertension: A Systematic Review of the Clinical-Effectiveness of Combination Therapy
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Drugs for Pulmonary Arterial Hypertension: A Systematic Review of the Clinical-Effectiveness of Combination Therapy

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April 2009

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.
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These individuals kindly provided comments on this report.

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Industry: The following manufacturers were provided with an opportunity to comment on an earlier version of this report: Actelion Pharmaceuticals Canada Inc., GlaxoSmithKline Inc., Pfizer Canada Inc. All comments that were received were considered when preparing the final report.

This report is a review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) that are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH, and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

Conflict of interest: Dr. Paul Hernandez participates on the advisory boards for GlaxoSmithKline Inc., Pfizer Canada Inc., and Actelion Pharmaceuticals Canada Inc. He has conducted research trials for GlaxoSmithKline Inc., Actelion Pharmaceuticals Canada Inc., and Eli Lilly Canada Inc. He has also received speaker’s honoraria from Actelion Pharmaceuticals Canada Inc.
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## ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>FPAH</td>
<td>familial pulmonary arterial hypertension</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HRQL</td>
<td>health-related quality of life</td>
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<td>IPAH</td>
<td>idiopathic pulmonary arterial hypertension</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<td>PAH</td>
<td>pulmonary arterial hypertension</td>
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<td>PH</td>
<td>pulmonary hypertension</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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EXECUTIVE SUMMARY

Context and Policy Issues
Pulmonary arterial hypertension (PAH) is a life-threatening, progressive condition with a poor prognosis when left unmanaged. Treatment options in PAH have increased over the past two decades, with regulatory approval of newer drugs and greater experience with combinations of existing drugs. Prostacyclin derivatives (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan, sitaxsentan, and ambrisentan), and phosphodiesterase-5 inhibitors (sildenafil) are all used in the management of the disease. This report will review the evidence of clinical-effectiveness and guidelines for the use of these agents in PAH, which could potentially help in decision making at the level of the health care system.

Research Questions
1. What is the clinical-effectiveness of combination therapy of drugs for idiopathic pulmonary arterial hypertension (IPAH) compared with monotherapy?
2. What are the guidelines for the use of drugs for IPAH?
3. What is the potential for expanded use of drugs for IPAH?

Methods
Published literature was obtained by cross-searching BIOSIS Previews, EMBASE, and MEDLINE on the OVID search system between January 2003 and December 2008. Parallel searches were performed on PubMed and the Cochrane Library (Issue 4, 2008) databases. Websites of regulatory agencies and health technology assessment and related agencies were also searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. These searches were supplemented by hand-searching the bibliographies of selected papers. Two individuals screened and selected articles for inclusion in the report.

Summary of Findings
There were four randomized controlled trials (RCTs) and two guidelines identified. No relevant meta-analyses, systematic reviews, or health technology assessment reports were identified.

One RCT assessed the effect of adding oral sildenafil to long-term intravenous epoprostenol in 267 patients with PAH. After 16 weeks, the adjusted mean change in the six-minute walk distance was 29.8 m for the sildenafil group and 1.0 m for the placebo group, a treatment difference of 28.8 m (95% confidence interval [CI] 13.9 to 43.8 m; P < 0.001) after adjusting for baseline walking distance and etiology using analysis of variance models. In patients with IPAH, the difference between groups was 33.9 m in favour of the sildenafil group (P value and 95% CI not reported). Sildenafil also had a beneficial effect on hemodynamic measurements and health-related quality of life.

Another RCT assessed the effect of adding inhaled iloprost to stable monotherapy with bosentan in 67 patients with PAH. After 12 weeks, the mean increase in post-inhalation six-minute walk distance from baseline was 30 m in the iloprost group and 4 m in the placebo group, a mean difference of 26 m (P = 0.051). The mean increase in pre-inhalation six-minute walk distance from baseline was 29 m in the iloprost group and 11 m in the placebo group, a mean difference of 19 m (P = 0.14). In 34% of iloprost-treated patients, the New York Heart Association class improved, compared with 6% of patients in the placebo group (P = 0.002). Time to clinical worsening and post-inhalation hemodynamics also favoured the iloprost group.

A third RCT assessed the efficacy and safety of combination bosentan and epoprostenol in 33 patients with severe PAH relative to epoprostenol alone. All patients were started on epoprostenol and then randomized to bosentan or placebo. After 12 weeks, differences between
groups in hemodynamics were not statistically significant, nor were differences in six-minute walk distance, dyspnea-fatigue rating, or change in New York Heart Association functional class. The authors concluded that the combination of bosentan and epoprostenol may be a therapeutic option for the management of patients with severe PAH.

