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The burden of comorbidities in pulmonary arterial hypertension

Irene M. Lang[1]* and Massimiliano Palazzini[2]

[1]*Department of Internal Medicine II, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria; and* [2]*Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via Zamboni, 33 - 40126 Bologna, Italy*

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Patients with comorbidities are often excluded from clinical trials, limiting the evidence base for pulmonary arterial hypertension (PAH)-specific therapies. This review aims to discuss the effect of comorbidities on the diagnosis and management of PAH. The comorbidities discussed in this review (systemic hypertension, obesity, sleep apnoea, clinical depression, obstructive airway disease, thyroid disease, diabetes, and ischaemic cardiovascular event) were chosen based on their prevalence in patients with idiopathic PAH in the REVEAL registry (Registry to EValuate Early and Long-term PAH disease management). Comorbidities can mask the symptoms of PAH, leading to delays in diagnosis and also difficulty evaluating disease progression and treatment effects. Due to the multifactorial pathophysiology of pulmonary hypertension (PH), the presence of comorbidities can lead to difficulties in distinguishing between Group 1 PH (PAH) and the other group classifications of PH. Many comorbidities contribute to the progression of PAH through increased pulmonary artery pressures and cardiac output, therefore treatment of the comorbidity may also reduce the severity of PAH. Similarly, the development of one comorbidity can be a risk factor for the development of other comorbidities. The management of comorbidities requires consideration of drug interactions, polypharmacy, adherence and evidence-based strategies. A multidisciplinary team should be involved in the management of patients with PAH and comorbidities, with appropriate referral to supportive services when necessary. The treatment goals and expectations of patients must be managed in the context of comorbidities.

Introduction

The definition of comorbidity was first proposed by Feinstein in 1970, as the presence of 'any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study'.[1] The development of comorbidities can be driven by genetics, lifestyle and societal factors, and/or the interaction of both.[2] Comorbidities in pulmonary arterial hypertension (PAH) may be present at the time of PAH diagnosis or may develop during the course of treatment for PAH. The concurrence of PAH and comorbidities increases the complexity of disease management for patients, who may require multiple pharmacological interventions to treat both PAH and the comorbidity.

At the current population level, approximately one in four adults lives with two or more chronic conditions.[3] In PAH, approximately three quarters of patients have at least one comorbidity,[4] with patients aged 65 years and over having a greater number of comorbidities.[4,5] Current research suggests that the presence of comorbid conditions in patients with PAH negatively affects outcomes.[6,7] To optimize patient care, it is important that the effects of comorbidities on PAH are well understood. The 2015 European

