Oral selexipag in methamphetamine-associated pulmonary arterial hypertension: Real-world analysis from TEAM PAH

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Introduction

- Pulmonary arterial hypertension (PAH) is a complex disease that leads to progressive right ventricular failure[1]
- Selexipag is an oral prostacyclin receptor agonist that delays disease progression and reduces the risk of hospitalization for PAH (GRIPHON trial)[2,3]
- Methamphetamine-associated PAH (meth-PAH) is increasingly recognized as a common, severe form of PAH with increased risk of heart failure and death compared with idiopathic PAH[4,5]
- Patients with meth-PAH represent an understudied population facing unique treatment challenges, with limited clinical data and recommendations from guidelines
- There is currently a lack of data on selexipag titration and persistence in this population

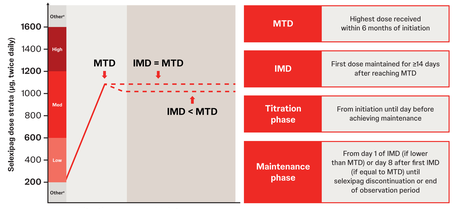
Objective

- To describe oral selexipag dosing patterns and persistence in patients with and without a history of methamphetamine use, using a multidisciplinary, nurse-directed protocol at an expert center in California, USA

Methods

- This was a single-center, retrospective chart review of all adult patients with a primary diagnosis of PAH initiated on oral selexipag between January 1, 2016, and March 31, 2023
- Patients were titrated to their individualized maintenance dose (IMD) using a multidisciplinary, nurse-directed protocol that entailed frequent follow-up to individually manage side effects and tailor selexipag titration
- Dosing patterns and persistence were reported during follow-up, which spanned from selexipag initiation (i.e., the index date) to the earliest of 14 months after index, the last assessment, lung transplant, or death
- Study definitions for titration and dosing were adapted from SelexiPag: tHe usErs dRug rEgistry (SPHERE) (**Figure 1**)[6]
- Demographic and clinical characteristics, including history of methamphetamine use (defined as documentation by a pulmonary hypertension clinician in the patient's medical record), were assessed at selexipag initiation, and dosing patterns and persistence were reported during follow-up
- Data were summarized using descriptive statistics, chi-square testing, and Kaplan–Meier analysis with log-rank testing. Adjustment for multiple testing was not applied

FIGURE 1. Study definitions adapted from SPHERE[6]



*The 'other' dose category includes doses <200 or >1600 µg twice daily.
IMD, individualized maintenance dose; **Med**, medium; **MTD**, maximum tolerated dose; **SPHERE**, SelexiPag: tHe usErs dRug rEgistry.

Results

Baseline demographic and clinical characteristics

- A total of 200 patients initiated oral selexipag, with a median observation period of 14 months
  - 82/200 (41%) patients had a history of methamphetamine use; of these, 17 (21%) reported active use
  - One patient whose history of methamphetamine use was recorded as 'unknown' was excluded, resulting in a final sample of 199 patients
- Relative to those with no history of methamphetamine use, patients with a history of methamphetamine use were significantly more likely to be male and White; they were also numerically more likely to be initiated on selexipag as a part of triple therapy and less likely to have transitioned from another prostacyclin pathway agent (**Table 1**)

TABLE 1. Baseline demographic and clinical characteristics (N=199)[a]

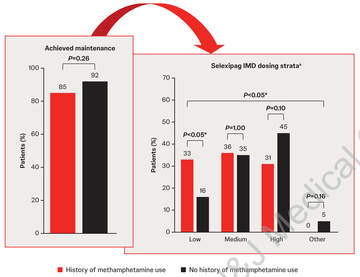
	History of methamphetamine use (n=82)	No history of methamphetamine use (n=117)
Median age	50 years	57 years
Female sex	57%	78%*
Race[b]		
White	70%	44%*
Hispanic/Latino	13%	25%
Black/African American	6%	10%
PAH etiology/disease factors		
Drug- or toxin-induced[c]	93%	6%*
WHO FC III/IV PAH	66%	56%
Median time from diagnosis[d]	1.7 years	1.4 years
Median REVEAL Lite 2 risk score[e]	6.0	6.0
Comorbidities[b]		
Systemic hypertension	38%	33%
Obstructive sleep apnea	32%	27%
CAD	22%	21%
Obesity (BMI ≥30 kg/m^2)	22%	15%
Diabetes	12%	18%
Triple therapy regimen (selexipag + ERA + PDE5i)	77%	67%
Transitioned from another PPA	6%	16%

*P<0.05 (chi-square test for difference between cohorts). [a]One patient who reported history of methamphetamine use as 'unknown' was excluded. [b]Categories shown represent the most common and are not mutually exclusive. [c]Drug- or toxin-induced etiology included drugs such as methamphetamine and fenfluramine/phentermine. Six patients with a history of methamphetamine use without documented drug- or toxin-induced PAH etiology had a multifactorial PAH etiology. [d]Diagnosis date was unknown in 26% of both patients with and patients without a history of methamphetamine use. [e]REVEAL Lite 2 scores were available for 23% of patients with a history of methamphetamine use and 19% of patients with no history of methamphetamine use. WHO functional class, vital signs (SBP and HR), 6MWD, BNP/NT-proBNP, and renal insufficiency (eGFR) were used to calculate the REVEAL Lite 2 score. Only patients with (i) no missing values, (ii) missing values for one of the six components, and (iii) missing values for two or more of renal insufficiency, SBP, and HR were included in the risk score calculation, based on Benza et al, 2021,[7] which showed good discrimination; c-statistic ≥0.70.
6MWD, 6-minute walk distance; **BMI**, body mass index; **BNP**, B-type natriuretic peptide; **CAD**, coronary artery disease; **eGFR**, estimated glomerular filtration rate; **ERA**, endothelin receptor antagonist; **HR**, heart rate; **NT-proBNP**, N-terminal pro-B-type natriuretic peptide; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase type 5 inhibitor; **PPA**, prostacyclin pathway agent; **REVEAL**, Registry to Evaluate Early and Long-Term PAH Disease Management; **SBP**, systolic blood pressure; **WHO FC**, World Health Organization functional class.