One additional RCT evaluating bosentan in mildly symptomatic patients also assessed the effect of combination therapy with bosentan and sildenafil. However, the results of the combination therapy were better described in abstract form. From this study, it was concluded that in mildly symptomatic PAH patients treated with sildenafil, add-on bosentan therapy improved hemodynamics and delayed clinical worsening, consistent with the effects seen in patients not receiving concomitant sildenafil.

The guidelines identified included recommendations about combination therapy in PAH and tended to be cautious with respect to combination therapy for PAH until more evidence is available.

Conclusions and Implications for Decision or Policy Making

Treatment guidelines for IPAH reserved combination therapy for more severe cases that fail to respond to monotherapy. As well, it is recommended that combination therapy take place under the supervision of experienced PAH-specialty practitioners or within the context of clinical trials. From the limited number of published RCTs, it appears that there may be some additional benefit from combinations of agents in PAH, but these studies have been relatively short in duration, and two of the three studies included only small numbers of patients. There are a number of RCTs of various combinations of agents underway that may help to clarify the clinical benefit of this treatment approach. Until these studies are completed, there may be insufficient evidence to make broad policy decisions about combination therapy in PAH. Such decisions may be best considered on a case-by-case basis. When additional evidence from the clinical trials currently underway becomes available, there could be some potential for expanded use of combination therapy if results are positive.
1 CONTEXT AND POLICY ISSUES

Pulmonary hypertension (PH) is a life-threatening, progressive condition with a poor prognosis when left unmanaged. It is characterized by increased pulmonary arterial pressure and secondary right ventricular failure. There are five different classifications of PH, one of which is pulmonary arterial hypertension (PAH), where the disease is primarily localized to the small pulmonary arteries. It is defined as a mean pulmonary artery pressure $\geq 25$ mm Hg with a pulmonary capillary wedge pressure $\leq 15$ mm Hg measured by cardiac catheterization at rest. PAH can occur with a variety of underlying medical conditions such as collagen vascular disease or HIV or drug exposures (e.g., anorexiants such as fenfluramine and dexfenfluramine), but it can also occur in the absence of such comorbid medical conditions (known as “idiopathic PAH” or IPAH). There are four functional New York Heart Association (NYHA) or World Health Organization classes of PAH based on the severity of symptoms (see Appendix 1: Functional Classifications for Pulmonary Hypertension) ranging from class I to class IV, with class IV being the most severe. The cause of PAH is not completely understood, but it is thought to include both genetic and environmental factors.

Treatment options in PAH have increased over the past two decades, with regulatory approval of newer drugs and greater experience with combinations of existing drugs. Calcium channel blockers (long-acting nifedipine or diltiazem, or amlodipine), prostacyclin derivatives (epoprostenol, treprostinil, iloprost), endothelin receptor antagonists (bosentan, sitaxsentan, and ambrisentan), and phosphodiesterase-5 inhibitors (sildenafil) are all used in the management of the disease. In IPAH, calcium channel blockers cause vasodilation, which can lower pulmonary arterial pressure, but are effective in less than 10% of patients. Thus, other treatment options are often required.

Individuals with PAH may under-produce prostacyclin, an eicosanoid which promotes vasodilation and inhibits vascular proliferation and platelet aggregation. In PAH, prostacyclin derivatives reduce right and left ventricular afterload and increase cardiac output and stroke volume. Epoprostenol is administered by continuous intravenous infusion through a central venous catheter using an ambulatory infusion pump. The initial dose is 2 ng/kg/minute, which can be increased until dose-limiting pharmacological effects result or a tolerance limit to the drug is established. Treprostinil is administered by continuous subcutaneous infusion through a self-inserted subcutaneous catheter using an infusion pump at an initial rate of 1.25 ng/kg/minute. The infusion rate can be increased up to 2.5 ng/kg/minute. It can also be administered intravenously. Iloprost (not currently available in Canada but available in the United States) is administered by inhalation six to nine times daily.

Individuals with PAH have increased circulating levels of endothelin-1, a potent vasoconstrictor. Endothelin receptor antagonists block the action of endothelin-1, which results in decreased pulmonary and systemic vascular resistance and increased cardiac output. Bosentan is administered orally at a dosage of 62.5 mg twice daily for four weeks and then increased to the recommended maintenance dosage of 125 mg twice daily, whereas sitaxsentan is administered orally at a dosage of 100 mg daily. Ambrisentan is initiated at 5 mg orally once daily, which may be increased to 10 mg once daily. Sildenafil is a phosphodiesterase-5 inhibitor approved for use in PAH in Canada.
and is administered orally at a dosage of 20 mg three times daily.11

The availability of newer treatment options for PAH impacts how the disease can be optimally managed.3 If a combination of agents is considered, it is important that rational combinations of therapies are used so that the clinical benefit to the patient can be maximized. This report will review the evidence of clinical-effectiveness and guidelines for the use of combination of agents in PAH, which could potentially help in decision making at the level of the health care system. As well, the potential for expanded use of these medications will also be considered, because this issue is important to consider in the context of a publicly funded health care system.