*Corresponding author. Tel: +43 14040046140, Email: irene.lang@meduniwien.ac.at

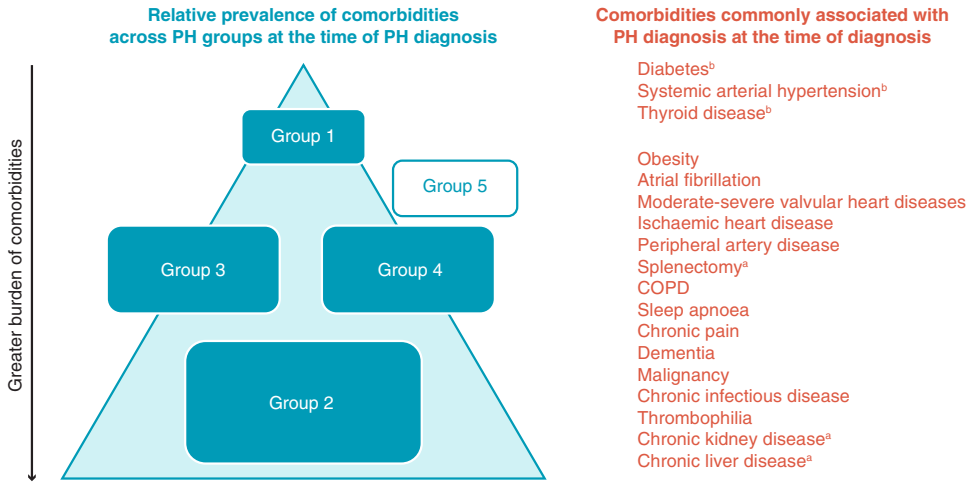

Figure 1 The burden of comorbidities observed across pulmonary hypertension groups at the time of diagnosis in authors' experience.[18-21] [a]Comorbidities that are typically associated with pulmonary hypertension Group 5, but may affect all groups. [b]Comorbidities that are typically associated with IPAH, but may affect all groups. This schematic is used to illustrate the typical scenarios the authors observe in clinic; it is not drawn to scale and is largely based on authors own experience rather than a robust body of evidence in the literature. The blue triangle and the rectangular 'Group' boxes represent the burden of comorbidity and thus, the placement of the pulmonary hypertension group boxes within the triangle, as well as their size, represent the relative prevalence of comorbidities in each group (with the lowest and largest group having the greatest prevalence). Group 5 pulmonary hypertension is shown outside the triangle because published data and the authors' findings from the clinic are not sufficient to draw conclusions from; there is no consensus on the prevalence of comorbidities in Group 5 pulmonary hypertension at the time of diagnosis. COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension.

Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend that assessments of patients with PAH should provide information on comorbidities.[8] Physicians should assess patients on a regular basis to identify clinically relevant comorbidities.[8]

The aim of this review is to explore how comorbidities affect the diagnosis and management of PAH. There are multiple causes of PAH; however, for the purpose of this review, known associations of PAH with connective tissue disease (CTD), HIV infection, portal hypertension, congenital heart disease, and schistosomiasis,[8] which can be classified as PAH sub-entities, are not considered comorbidities of PAH. Similarly, combinations of Group 1 pulmonary hypertension (PH) with Groups 2–5 PH are not discussed in detail, given these are classified as multiple causes of PH. Furthermore, pregnancy as an important transient comorbidity is not addressed here but is discussed elsewhere.[9] Comorbidities discussed in this review were selected based on those with the greatest (>10%) prevalence in idiopathic PAH from the REVEAL Registry (Registry to EValuate Early and Long-term PAH disease management),[10] which included patients from over 50 centres in the USA. These comorbidities were: systemic hypertension, obesity, sleep apnoea, clinical depression, obstructive airway disease, thyroid disease, diabetes mellitus, and ischaemic cardiovascular event.[10] This is not an exhaustive list and there are many other comorbidities associated with PAH that have been discussed elsewhere, such as anaemia,[11] chronic kidney disease,[12] chronic liver disease,[13] chronic pain,[14,15] chronic muscle disease,[16,17] frailty, peripheral vascular disease, cancer, and dementia. All comorbidities add a significant burden to PAH patients' lives, as well as their caregivers, and presents a challenge to the treating physician. It is also important to note that, across all PH diagnoses, PAH (Group 1) patients typically present with the fewest comorbidities at the time of diagnosis (*Figure 1*). Summarizing the latest guidance on all of the above-listed comorbidities for all the PH groups is beyond the scope of this review, and condition-specific considerations are therefore limited to those with the greatest (>10%) prevalence in idiopathic PAH from the REVEAL Registry.

The impact of comorbidities on diagnosing pulmonary arterial hypertension

Comorbidities in pulmonary arterial hypertension

The concurrence of PAH and comorbidities (*Figure 2*) increases the complexity of disease identification and management. Patients may require multiple pharmacological therapies or medical interventions for PAH and comorbidities, which can affect the choice of PAH-specific therapies due to drug interactions, dosing regimens, or contraindications. Similarly, patients may require care services to be co-ordinated and a multidisciplinary team to manage their conditions.[22] However, patients with comorbidities are frequently excluded from clinical trials, and as such there is a paucity of data on the effectiveness of PAH-specific therapies in patients with multiple comorbid conditions.

