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Original Research

Practical management of oral treprostinil in patients with pulmonary arterial hypertension: Lessons from ADAPT, EXPEDITE, and expert consensus

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A R T I C L E I N F O

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A B S T R A C T

Background: Oral treprostinil is a prostacyclin analogue approved to treat pulmonary arterial hypertension (PAH) by delaying disease progression and improving exercise capacity. Higher doses of oral treprostinil correlate with increased treatment benefit. Titrations may be challenging due to common side effects of prostacyclin-class therapies.

Study design and methods: The multicenter, prospective, real-world, observational ADAPT Registry study followed adult patients with PAH for up to 78 weeks after initiating oral treprostinil (NCT03045029). Dosing, titration, and transitions of oral treprostinil were at the discretion of the prescriber. Patient-reported incidence and treatment of common side effects were collected to understand side effect management and tolerability. Insights from literature and expert recommendations were added to provide a consolidated resource for oral treprostinil use.

Results: In total, 139 participants in ADAPT completed ≥1 weekly survey; (median age 60.0 years, 76 % female). Median treatment duration of oral treprostinil was 13.1 months. During early therapy (Months 1–5), 62 % (78/126) of patients reported headache and diarrhea, and 40 % (50/126) reported nausea. At Month 6, many patients who reported side effects during early therapy reported an improvement (61 % headache, 44 % diarrhea, 70 % nausea). Common side effect treatments, including acetaminophen, loperamide, and ondansetron, were effective. Approximately one-quarter of patients reporting the most common side effects were untreated at Month 6.

Conclusion: Patient selection for, and initiation and titration of, oral treprostinil should be individualized and may include parenteral treprostinil induction-transition for faster titration. Assertive side effect management may help patients reach higher and more efficacious doses of oral treprostinil.

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Abbreviations

BID	twice daily
DP1	prostaglandin D receptor 1
EP2	prostaglandin E receptor 2
FC	functional class
HCP	healthcare professional
IQR	interquartile range
IV	intravenous
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro B-type natriuretic peptide
PAH	pulmonary arterial hypertension
SC	subcutaneous
TDD	total daily dose
TID	three times daily
WHO	World Health Organization

1. Introduction

Pulmonary arterial hypertension (PAH) causes progressive narrowing of the pulmonary vasculature, leading to increased vascular resistance and pulmonary pressures [1]. PAH pathophysiology is characterized by imbalances in one or multiple vasoactive pathways, including nitric oxide (NO), endothelin, and prostacyclin [1]. Treprostinil, available in parenteral, inhaled, and oral formulations, is an available therapy that targets the prostacyclin pathway [2–5].

Treprostinil is a prostacyclin analogue, which also has a high affinity for prostaglandin E receptor 2 (EP2) and prostaglandin D receptor 1 (DP1) [6]. Through activation of prostacyclin, EP2, DP1, and peroxisome proliferator–activated receptors, treprostinil causes direct vasodilation of pulmonary and systemic arterial vascular beds, inhibition of platelet aggregation, and inhibition of smooth muscle cell proliferation [4,6,7]. Preclinical data suggest treprostinil could additionally exert anti-inflammatory and antifibrotic effects in the lungs [8,9].

Oral treprostinil (ORENITRAM®) is approved to treat PAH by delaying disease progression and improving exercise capacity [4,10,11]. The phase 3, placebo-controlled FREEDOM-M study led to Food and Drug Administration approval of oral treprostinil by demonstrating improvements in exercise capacity in treatment-naïve patients with PAH. Later, the phase 3 FREEDOM-EV placebo-controlled trial showed that combination therapy with oral treprostinil led to a decreased risk of clinical worsening, which was driven by a 61 % reduction in disease progression [11]. Treatment with oral treprostinil facilitated improvements in PAH risk scores at Week 12 and later, World Health Organization (WHO) functional class, and plasma levels of N-terminal pro B-type natriuretic peptide (NT-proBNP) [11,12]. A hemodynamic substudy within the FREEDOM-EV trial showed a significant decrease in pulmonary vascular resistance and significant increases in pulmonary arterial compliance and cardiac output compared with placebo [13].