2 RESEARCH QUESTIONS

1. What is the clinical-effectiveness of combination therapy of drugs for idiopathic pulmonary arterial hypertension (IPAH) compared with monotherapy?

2. What are the guidelines for the use of drugs for IPAH?

3. What is the potential for expanded use of drugs for IPAH?

3 METHODS

Published literature was obtained by cross-searching BIOSIS Previews, EMBASE, and MEDLINE on the OVID search system between January 2003 and December 2008. Regular alerts were established on BIOSIS, EMBASE, and MEDLINE, and information retrieved through alerts is current to January 19, 2009. Parallel searches were performed on PubMed and the Cochrane Library (Issue 4, 2008) databases. Filters were applied to limit the retrieval to systematic reviews, health technology assessments, meta-analyses, and randomized controlled trials for Question 1 and to guidelines for Question 2. Information pertaining to Question 3 was gathered through input of the manufacturers of the individual drugs.

Websites of regulatory agencies and health technology assessment and related agencies were also searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. The Google search engine was used to search for a variety of information on the Internet. These searches were supplemented by hand-searching the bibliographies of selected papers.

Two individuals screened and selected articles for inclusion in the report. Both individuals carried out an initial broad screening of abstracts from the literature search, and the results were compared. Full text articles were obtained for all citations that were selected by either individual. On receipt of the full text articles, agreement was reached as to which articles should be included in the report.

The criteria for article inclusion were as follows:

Study Design: Systematic reviews, health technology assessments, meta-analyses, randomized controlled trials, or evidence-based guidelines.

Population: Patients of any age with IPAH (formerly known as “primary pulmonary hypertension”).

Intervention: Any combination of prostacyclin derivatives (epoprostenol, treprostinil, iloprost); endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan); and phosphodiesterase-5 inhibitors (sildenafil). Patients could also be using a calcium channel blocker.

Comparator: Monotherapy with a prostacyclin derivative (epoprostenol, treprostinil, iloprost); endothelin receptor antagonist (bosentan, sitaxsentan, ambrisentan); or phosphodiesterase-5 inhibitor (sildenafil). Patients could also be using a calcium channel blocker.
Outcome: Any clinical outcome or evidence-based guideline.

For this report an HTA is defined as a report that examines clinical- and cost-effectiveness, contains a budget impact analysis, and addresses ethical and psychosocial issues. The meta-analyses would also have to be based on a systematic review.

HTIS reports are organized so that the higher-quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and evidence-based guidelines.

4 SUMMARY OF FINDINGS

There were four randomized controlled trials (RCTs)\textsuperscript{12-15} and two guidelines identified.\textsuperscript{3,16} For one study,\textsuperscript{14} the results of the combination therapy were better described in abstract form.\textsuperscript{17} No relevant meta-analyses, systematic reviews, or health technology assessment reports were identified.

4.1 Randomized Controlled Trials

In 2008, Simonneau et al.\textsuperscript{15} published a 16-week double-blind, placebo-controlled, parallel group study to assess the effect of adding oral sildenafil to long-term intravenous epoprostenol in 267 patients with PAH (IPAH or PAH associated with anorexiant use, connective tissue disease, or corrected congenital heart disease). Patients were recruited in 41 academic centres or hospitals in 11 countries, with four centres located in Canada. Patients aged 18 years and older (16 years in the US) who had been on intravenous epoprostenol for three months or longer, with a stable dose for at least four weeks, were included. Patients were excluded if they had six-minute walk distances less than 100 m or greater than 450 m; another condition affected their six-minute walk distance; they were being treated with bosentan, nitrates, or nitric oxide donor drugs; they had retinopathy or chronic obstructive pulmonary disease; they had severe impairment of hepatic function; or they were pregnant or lactating. Patients were randomized to placebo (n = 133) or sildenafil 20 mg three times daily (n = 134), which was increased to 80 mg three times daily, as tolerated. The primary study end point was the change in exercise capacity measured by six-minute walk distance. Secondary end points included hemodynamic measurements, time to clinical worsening, Borg dyspnea score, and health-related quality of life (HRQL) measured using the SF-36. The significance of changes from baseline were assessed using analysis of variance models, adjusted for baseline walking distance and etiology.\textsuperscript{18}