In populations of patients with three or more of the following comorbidities: body mass index (BMI) $\geq 30\,kg/m^2$; hypertension; diabetes; and coronary disease, patients experienced a similar treatment effect compared with those with two or fewer comorbidities. A *post hoc* analysis of the GRIPHON study revealed that selexipag was as effective in patients with three or more comorbidities ($n = 99$) as those with two or fewer ($n = 653$), and safety profiles for both subgroups were similar and consistent with the known profile of selexipag.[23] In the AMBITION study, patients with three or more comorbidities ($n = 105$) experienced a

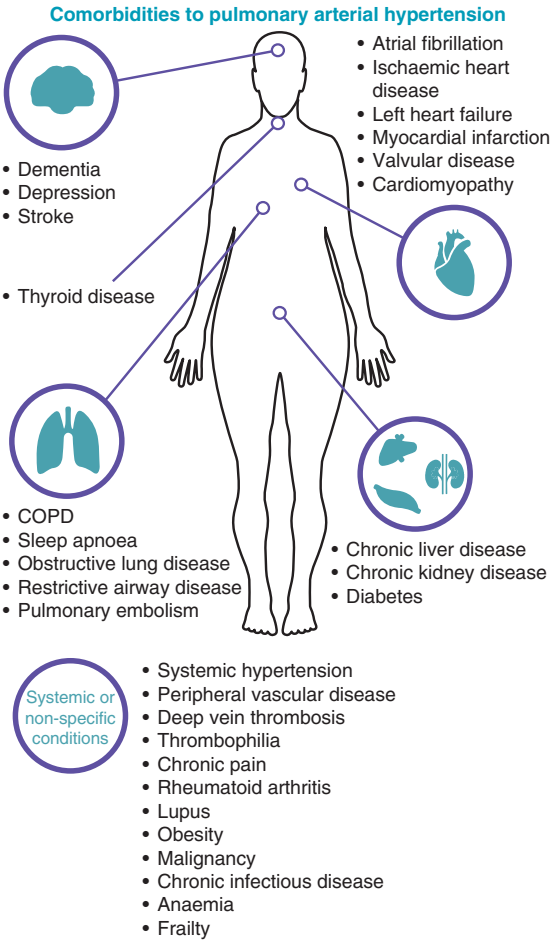

Figure 2 Comorbidities that have been reported in patients with idiopathic pulmonary arterial hypertension. Comorbidities are those reported in the REVEAL registry[10] and supplemented by the authors' clinical experience. COPD, chronic obstructive pulmonary disease.

similar treatment effect to first line combination therapy of ambrisentan and tadalafil compared with patients who had two or fewer comorbidities ($n = 500$), with good tolerability.[24] Similar responses to treatment (World Health Organization functional class; exercise capacity and natriuretic peptide levels) were also observed after 12 months between patients (with $\geq$3 comorbidities, $n = 139$; with $\leq$2 comorbidities, $n = 421$) in an analysis of the COMPERA registry, who were receiving either an endothelin receptor antagonist (ERA), a phosphodiesterase-5 inhibitor (PDE-5), or a prostacyclin analogue or combination therapy.[25]

Differentiation of pulmonary hypertension groups

Pulmonary hypertension is a complex disease with several possible causes, which are not always mutually exclusive and management is made more difficult in cases where a patient's diagnosis includes multiple PH groups. For example, there is high prevalence of left heart disease and/or interstitial lung disease in patients with CTD, thus it can be difficult to distinguish whether Group 1 (PAH associated with CTD), Group 2 (PH due to left heart disease), or Group 3 (PH due to lung diseases and/or hypoxia) is the leading or primary condition.[8,26] It is important to identify the primary condition driving PH progression to ensure appropriate treatment.[8] For example, the use of PAH-specific therapies is not recommended in patients with Groups 2 and 3 PH and there is a paucity of evidence regarding their efficacy in these patients.[8]