Oral treprostinil exhibits a consistent dose–response relationship, meaning higher doses correlate with an increase in treatment benefit. This was described in several post-hoc analyses of the phase 3 FREEDOM-EV and FREEDOM-C/C2 trials, which demonstrated that higher doses of oral treprostinil were associated with improved functional outcomes for patients with PAH [14,15]. Additionally, higher doses of oral treprostinil were associated with a significant prolongation in time to first PAH-related hospitalization and all-cause hospitalization, and greater improvements in the 6-minute walk distance (6MWD) [16]. However, titrating to higher doses may be challenging due to commonly experienced side effects (i.e., expected effects) of treprostinil therapy. There are several non-pharmacologic and pharmacologic methods to help manage these side effects, which in turn can help patients tolerate therapy and achieve higher doses of oral treprostinil [4,10,11].

We aim to provide a consolidated resource for the management of expected side effects experienced by patients taking oral treprostinil. Here, we provide insight from the literature and include expert recommendations. We support these expert consensus findings with an analysis of the ADAPT prospective registry, which describes the side effect profile and management of real-world oral treprostinil therapy in patients with PAH (ClinicalTrials.gov identifier NCT03045029; see online appendix for further details).

2. Practical management of oral treprostinil

2.1. Patient selection and dosing

Clinical trials of oral treprostinil in PAH have mainly enrolled patients classified as WHO functional class (FC) II or III [10,11,17,18]. Updated PAH treatment guidelines recommend treating patients by risk category rather than FC alone [19]. In the FREEDOM-EV trial, 49 % of patients were intermediate-low risk and 23 % were intermediate-high risk by COMPERA at baseline [12]. Thus far, oral treprostinil has demonstrated efficacy in a heterogenous group of patients with characteristics of intermediate-risk PAH [10,11,20,21].

Effective use of oral treprostinil begins with appropriate patient selection and dosing strategy. Two Delphi expert consensus statements have been completed related to patient selection and dosing considerations for oral treprostinil [22,23]. Experts have recommended oral treprostinil in patients with a mix of low- and intermediate-risk parameters who are receiving dual background therapy with an endothelin receptor antagonist and an NO pathway-targeting agent; who have stable disease and adequate time to titrate therapy; who aim to reach low-risk status; and who are inappropriate for, or refuse, parenteral or inhaled prostacyclin class therapy [22,23].

Treatment initiation can differ depending on previous exposure to prostacyclin-class therapies. Prostacyclin-naïve patients may be initiated slowly with de novo dosing or rapidly up-titrated on oral treprostinil following parenteral induction [11,20]. Prostacyclin-experienced patients currently receiving another prostacyclin-class therapy might transition to higher doses of oral treprostinil when appropriate. Oral treprostinil is contraindicated in individuals with severe hepatic impairment (Child–Pugh group C) [4]. Co-administration of oral treprostinil and gemfibrozil (a CYP2C8 enzyme inhibitor) increases exposure to treprostinil [4].

2.2. Prostacyclin-naïve patients

Initiation strategy should be selected based on the patient's needs and risk profile. De novo dosing should be initiated at a low dose of oral treprostinil with slow up-titration once weekly, as tolerated, to limit side effects, whereas parenteral induction and transition to bioequivalent doses of oral treprostinil can lessen the side effects when initiating oral treprostinil, allowing for faster dose escalation [21,24]. The FREEDOM-EV and EXPEDITE studies are examples of these two different approaches (Fig. 1) [11,20].

2.2.1. De novo dosing

De novo dosing could be suitable for lower-risk patients (low or intermediate-low risk) with less severe disease. The recommended starting dose of oral treprostinil is 0.125 mg three times daily (TID), or 0.25 mg twice daily (BID) (Fig. 2); however, real-world and expert consensus data indicate that TID dosing is preferred and more common [4,21–24]. Compared with BID dosing, TID dosing reduces peak-to-trough plasma treprostinil fluctuations and may reduce the frequency and severity of side effects, facilitating dose up-titration [21,24].

