Transitioning prostacyclin pathway agents to oral selexipag in patients with pulmonary arterial hypertension: A systematic literature review

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Background

- Pulmonary arterial hypertension (PAH) is a rare, progressive, and chronic disease with no cure, with an estimated incidence of 1.4 cases per 100,000 person-years in the United States.[1,2] PAH is characterized by increased pulmonary vascular resistance and elevated pressure in the pulmonary arteries due to their narrowing or obstruction, leading to increased right ventricular workload and eventual right heart failure[1,2]
- Oral selexipag is an IP receptor agonist indicated to delay disease progression and reduce the risk of PAH-related hospitalization, as demonstrated in GRIPHON, the largest PAH clinical trial to date[2–4]
- Transitioning patients with PAH from parenteral or inhaled prostacyclins to an oral IP receptor agonist is an area of emerging clinical interest[5]
- The decisions to undergo these transitions are informed by shared decision-making through provider conversations with patients[6]
- In the appropriate patient, transitioning to oral selexipag may be an option, but the evidence supporting this is limited, typically to case series

Objective

This systematic literature review (SLR) examined published evidence to better understand clinical scenarios where adult patients transitioned from other prostacyclin pathway agents (PPAs) to oral selexipag

Methods

- An SLR was conducted to identify literature published from January 1, 2015, to September 25, 2024. The searches were conducted in Embase and Medline databases utilizing the OVID® search platform, with searches tailored to the relevant databases
- Supplementary gray literature searches of eight conferences from the last 3 years (2022–2024) were also conducted to identify relevant conference abstracts
- Articles were independently screened by two reviewers at abstract and full-text stage, with relevant data extracted by a single reviewer
- Publications were screened using Population, Intervention, Comparator, Outcomes and Study design (PICOS) criteria, focusing on studies reporting outcomes related to transitioning from other PPAs to oral selexipag in adults (≥18 years) with PAH. Studies focusing solely on pediatric populations (<18 years) were tagged for reference but excluded from results reporting
- Additionally, interventions of interest included three PPAs administered through various administration routes: epoprostenol (intravenous), selexipag (oral), treprostinil (oral, intravenous, subcutaneous, or inhaled)
- The Joanna Briggs Institute Handbook for Evidence Synthesis was utilized to assess study quality and risk of bias

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Results

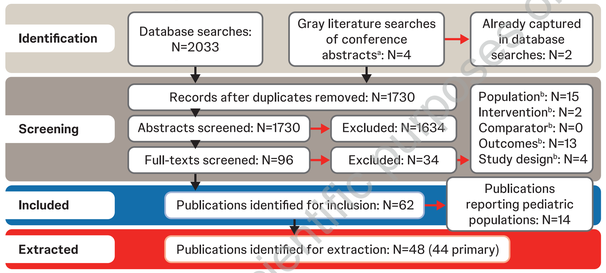
Included publications

- A total of 1730 publications were identified from database searches, which were supplemented with four publications identified from gray literature searches
- Following abstract and full text screening, 48 publications were deemed relevant based on the PICOS criteria. Of these, four were identified as secondary publications through study mapping and not taken forward for extraction, resulting in 44 primary publications for inclusion in the SLR (**Figure 1**)

Transition protocols

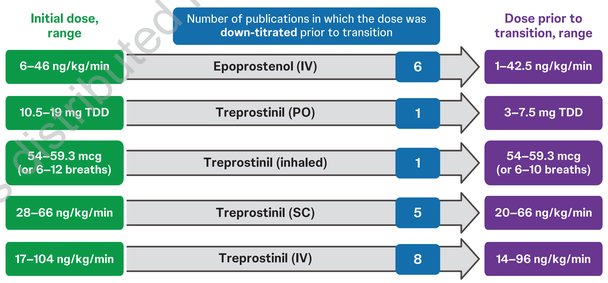
- Among the publications reporting transition protocols, there was considerable variability in methods used for transition, as well as in the level of detail provided
  - Cross-titration (tapering the current PPA treatment while simultaneously initiating and increasing the dose of oral selexipag) was the most commonly reported approach for transition to oral selexipag (N=17); however, transition protocols were nuanced, typically aligned with the practice setting and customized to individual patient needs
  - A total of 25 publications reported on the setting of transitions to selexipag:
    - **Outpatient:** 25 individual transitions
    - **Inpatient:** 22 individual transitions
    - **Inpatient and outpatient:** four individual transitions
  - The dosing of treatments received by patients with PAH prior to transitioning to oral selexipag varied widely across publications, highlighting the individualized approach for determining dosing and transition strategies (**Figure 2**)

FIGURE 1: PRISMA flow diagram



[a]Congresses included ACC, AHA, ATS, CHEST, ERS, ESC, HFSA, ISHLT, PHA, PHPN, PVRI, and SCCM. [b]PICOS criteria used to define the scope of the SLR.