Common comorbidities such as ischaemic left heart disease, diabetes, or aortic valve stenosis increase pulmonary artery wedge pressure, which can lead to diagnostic uncertainty in the presence of precapillary disease. For example, severe aortic stenosis in a case of precapillary PH (such as Eisenmenger syndrome) can lead to combined pre- and post-capillary disease, for which the outcomes with PAH-approved therapies are uncertain.[8]

Confounding the diagnosis of pulmonary arterial hypertension

The presence of comorbidities can lead to delayed diagnosis by masking the symptoms of PAH,[27] particularly due to difficultly identifying and differentiating between non-specific symptoms of PAH such as dyspnoea, fatigue, syncope and chest pain, and symptoms of common comorbidities. Research has shown that patients may experience symptoms for a number of years before receiving a diagnosis of PAH.[28,29] Given the progressive nature of PAH, a delayed diagnosis and subsequent delay to treatment initiation can have severe consequences. The importance of screening patients for PAH to allow treatment to be started in a timely manner is discussed in more detail in a review focused on screening, also in this supplement.[30] The presence of comorbidities, such as systemic hypertension, obstructive airway diseases, and obesity, can also confound the interpretation of prognostic tests for PAH such as the 6-min walk test, contributing to a delay in diagnosis. The diagnostic PAH sign of interventricular septum flattening may be mitigated by concurrent increase in left ventricular pressures, such as in the course of cardiomyopathy. It is therefore important that results are interpreted in the context of known comorbidities.[6]

One example of a population with a high prevalence of comorbidities is in the elderly. Among patients with idiopathic PAH, approximately a quarter of older patients ($\geq$65 years) were found to have at least four of the following comorbidities: systemic hypertension, diabetes, ischaemic stroke, ischaemic heart disease, atrial fibrillation, obesity, or kidney dysfunction, compared with less than 7% of those aged under 65 years.[4] Patients aged over 50 years with PAH were diagnosed with more advanced, severe disease compared with patients younger than 50 years in a review of the UK registry of patients with idiopathic, heritable, or anorexigen-induced PAH.[5] Management considerations for an older population with PAH are discussed in more depth in a separate review in this supplement.[31]

Management considerations with comorbidities and pulmonary arterial hypertension

Patients with PAH and comorbidities are likely to be on complex pharmacological treatment regimens that need

close monitoring and regular adjustment, with an overview by physicians from different specialties. A multidisciplinary team and network are therefore important when patients with PAH are also being treated for comorbidities. Patients with PAH and comorbidities may require different aspects of care including cardiac exercise rehabilitation (for peripheral artery disease, heart failure, myocardial infarction, and atrial fibrillation) and surgical interventions, in addition to multiple pharmacological therapies.[32–37] Patients may also require additional support in their daily lives from social workers, occupational therapists, and psychotherapists. Treatment interventions, and expectations must be managed in the context of comorbidities,[8] and the goals of patients with PAH may need to be reassessed following, or in preparation for, major surgical procedures required to manage a comorbidity.

The ESC/ERS treatment algorithm for treating patients with PAH[8] was developed for patients with no significant cardiovascular comorbidities.[38] An amended treatment algorithm that was endorsed by the Cologne Consensus Conference in 2018, takes into account patients with cardiopulmonary comorbidities, and recommended that oral monotherapy should be the first initiated treatment for PAH, regardless of risk category.[38] Treatment should then be escalated in the case of an inadequate clinical response.[38] This recommendation was made based on the lack of efficacy data in the population of patients with cardiovascular comorbidities, in addition to safety concerns arising from a high incidence of drug discontinuations attributed to adverse events.[38]

Condition-specific considerations

Systemic hypertension and ischaemic cardiovascular events

Systemic hypertension increases the risk of cardiovascular morbidity/mortality, including coronary events and stroke.[39] Up to three-quarters of patients who experience a first stroke or myocardial infarction have concomitant systemic hypertension.[40]

Lifestyle modifications should be used to decrease the required dose levels of anti-hypertensive drugs, where appropriate.[39] The use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and calcium channel blockers have all been found to cause a similar reduction in cardiovascular events on the basis of decreased blood pressure.[39] Care must be taken when PAH-specific therapies are used concomitantly with anti-hypertensive medications due to the risk of excessive systemic hypotension.[8] The use of beta-blockers as a first line anti-hypertensive drug should be avoided in PAH patients.