Overall, 72% of patients had Functional Class III or IV PAH, and 79% had IPAH. After 16 weeks, the adjusted mean change in the six-minute walk distance was 29.8 m for the sildenafil group and 1.0 m for the placebo group, an adjusted treatment difference of 28.8 m (95% CI 13.9 to 43.8 m; P < 0.001). In patients with IPAH, the difference between groups was 33.9 m in favour of the sildenafil group (P value and 95% CI not reported). The adjusted mean change in pulmonary arterial pressure was −2.8 mm Hg in the sildenafil group and 1.1 mm Hg in the placebo group, a difference of −3.8 mm Hg (95% CI −5.6 to −2.1 mm Hg). There was also a significant relative increase in cardiac output of 0.9 L/minute (95% CI 0.5 to 1.2 L/minute) for patients in the sildenafil group. Sildenafil also had statistically significant beneficial effects on other hemodynamic measurements (systemic vascular resistance, pulmonary vascular resistance, and heart rate). Time to first clinical worsening event was significantly longer in the sildenafil group (P = 0.002). Differences in Borg dyspnea scores were not significant. After 16 weeks, improvements in physical functioning, general health, vitality, social functioning, and mental health on the SF-36 favoured sildenafil over placebo. The authors concluded that sildenafil may be used in combination with epoprostenol to improve exercise capacity in PAH, particularly in stable patients with PAH who remain symptomatic despite long-term
intravenous epoprostenol treatment. Limitations to this study included some missing end point data for the six-minute walk test, the majority of which was in the placebo group. As well, dosage of sildenafil used in this study was higher than the approved dosage of 20 mg three times daily in Canada. However, this study was started prior to the completion of a pivotal trial comparing the 20 mg, 40 mg, and 80 mg doses, which led to the approval of the 20 mg dose with regulatory agencies. This study was relatively short in duration, and as such, long-term safety and efficacy data for the combination therapy could not be determined. The generalizability of these findings is somewhat limited by the discrepancy between the dose that was used and the approved dose in Canada. As well, the authors stated that it is more common to start treatment with first-line oral therapy and then add intravenous epoprostenol therapy as needed. It is not clear if the results seen in this study could be generalized to the more common treatment scenario.

In 2006, McLaughlin et al.\textsuperscript{12} published a randomized, multi-centre, double-blind, placebo-controlled trial of 5 µg of inhaled iloprost added to stable monotherapy with bosentan (125 mg twice daily) for 12 weeks in 67 patients with PAH. Patients 10 to 80 years old, with symptomatic PAH and who were treated with bosentan for four months or longer were included in the study and were randomized to receive iloprost (n = 34) or placebo (n = 33). As well, patients had to have six-minute walk distances of 100 m to 425 m, resting mean pulmonary artery pressures greater than 25 mm Hg, pulmonary capillary wedge pressures less than 15 mm Hg, and pulmonary vascular resistances of 240 dyn s/cm\textsuperscript{5} or greater. Patients were excluded if they had thromboembolic disease, unmanaged obstructive sleep apnea, portal hypertension, chronic liver disease or renal insufficiency, left-sided or unrepaired congenital heart disease, or substantial obstructive or restrictive lung disease. Patients could be concurrently treated with anticoagulants, vasodilators, diuretics, cardiac glycosides, or supplemental oxygen, but not phosphodiesterase-5 inhibitors or other prostanoids.