FIGURE 2: Dosing and down-titration of PPA treatment prior to transition to oral selexipag



- Publications specifying transition protocols generally followed GRIPHON trial/US Food and Drug Administration label recommendations, with doses starting at 200 mcg twice daily (BID) and titrating by 200 mcg BID increments to a maximum dose of 1600 mcg BID (**Figure 3**)
- Overall, 32 transitions from treprostinil and 16 from epoprostenol to oral selexipag were identified, with two publications not specifying the prior transitioned PPA (**Figure 4**)

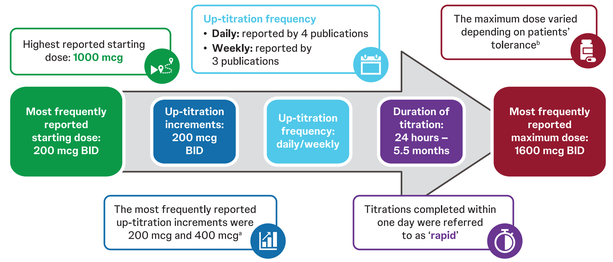
Included patient populations

- This SLR identified a heterogeneous population of patients with PAH that underwent transition to oral selexipag
- Patient ages ranged from 19 to 78 years, and baseline comorbidities varied widely, including interstitial lung disease, paroxysmal atrial fibrillation, and sarcoidosis
- Patients ranged from FC I to IV, as classified by either WHO or NYHA FC
- Risk score (mainly assessed through the REVEAL 2.0 risk stratification model as used in six publications) also varied among patients (ranging from 3 to 11)
- Reasons for transitioning from other PPAs to oral selexipag were highly specific to the patients, with factors including patient preference, complications associated with the administration route, clinical worsening, and prostacyclin side effects

Transition outcomes

- Overall, transition success (explicitly defined by study authors in the publication) was assessed for 258 of the 403 identified transitions to oral selexipag, of which 193 were deemed successful (75%)
- Assessment of success was highly specific to each publication and was often carried out through a combination of measured outcomes and patient-specific objectives for each case

FIGURE 3: Oral selexipag titration protocols



[a]One publication reported step-wise increments (increasing the morning dose before the evening dose). [b]The maximum oral selexipag dose exceeded the recommended maximum dose (1600 mcg BID) in some cases.

FIGURE 4: Number of publications reporting on the PPA treatment prior to transition to oral selexipag[a]

[a]The total number of administration routes may exceed the total number of publications, as some may have reported results for more than one route of administration. [b]Seven publications did not specify the route of administration for epoprostenol; however, as IV is the only approved route, this has been inferred as the administration route. [c]Specific route of administration not defined further than 'parenteral'.

Key takeaway

This SLR identified a high degree of heterogeneity in transition approaches; however, the majority of transitions were deemed successful, as explicitly defined by the study authors in their respective publications

Conclusions

- **Transition outcomes are likely to be improved when clinicians and patients collaboratively assess safety, risks, and benefits**
- **Transition protocols vary widely and are adapted to individual patient needs, based on their risk status and risk score, clinical presentation, and the center's experience**
- **Transitions were performed in either inpatient or outpatient settings, often combining approaches for safety and convenience**
- **Patient heterogeneity and newer treatments complicate transition strategies and highlight the need for continuous updates**
- **Transitioning from other PPAs to oral selexipag is feasible in some patients, but an approach on how to do this may benefit from standardized, evidenced-based recommendations**

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Disclosures

All authors reviewed and contributed to the content of the poster and had authority in the decision to submit the poster.

CB, **GD**, and **WH** are employees of Johnson & Johnson. In addition, **GD** and **WH** are shareholders of Johnson & Johnson. **DB**, **PO'D**, **CO**, and **LVM** are employees of Adelphi Values PROVE, who were contracted by Johnson & Johnson to conduct this research.

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ABBREVIATIONS:

ACC, American College of Cardiology; **AHA**, American Heart Association; **ATS**, American Thoracic Society; **BID**, twice daily; **CHEST**, American College of Chest Physicians; **EPO**, epoprostenol; **ERS**, European Respiratory Society; **ESC**, European Society of Cardiology; **FC**, functional class; **HFSA**, Heart Failure Society of America; **ISHLT**, International Society for Heart and Lung Transplantation; **IV**, intravenous; **NR**, not reported; **NYHA**, New York Heart Association; **PAH**, pulmonary arterial hypertension; **PHA**, Pulmonary Hypertension Association; **PHPN**, Pulmonary Hypertension Professional Network; **PICOS**, Population, Intervention, Comparator, Outcomes and Study design; **PO**, oral; **PPA**, prostacyclin pathway agent; **PVRI**, Pulmonary Vascular Research Institute; **REVEAL**, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; **SC**, subcutaneous; **SCCM**, Society of Critical Care Medicine; **SLR**, systematic literature review; **TDD**, total daily dose; **TREP**, treprostinil; **WHO**, World Health Organization.

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