Calcium channel blockers can also be used in the treatment of PAH, and relatively high doses are needed to provide a benefit in idiopathic PAH following vasoreactivity testing.[8] Patients with PAH who are treated with calcium channel blockers should be monitored closely, with complete reassessment (including right heart catheterization) after 3–4 months of therapy.[8] Similarly, patients who have had an ischaemic stroke are likely to be taking anti-coagulants,[41] such as warfarin. The potential benefits of anticoagulation therapy in idiopathic PAH are unclear due to contrasting evidence. Analyses of the REVEAL Registry and GRIPHON study did not demonstrate a survival benefit for patients with PAH taking anticoagulants, compared with those who were not.[42,43] However, analysis of the COMPERA registry showed that during the 3-year follow-up, there was a significantly lower mortality rate in patients receiving anticoagulants compared with the non-anticoagulated group.[44] Careful monitoring of patients using bosentan and warfarin is required, as bosentan increases warfarin metabolism and subsequent dose adjustments may be necessary.[8]

Obesity

The prevalence of obesity in patients with PAH is between 30% and 40%.[10,45] Increased mortality has been observed in patients with BMI $\geq$40 kg/m^2 with PAH aged under 65 years (hazard ratio = 3.01),[45] and a higher BMI ($\geq$30 kg/m^2) has been associated with worse functional class.[6] Not surprisingly, patients with obesity and PAH also had significantly lower 6-min walk distances than patients without obesity.[46] These findings indicate that weight management is an important consideration in patients with PAH and who have obesity.[45] The presence of obesity must be considered when using the 6-min walk test as a prognostic tool for PAH, as it may act as a confounding factor but may also contribute to PAH severity.[47]

Bariatric surgery for patients with obesity can positively affect PH with lower right ventricular systolic pressure (RVSP)[48] and pulmonary artery pressure.[49] In patients with PH and a pre-operative RVSP $\geq$35 mmHg who underwent bariatric surgery there was no mortality in the first 30 days following surgery, indicating that bariatric surgery can be performed safely in this population without the need for bridging therapies to improve PH.[48]

Obesity is linked to a number of other conditions such as sleep apnoea, insulin resistance, and obesity hypoventilation syndrome, all of which have been linked to the development of PH.[50] Thus, reductions in body weight can lead to improvement in or resolution of these associated conditions as well as an improvement of PH.

Sleep apnoea and obstructive airway disease

In the REVEAL Registry, obstructive airway disease was defined as obstructive lung disease (including asthma and bronchiectasis), reactive airways disease, and chronic obstructive pulmonary disease (COPD).[10] Most of these conditions, in addition to sleep apnoea, which was considered a separate comorbidity, are classified as a cause of Group 3 PH.[8] Due to this, there is a paucity of research and evidence into the management of these comorbidities and PAH, despite their presence in approximately one-quarter of patients with PAH.[10]

When sleep apnoea is present in combination with comorbidities that also cause hypoxaemia, patients commonly present with more severe PH.[50] Sleep apnoea is associated with increased pulmonary artery pressure, which can be reduced by treatment with continuous positive airway pressure.[51] During the daytime, patients with PAH and sleep apnoea display lower arterial oxygen and higher arterial carbon dioxide tension compared with patients without PAH,[52] which may necessitate supplemental

oxygen therapy. There is limited evidence of a benefit of PAH-specific therapies in Group 3 PH (due to lung diseases and/or hypoxaemia),[8] therefore, in our opinion, when patients with PAH present with or develop conditions such as sleep apnoea and COPD physicians should carefully monitor for the absence or loss of efficacy of PAH-specific therapies. The potential effects of PAH-specific therapies on the symptoms and progression of the lung disease must also be considered.[8]