Oral treprostinil should be individualized and titrated to the highest tolerated dose (maximum total daily dose [TDD] 120 mg) to optimize

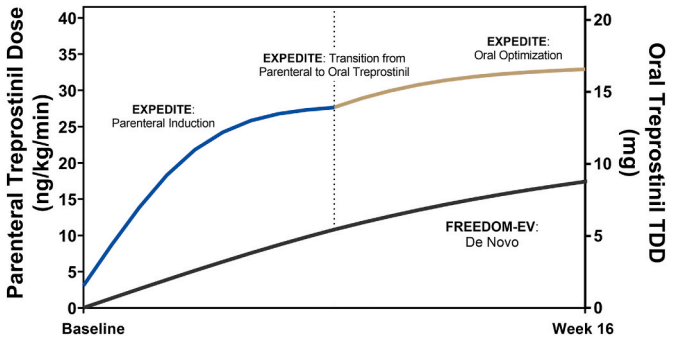

Fig. 1. Representations of de novo and parenteral induction dosing strategies for initiating oral treprostinil therapy for prostacyclin-naïve patients.

The parenteral induction (EXPEDITE) method is presented as representative treprostinil dosing based on the median treprostinil doses in the EXPEDITE study, with the assumption of a patient weighing 70 kg [20]. A conversion formula for parenteral to oral treprostinil is available in the oral treprostinil package insert [4]. The de novo curve is representative of the reported median FREEDOM-EV dosing, truncating the curve at Week 16 [11]. TDD, total daily dose.

therapeutic impact. Once-weekly dose titration may help decrease the risk of oral treprostinil-associated side effects and simplify the dose titration schedule for patients and their care team. Alternatively, an extended titration period can be used if needed. In the context of the FREEDOM-EV clinical trial, aggressive TID dosing (i.e., more rapid than 0.125 mg TID weekly) resulted in a median TDD of ~9 mg at Week 16 (Fig. 1) [11]. A post-hoc analysis of FREEDOM-EV indicated that patients treated with ≥3 mg TID had greater clinical responses compared to the placebo group and patients achieving <3 mg TID, indicating that a dose ≥3 mg TID may be a reasonable initial dose target in clinical practice [15].

2.2.2. *Parenteral induction and oral transition*

For prostacyclin-naïve patients who would benefit from reaching therapeutic doses more quickly (intermediate-low or intermediate-high risk), a short course of parenteral induction followed by cross-titration to bioequivalent dosing of oral treprostinil might be appropriate [25]. This treatment approach can also be considered for patients who are inappropriate candidates for long-term parenteral therapy because they are unwilling or unable to commit to routine subcutaneous (SC) or intravenous (IV) administration. Implementing an induction therapy approach may improve the tolerability profile associated with titration of oral treprostinil.

The EXPEDITE study, evaluating the effectiveness of a short course of IV/SC induction therapy on the tolerability and time to effective dosing with oral treprostinil, showed that 79 % of patients achieved an oral treprostinil TDD of ≥12 mg at Week 16 [20]. The mean TDD at Week 16 was 16.4 mg [20]. Investigators in EXPEDITE had flexibility within the protocol, and representative dosing strategies were recently published

Patient selection			
Intermediate and low-risk stratifications		Dual background therapy	
Low-risk goal		Inappropriate for/refuse other prostacyclins	
Patient education			
Expected effects	Proactive side effect management	Titration schedule	Patient support programs
Resources			
Specialty pharmacy		Titration kit	
Dosing strategies			
Prostacyclin naive: De novo dosing or induction-transition		**Prostacyclin experienced:** Transition	
Titration – Prostacyclin-naïve patients			
De novo		Parenteral induction-transition	
• Titrate 0.125 mg TID/week with food (0.25 mg BID) • TID preferred, dose every 6–8 hours • Target dose: ≥3 mg TID at 6 months • Titrate to tolerance and therapeutic effect		• IV/SC treprostinil: Initiate and titrate to highest tolerated and effective dose • Evaluate clinical status and ability to transition • Calculate the oral treprostinil target dose: – 0.0072 mg × IV/SC dose (ng/kg/min) × weight (kg) = TDD – 5 ng/kg/min ~1 mg TID in a 70 kg patient* • Cross-taper IV/SC treprostinil over 1–21 days (based on EXPEDITE study[20,26]) • After reaching target, continue to titrate oral treprostinil by 0.125 mg as needed	

*Based on pharmacokinetic data for systemic exposure, for patients who weigh ~70 kg and have no other confounding factors (i.e., liver dysfunction or receiving a CYP2C8 modifier).[25]

BID, two times daily; IV, intravenous; SC, subcutaneous; TID, three times daily; TDD, total daily dose.