All patients except one in the placebo group had NYHA class III or IV PAH, and 55% had IPAH. After 12 weeks, the mean increase in post-inhalation six-minute walk distance from baseline was 30 m in the iloprost group and 4 m in the placebo group, a mean difference of 26 m (P = 0.051). In the IPAH group, the mean difference in increase in six-minute walk distance from baseline was 25 m (P value not reported). The mean increase in pre-inhalation six-minute walk distance from baseline was 29 m in the iloprost group and 11 m in the placebo group, a mean difference of 19 m (P = 0.14). Differences in Borg dyspnea scores were not significant. NYHA class improved in 34% of patients in the iloprost group, compared with 6% of patients in the placebo group (P = 0.002). In patients with IPAH, 37.5% had improvements in NYHA class. Time to clinical worsening was significantly longer in the iloprost group than in the placebo group (P = 0.02). In terms of hemodynamics, there was significant improvement in post-inhalation mean pulmonary artery pressure (P < 0.001) and pulmonary vascular resistance (P = 0.007) in the iloprost group relative to placebo, but not for the pre-inhalation measurements. The authors concluded that adding iloprost to oral bosentan was a safe and effective treatment approach for PAH. One limitation of this study is that there was no description or protocol of how the dose was determined, titrated, or individualized for each patient. The authors reported only an average of 5.6 inhalations per day. The small sample size is another limitation to this study, as is the relatively short duration of follow-up and failure to assess important outcomes such as HRQL and mortality. A limitation that the authors pointed out in their discussion was that iloprost requires administration approximately six times per day, which may be inconvenient for patients. In terms of generalizability, it is not clear if the results would be applicable to individuals with less severe PAH. As well, iloprost is not currently available in Canada. Finally, not all results were reported for the IPAH group alone; thus, it is not clear if similar benefit would be observed for all of the outcomes in IPAH patients.
In 2004, Humbert et al. published the Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH (BREATHE-2) study to assess the efficacy and safety combination bosentan and epoprostenol in 33 patients with severe PAH. This 16-week study was conducted in four centres in the US and three centres in Europe. All patients started on epoprostenol treatment (2 ng/kg/minute) and were then randomized to receive bosentan at an initial dosage of 62.5 mg twice daily for four weeks, then 125 mg twice daily thereafter (n = 22) or placebo (n = 11). The epoprostenol dose was increased to 4 ng/kg/minute in all patients another two days later, and was increased at two week intervals to reach a target dose of 12 to 16 ng/kg/minute between weeks 14 and 16. The primary outcome measure was the change from baseline to week 16 in total pulmonary resistance. Secondary outcome measures included the change in cardiac index, pulmonary vascular resistance, mean pulmonary artery pressure, mean right atrial pressure, six-minute walk distance, the dyspnea-fatigue rating, and modified NYHA functional class of PAH.

All patients had NYHA Class III or IV PAH, and 27 of the 33 patients had primary PAH (now referred to as “IPAH”). The decrease in total pulmonary resistance was $-36.3\% \pm 4.3\%$ (mean ± standard error of the mean) in the bosentan/epoprostenol group, and $-22.6\% \pm 6.2\%$ in the placebo/epoprostenol group ($P = 0.08$). Cardiac index, pulmonary vascular resistance, mean pulmonary atrial pressure, and mean right atrial pressure improved from baseline in both treatment groups, with larger improvements being seen in the bosentan/epoprostenol group; however, differences between groups were not statistically significant. The median increase in the six-minute walk distance was 68 m in the bosentan/epoprostenol group and 74 m in the placebo/epoprostenol group. The difference between groups was not statistically significant. The median improvement in dyspnea-fatigue rating was 1.0 unit in the placebo/epoprostenol group, and did not change in the bosentan/epoprostenol group. Functional class of PAH improved for 59% of patients in the bosentan/epoprostenol group and for 45% of patients in the placebo/epoprostenol group. The difference between groups was not statistically significant for six-minute walk distance, dyspnea-fatigue rating, or change in NYHA functional class. The authors concluded that the combination of bosentan and epoprostenol may be a therapeutic option for the management of patients with severe PAH. Limitations of this study included the small sample size, unequal distribution of females, scleroderma and clinical signs of heart failure between groups, short duration of follow-up, lack of assessment of mortality and HRQL, and lack of information on how the study sample was selected. Generalizability of the study may also be limited by the small sample size. As well, it is not clear if similar results would be expected in patients with less severe disease or if the sample was restricted to only patients with IPAH.

One additional RCT evaluating bosentan in mildly symptomatic patients also assessed the effect of combination therapy with bosentan and sildenafil; however, the results for combination therapy were better described in abstract form http://meeting.chestjournal.org/cgi/reprint/132/4/487. In this six-month study, the impact of combination therapy with bosentan and sildenafil was assessed in a subgroup of patients as a secondary objective. The analysis presented in the abstract assessed the effect of bosentan versus placebo and the effect of bosentan combined with sildenafil versus placebo. There was no direct comparison between the bosentan and bosentan combined with sildenafil groups. From these analyses, it was concluded that in mildly symptomatic PAH patients treated with sildenafil, add-on bosentan therapy improved hemodynamics and delayed clinical worsening, consistent with the effects seen in patients not receiving concomitant sildenafil. The sample size of this study was small, which may impact the generalizability of the results. As well, patients with IPAH and those with PAH secondary to HIV, congenital heart disease, and connective tissue disease were included. It is not clear if the same results would be expected for only those with IPAH.
4.2 Guidelines

In 2008, the National Pulmonary Hypertension Centres of the UK and Ireland published a consensus statement on the management of PAH in clinical practice in the UK and Ireland. The purpose of the statement was to update their 2001 recommendations and inform those who deliver health care to individuals with PAH. The processes used to arrive at this consensus statement were not detailed in the publication, but the following rationale was given for not grading the level of evidence or providing strengths of recommendation:

We have not sought to replicate international guidelines and thus there is no grading of evidence or recommendations. Instead this consensus statement is intended to complement these PAH guidelines with specific emphasis on UK and Irish practice, as well as to extend them to other forms of PH. (pii2)16

The recommended treatment algorithm for IPAH can be found in Appendix 2.