Titration and individualized dosing

- The majority of patients with a history of methamphetamine use achieved maintenance on oral selexipag, which was similar to those with no history of use (85% vs 92%, P=0.26) (**Figure 2**)
- Patients with a history of methamphetamine use had a lower IMD (median IMD, 800 vs 1000 µg twice daily), with more patients in the low-dose stratum (33% vs 16%, P<0.05) than those with no history of use (**Figure 2**)

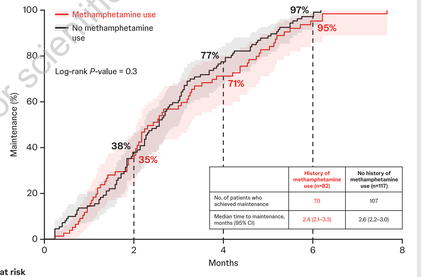
FIGURE 2. Selexipag dosing strata among patients who achieved maintenance



*Percentages may not add to 100% due to rounding. *Chi-square test for difference between cohorts.
IMD, individualized maintenance dose.

- Time to maintenance was similar across the two cohorts, with roughly one-third achieving maintenance within 2 months of initiation and >90% within 6 months (median, 2.4 months and 2.6 months for those with and without a history of methamphetamine use, respectively; P=0.3) (**Figure 3**)
- Median time between dose escalations during titration was 14.5 days for patients with a history of methamphetamine use and 14.0 days for those with no history of use

FIGURE 3. Kaplan–Meier plot for time to maintenance

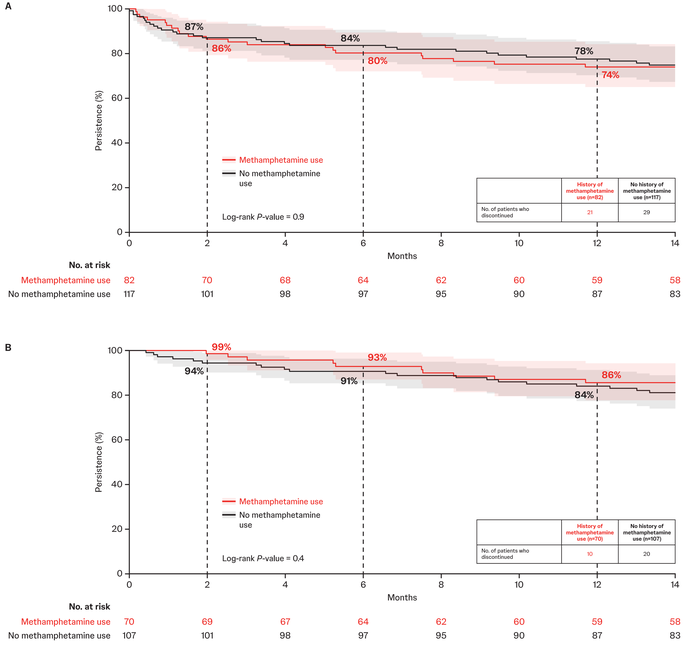


CI, confidence interval.

Selexipag persistence

- At 12 months, patients with and without a history of methamphetamine use had similar persistence to oral selexipag (74% and 78%, respectively) (**Figure 4A**)
- Similarly, among patients achieving maintenance, patients with versus without a history of methamphetamine use had similar persistence at 12 months (86% vs 84%) (**Figure 4B**)
- The highest rates of discontinuations occurred in the first 2 months after selexipag initiation (14% methamphetamine use, 13% no methamphetamine use) and more than two-thirds of discontinuations were due to an inability to tolerate treatment
- In total, 49% of patients with and 39% of patients without a history of methamphetamine use experienced severe adverse events during the observation period

FIGURE 4. Kaplan–Meier plot for selexipag persistence during the entire observation period for (A) all patients and (B) those who reached maintenance



Limitations

- **History of methamphetamine use may not be reliably reported in electronic medical records and does not necessarily equate to meth-PAH etiology**
- **Other limitations include missing data elements (e.g., risk parameters), lack of information on variables not ascertained in routine patient care, and limited generalizability to patients with barriers to accessing or receiving care**

Conclusions

- **This study provides novel data describing oral selexipag dosing patterns in patients with PAH and a history of methamphetamine use**
- **Using a multidisciplinary, nurse-directed protocol, most patients with a history of methamphetamine use were successfully titrated to their IMD and persisted on treatment, supporting oral selexipag as a viable option for this at-risk population**
- **Despite similar time to maintenance and comparable levels of persistence in both groups, patients with a history of methamphetamine use had lower IMDs, highlighting the importance of multidisciplinary care with frequent patient contact, side effect management, and titration individualization**

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Disclosures

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An interim analysis of these results was presented at the ATS 2025 International Conference; San Francisco, CA, USA; May 16–21, 2025

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