Clinical depression

Clinical depression was observed in over 25% of patients with idiopathic PAH in the REVEAL Registry.[10] However, there is some concern that the diagnosis of depression may be missed due to the overlapping symptoms of fatigue and apathy for PAH and depression.[53] Furthermore, less than 25% of PH patients with a psychiatric diagnosis go on to receive psychiatric treatment.[54] Given the progressive and debilitating nature of PAH, paired with the changes in lifestyle such as job loss and financial concerns, screening, identification, diagnosis and treatment of depression in this population should be prominent in PAH management.[53]

Despite the prevalence of depression in patients with PAH, optimal pharmacological approaches are not well defined.[55] In the general population, psychotherapy is recommended in mild depression, with the addition of pharmacological therapies for moderate-to-severe depression. Selective serotonin reuptake inhibitors (SSRIs) have been associated with higher risk of mortality and clinical worsening in patients with PAH, compared with patients not taking SSRIs.[56] Patients with PAH may also consider joining patient support groups to help them cope with the uncertainty associated with the disease.[55,57]

Thyroid disease

Thyroid disorders are classified as mechanisms for the development of Group 5 PH[8]; however, thyroid disease is also commonly observed concomitantly in patients with PAH (either present during the initial assessments or developing during the course of PAH).[10,58] In both hypothyroidism and hyperthyroidism, cardiac output and pulmonary vascular resistance (PVR) are increased, which in turn can act as a driver for PH.[59,60] As such, tests of thyroid function should be conducted as part of the investigation into PAH, and in established PAH, thyroid function tests should be conducted at least once a year or in cases of rapid deterioration.[8,60]

Early and aggressive treatment of patients with PAH and hyperthyroidism is critical, due to potentially fatal complications of thyroid disease.[61] The increases in cardiac output and PVR can be reversed with beta-blockers and antithyroid medications such as propylthiouracil and saturated solutions of potassium iodide, and can return the patient to a euthyroid state.[59,61] Beta-blockers are not ordinarily recommended for patients with PAH but can be used when necessitated by the presence of comorbidities.[8] For example, there is the potential for a drug–drug interaction between sildenafil, which is metabolized by cytochrome (CYP)-3A4, and those beta-blockers that are CYP3A4 substrates.[8] The concomitant use of PAH-specific therapies and beta-blockers should also be carefully managed to avoid excessive systemic hypotension.[8]

Diabetes

Glucose intolerance and insulin resistance are increasingly thought to influence both the pathogenesis and prognosis of PAH,[62] and diabetes as a comorbid condition to idiopathic or heritable PAH reduces right ventricular function.[63] Patients with PAH and diabetes have been shown to have significantly lower 10-year survival compared with PAH patients without diabetes.[63] Identification and mitigation of modifiable risk factors for diabetes, and targeted treatment of diabetes if it develops, may delay PAH progression and improve patient quality of life.[62] Patients should be educated about the risks of diabetes and PAH, and there should be regular testing for diabetes in these patients.[62]

Considerations regarding polypharmacy

Polypharmacy has been associated with poor treatment outcomes in the general population, which may be due to the adverse side effects of drugs, drug interactions, and/or non-adherence to the treatment regimen,[64] and the impact of multiple medical conditions.[65] In a study of 174 patients with PAH, the median number of drugs per patient was nine, and over 80% were taking five drugs or more.[66] The side-effect profiles of PAH-specific therapies are well documented when used as monotherapy or in combination; however, new side effects may be observed when concomitantly administered with therapies for other conditions. Drug–drug interactions must also be considered (*Table 1*). For instance, PDE-5 inhibitors for PAH, such as sildenafil, cannot be concomitantly used with nitrates, which are used to treat a number of coronary conditions,[70] and there are known interactions between anticoagulants and both prostacyclin analogues and ERAs, which contraindicate their concomitant use.[71]