The following drug therapy recommendations were made:

41. Patients with IPAH, FPAH and anorexigen APAH and a positive vasoreactivity response should be treated with high doses of calcium channel blockers. Since only half will respond chronically, it is important to ascertain normalization or near-normalization of PAH at follow-up. (pii18)16

42. If patients taking high dose calcium channel blockers demonstrate no clinical improvement after 1 month or are unable to achieve functional class I or II with associated improvement in haemodynamics over 3 months, then they should be treated as non-responders. (pii18)16

43. Individuals who demonstrate an inadequate response to monotherapy should be considered for a combination of two or more disease-targeted therapies. (pii27)16

44. Where combination therapy is to be used, patients should be entered into a clinical trial where possible. (pii27)16

45. In the absence of a clinical trial, there is sufficient expert consensus to proceed with combination therapy while the patient’s response to treatment is carefully monitored with consistent measures linked to national audit. (pii27)16

46. Patients with IPAH, FPAH or anorexigen-induced PAH should be managed according to the algorithm in fig 4. (pii28)16

In 2007, the American College of Chest Physicians updated their 2004 guidelines on medical therapy for PAH to include newer therapies for the condition. A consensus panel was convened for the purpose of updating the previous evidence-based guidelines. A systematic search of the literature was used, and studies of prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors were included. Studies conducted in patients with known or suspected IPAH or PAH occurring in association with underlying collagen vascular disease, and congenital heart disease were included, whereas studies of pulmonary hypertension associated with chronic obstructive pulmonary disease or other parenchymal lung disease, high altitude PH, or cardiac disease (except congenital heart disease) were excluded. Recommendations were graded as outlined in Appendix 3 and were assigned strengths of recommendation based on the quality of the evidence and the net benefit of the therapy to the patient. Details of both can be found in the appendix. The treatment algorithm from the guideline is based on functional class of the disease and can be found in Appendix 4. The following drug therapy recommendations were unchanged from the 2004 guidelines:

Patients with IPAH, in the absence of right-heart failure, demonstrating a favorable acute response to vasodilator (defined as a fall in PAPm of at least 10 mm Hg to ≤40 mm Hg, with an increased or unchanged cardiac output), should be considered candidates for a trial therapy with an oral calcium-channel antagonist. (Level of evidence: low; benefit: substantial; grade of recommendation: B)
Patients with PAH associated with underlying processes such as scleroderma or congenital heart disease, in the absence of right-heart failure, demonstrating a favorable acute response to vasodilator (defined as a fall in pulmonary artery pressure of at least 10 mm Hg to $\leq 40$ mm Hg, with an increased or unchanged cardiac output), should be considered candidates for a trial of therapy with an oral calcium channel antagonist. (Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/B)

In patients with PAH, CCBs should not be used empirically to treat PH in the absence of demonstrated acute vasoreactivity. (Level of evidence: expert opinion; benefit: substantial; grade of recommendation: E/A)

Patients with IPAH should receive anticoagulation with warfarin. (Level of evidence: fair; benefit: intermediate; grade of recommendation: B) (p1919)

The following drug therapy recommendations were made in the updated 2007 guidelines. It should be noted that at the time of publication, not all drugs included in the present report had regulatory approval in the United States. For example, the endothelin receptor antagonists sitaxsentan and ambrisentan were not yet approved.

**Functional class II**

PAH patients in functional class II who are not candidates for, or who have failed, CCB therapy, may benefit from treatment with:

Sildenafil (Level of evidence: good; benefit: substantial; grade of recommendation: A)

Subcutaneous treprostinil (Level of evidence: low; benefit: small/weak; grade of recommendation: C. Although treprostinil is FDA approved for use in patients in functional class II, it would seldom be recommended in such patients due to the complexity of administration, side effects, and cost.)

IV treprostinil (Level of evidence: low; benefit: small/weak; grade of recommendation: C. Although treprostinil is FDA approved for use in patients in functional class II, it would seldom be recommended in such patients due to the complexity of administration, side effects, and cost.)

**Functional class III**

PAH patients in functional class III who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with:

Endothelin receptor antagonists (bosentan), or sildenafil, in no order of preference (Level of evidence: good; benefit: substantial; grade of recommendation: A)

IV epoprostenol (Level of evidence: good; benefit: substantial; grade of recommendation: A)

Inhaled iloprost (Level of evidence: good; benefit: intermediate; grade of recommendation: A)

Subcutaneous treprostinil (Level of evidence: fair; benefit: intermediate; grade of recommendation: B)

IV treprostinil (Level of evidence: low; benefit: intermediate; grade of recommendation: C) (p1926)

With regards to combination therapy, the following statement was made:

It is anticipated that we will soon have evidence regarding the use of add-on and combination therapy. Until additional evidence becomes available, add-on or combination therapy might be considered in the context of enrollment into clinical trials. (p1927)

**Functional class IV**

PAH patients in functional class IV who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with IV epoprostenol (treatment of choice). (Level of evidence: good; benefit: substantial; grade of recommendation: A)

Other treatments available for the treatment of functional class IV PAH patients include, in no hierarchical order:

Endothelin receptor antagonists (bosentan) (Level of evidence: fair; benefit: intermediate; grade of recommendation: B)
Inhaled iloprost (Level of evidence: fair; benefit: intermediate; grade of recommendation: B)

Subcutaneous treprostinil (Level of evidence: fair; benefit: intermediate; grade of recommendation: B)

Sildenafil (Level of evidence: low; benefit: intermediate; grade of recommendation: C)

IV treprostinil (Level of evidence; low; benefit: intermediate; grade of recommendation: C) (p1926)

4.3 Expanded Use

There is some potential for expanded use of agents used in the management of PAH. Currently, a new formulation of bosentan for pediatric use is being developed and studied, which could potentially expand its use to the pediatric population with PAH. Pediatric studies with ambrisentan are currently under discussion with the FDA and the European Medicines Agency (Personal communication, Dr. Nazli Topors, GlaxoSmithKline Inc., February 2009).

As well, there are several ongoing studies of combination therapy between bosentan and sildenafil, which, assuming positive results, could lead to expanded use of this specific combination. There are also ongoing trials of sitaxsentan combined with sildenafil and ambrisentan combined with sildenafil in PAH. As well, one additional study of ambrisentan combined with sildenafil in PAH will begin recruiting patients in 2009. (Personal communication, Dr. Nazli Topors, GlaxoSmithKline Inc, February 2009). If these trials have positive results, use of these combinations may increase.

Several of the agents (epoprostenol, treprostinil, and bosentan) are approved for use in Canada in patients with functional class III or IV PAH who have not responded adequately to conventional therapy. It is possible that these agents could be used in patients with less severe disease or prior to assessing the response to conventional therapy. Further, there are other agents that are still investigational in Canada such as tadalafil (a phosphodiesterase-5 inhibitor) and iloprost (a prostacyclin derivative). Availability of these agents could increase the use of combination therapy.

Actelion Pharmaceuticals is also investigating bosentan’s potential in other endothelin-related diseases such as idiopathic pulmonary fibrosis.

4.4 Limitations

Four RCTs were identified that assessed combination therapy, but no meta-analyses or health technology assessment reports were identified. Generally speaking, the identified RCTs tended to be short in duration, which impeded the ability to explore important long-term outcomes such as HRQL and mortality. It should be noted, however, that PAH is a relatively rare disease, which may impede the ability to recruit a sufficient number of patients to evaluate such outcomes over the longer term. As well, although studies were identified that assessed combination therapy with 1) a prostacyclin derivative and a phosphodiesterase-5 inhibitor, 2) a prostacyclin derivative and an endothelin receptor antagonist, and 3) a phosphodiesterase-5 inhibitor and an endothelin receptor antagonist, it is not clear if the results of such studies would be generalizable to other drugs in the same class or whether they would be specific to the particular drugs studied. In other words, it is not clear if class effects could be assumed. In addition, it is not clear whether the observed differences in outcomes between combination and monotherapy would be considered clinically important. For example, a gain of 30 m on the six-minute walk distance may not be relevant to patients. Finally, most studies included only patients with more severe disease (Class III or IV PAH). Thus, it is not known if similar results would be expected in less severe disease. That said, the identified guidelines recommend combination therapy only in patients with Class III or IV PAH.
5 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Treatment guidelines for IPAH reserved combination therapy for more severe cases that fail to respond to monotherapy. As well, it is recommended that combination therapy take place under the supervision of experienced PAH-specialty practitioners or within the context of clinical trials. The guidelines tend to be cautious with respect to combination therapy for IPAH until more evidence is available. From the limited number of published RCTs, it appears that there may be some additional benefit from certain combinations of agents in PAH, but these studies have been relatively short in duration and two included only small numbers of patients and included patients with PAH of different etiologies (i.e., some patients had IPAH, whereas others had PAH associated with other conditions). There are a number of RCTs of various combinations of agents underway that may help to clarify the clinical benefit of this treatment approach. Until these studies are completed, evidence to make broad policy decisions about combination therapy in PAH may be insufficient. Decisions to fund combination therapy may be best considered on a case-by-case basis until further evidence is available. When additional evidence from the clinical trials currently underway becomes available, there could be some potential for expanded use of combination therapy if results are positive.