Adherence may reduce as the number of medications increases, and patients may not notice the short-term effects of occasional missed doses[72]; however, given the progressive nature of PAH, the loss of steady-state from repeated missed doses may have negative consequences for longer-term disease progression. Therefore, patient education through appropriate communication channels is important to maintain adherence.[72] The dosing regimen of PAH-specific therapies should also be considered in patients who are taking multiple medications.[73] For instance, ambrisentan, macitentan, and tadalafil are taken once per day, bosentan and selexipag are taken twice per day, and sildenafil and riociguat are taken three times daily. The pill burden of each therapy should be considered when deciding on medications for monotherapy or combination therapy, in addition to treatment regimens for comorbidities. Older adults with PAH are the most likely to have multiple comorbidities, and the administration of complex therapy regimens in these patients is more challenging.[72] This is discussed in more detail in a specific review on management of PAH in older patients, which is also in this supplement.[31]

Table 1 Potentially significant drug interactions with drugs approved for PAH

PAH drug	Mechanism of interaction	Interacting drug	Interaction
Ambrisentan	?	Cyclosporine, Ketoconazole	Caution is required in the co-administration of ambrisentan with ketoconazole and cyclosporine.
Bosentan	CYP3A4 inducer	Sildenafil	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	Cyclosporine	Cyclosporine levels fall 50%; bosentan levels increase 4-fold. Combination contraindicated.
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course.
	CYP3A4 substrate	Ketoconazole	Bosentan levels increase two-fold.
	CYP3A4 substrate + bile salt pump inhibitor	Glibenclamide	Increase incidence of elevated aminotransferases. Potential decrease of hypoglycaemic effect of glibenclamide. Combination contraindicated.
	CYP2C9 and CYP3A4 substrate	Fluconazole, amiodarone	Bosentan levels increase considerably. Combination contraindicated.
	CYP2C9 and CYP3A4 inducers	Rifampicin, phenytoin	Bosentan levels decrease by 58%. Need for dose adjustment uncertain.
	CYP2C9 inducer	HMG CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with atorvastatin. Cholesterol level should be monitored.
	CYP2C9 inducer	Warfarin	Increase warfarin metabolism, may need to adjust warfarin dose. Intensified monitoring of warfarin recommended following initiation but dose adjustment usually unnecessary.
	CYP2C9 and CYP3A4 inducers	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable.
Macitentan			To be determined.
Selexipag			To be determined.
Sildenafil[67]	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	HMG CoA reductase inhibitors	May increase simvastatin/atorvastatin levels through competition for metabolism. Sildenafil levels may increase. Possible increased risk of rhabdomyolysis.
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and saquinovir increase sildenafil levels markedly.
	CYP3A4 inducer	Phenytoin	Sildenafil level may fall.
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase. May not require dose adjustment for a short course.
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment.
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment.
	cGMP	Nitrates, Nicorandil Molsidomine	Profound systemic hypotension, combination contraindicated.
Tadalafil[68]	CYP3A4 substrate	Bosentan	Tadalafil exposure decreases by 42%, no significant changes in bosentan levels.[68] May not require dose adjustment.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.
Riociguat[69]	cGMP	Sildenafil, other PDE-5 inhibitors	Hypotension, severe side effects, combination contraindicated.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.

cGMP, cyclic guanosine monophosphate; PDE-5, phosphodiesterase type-5; ?, unknown.
See also updated official prescribing information for each compound.
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Conclusions

Comorbidities can mask the symptoms of PAH, which can lead to a delayed diagnosis and deleterious consequences for disease progression and survival. Similarly, the presence of comorbidities increases the difficulty of evaluating disease progression and treatment effects by confounding prognostic assessments. The management of comorbidities in addition to PAH should consider drug interactions, polypharmacy, adherence and evidence-based strategies. Thus, it is important that any and all comorbidities are identified and diagnosed so that each patient receives the optimal treatment regimen. A multidisciplinary team approach is essential in the management of patients with PAH

and comorbidities. In addition to management by physicians of different specialties, patients may require social, financial, and psychological support. Furthermore, healthcare professionals must manage each patient's treatment goals and expectations in the context of comorbidities.

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