6 REFERENCES


Institutes of Health; 2008. NCT00796510. Available: [link]


APPENDIX 1: Functional Classifications for Pulmonary Hypertension

New York Heart Association World Health Organization Functional Classification of Pulmonary Hypertension

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Patients with pulmonary hypertension resulting in pronounced limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity. (p2255)
APPENDIX 2: Treatment Algorithms from the Consensus Statement on the Management of Pulmonary Hypertension in Clinical Practice in the UK and Ireland (pii26)\(^{16}\)

![Treatment Algorithm Diagram]

Figure 4. Algorithm for the management of idiopathic, familial and anorexigen-induced pulmonary arterial hypertension. The prefixes 1st and 2nd indicate preferred and alternative drugs based on the quality and the weight of evidence assessed by the Consensus Meeting. APAH, associated pulmonary arterial hypertension; FPAH, familial pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; WHO, World Health Organization.

APPENDIX 3: Level of Evidence, Grade of Recommendation and Net Benefit from the American College of Chest Physician’s Medical Therapy for Pulmonary Arterial Hypertension Clinical Practice Guidelines (p1921)³

Good Evidence is based on good randomized controlled trials or meta-analyses.
Fair Evidence is based on other controlled trials or RCTs with minor flaws.
Low Evidence is based on nonrandomized, case-control, or other observational studies.
Expert opinion Evidence is based the consensus of the carefully selected panel of experts in the topic field.

Net benefit
Substantial
Intermediate
Small/weak
None
Conflicting
Negative

Strength of recommendation
A Strong recommendation
B Moderate recommendation
C Weak recommendation
D Negative recommendation
I No recommendation possible (inconclusive)
E/A Strong recommendation based on expert opinion only
E/B Moderate recommendation based on expert opinion only
E/C Weak recommendation based on expert opinion only
E/D Negative recommendation based on expert opinion only(p1921)³
APPENDIX 4: Treatment Algorithm from the American College of Chest Physician’s Medical Therapy for Pulmonary Arterial Hypertension Clinical Practice Guidelines (p1925)³

![Diagram of treatment algorithm]

* Not in order of preference.

Figure 1. Treatment algorithm for PAH. The recommended therapies presented in this algorithm have been evaluated mainly in those with IPAH, or PAH associated with connective tissue disease or anorexinplus. Extrapolation to other forms of PAH should be made with caution. Countriespecific regulatory agency approval status and functional class indications for PAH medications vary. (1) Anticoagulation should be considered for patients with IPAH, and patients with an individual other than the administration of an IV prostacyclin, in the absence of contraindications. Dicoumarins and oxygen should be added as needed. (2) A positive acute vasodilator response is defined as a fall in PAHr of ≥ 10 mm Hg to ≤ 40 mm Hg with an unchanged or increased cardiac output when challenged with labeled nitric oxide IV, epoprostenol, or IV adenosine. (3) Consideration should be given to using a PAH-specific medication such as a phosphodiesterase 5 inhibitor, endothelin receptor antagonist, or prostacyclin as first-line treatment instead of a CCB in patients with PAH that is not IPAH or PAH associated with anorexin plus, or in those in an advanced functional class (C) who have undergone a long-term response to a CCB monotherapy in the former and poor prognostic in the latter. (4) Sustained response to CCB therapy is defined as being in functional class ≤ I with normal or near-normal hemodynamics after several months of treatment. (5) The risks and benefits of treatment in early PAH should be considered. (6) First-line therapy for functional class III includes bosentan, sildenafil, epoprostenol, labeled nitric oxide, and prostanoid (see text for details). (7) Most experts recommend IV epoprostenol as first-line treatment for unstable patients in functional class IV. (8) The cost-effectiveness of combination treatment regimens are underway. Designators [A], [B], [C], [D], and [E] are defined in Table 2. *Not in order of preference. SC = subcutaneous.