Fig. 2. Strategies for successfully initiating oral treprostinil [4].

*Based on pharmacokinetic data for systemic exposure, for patients who weigh ~70 kg and have no other confounding factors (i.e., liver dysfunction or receiving a CYP2C8 modifier) [25].

BID, two times daily; IV, intravenous; SC, subcutaneous; TID, three times daily; TDD, total daily dose.

[26]. Patients initiated on either IV or SC parenteral prostacyclin reached a mean dose of 27 ng/kg/min prior to transitioning to oral treprostinil. Participants transitioned in inpatient and outpatient settings, with most transitioning to oral treprostinil at Week 8. Inpatient transitions occurred over 1–2 days, and transitions in the outpatient setting occurred over 4–6 days. Parenteral initiation allowed patients to achieve 1.5 to 2 times higher dose of oral treprostinil at Week 16 compared with previously reported de novo oral treprostinil initiation (Fig. 1) [24]. In clinical practice, there are reports of a more aggressive, rapid parenteral induction approach using 1- to 2-week courses of parenteral therapy in an inpatient setting for patients with severe PAH who have complicating factors precluding parenteral therapy, and these induction courses have been successful with appropriate supervision [27,28].

2.3. Prostacyclin-experienced patients

Patients currently utilizing other prostacyclin-class formulations could consider transitioning to oral treprostinil. Hemodynamically stable patients who have a lower risk profile and are responding to parenteral prostacyclin therapy may prefer transitioning to oral treprostinil. Transitioning from parenteral treprostinil can lead to higher doses of oral treprostinil and greater tolerability. Patients reaching dose limits on other prostacyclin therapies or at risk for discontinuation due to tolerability might also be transition candidates. Clinical trial evidence is supported by real-world data indicating that patients transitioning from other forms of treprostinil achieve higher doses of oral treprostinil [24].

2.3.1. Transition from long-term parenteral therapy

Some patients with PAH who respond well to parenteral therapy can reasonably transition from parenteral to oral treprostinil. A previous multicenter, open-label study found this method safe and effective for hemodynamically stable PAH patients with a lower risk profile [21]. The group had a median (range) of 3.5 (0.6–9.3) years on parenteral treprostinil at transition, at a median (range) parenteral dose of 57 (25–111) ng/kg/min. After 5 days, 31/33 patients (94%) had completed the transition to oral treprostinil, and they maintained exercise capacity, right heart imaging, and hemodynamic parameters through 24 weeks [24].

2.3.2. Transition from other prostacyclin therapies

In patients who reach the maximal dose of inhaled treprostinil or the prostacyclin agonist selexipag or in those who find these therapies intolerable, transition to oral treprostinil may be considered. An expert consensus on switching between inhaled and oral treprostinil recommended appropriate candidates as those who have achieved WHO FC II or lower, who are in stable condition and have no evidence of right ventricular failure [29]. A retrospective chart review of 29 patients transitioning from inhaled to oral treprostinil found that two-thirds transitioned directly to oral therapy rather than cross-titrating [30]. Most patients transitioned due to intolerance to or side effects from inhaled therapy, and 66 % persisted on oral treprostinil for at least 1 year [30].

A recent analysis of 10 patients enrolled in the ADAPT Registry demonstrated that patients can safely transition from selexipag to oral treprostinil. Seven patients transitioned due to worsening PAH or lack of efficacy on selexipag; the remaining transitioned due to selexipag tolerability issues. At the time of transition, patients had been receiving selexipag for a median (range) of 66 (4–206) weeks and had a median (range) TDD of selexipag of 2800 (400–3200) μg. Transitions occurred in the outpatient setting and utilized either cross-titration or abrupt stop/start without parenteral bridging [31]. In the six patients who cross-titrated, transition occurred over a median (range) of 6 (3–19) weeks. At last follow-up after transition from selexipag, patients reached a median (range) TDD oral treprostinil of 12.0 (7.75–22.5) mg. Notably, 50% of patients demonstrated clinical improvement after the transition to oral treprostinil using a modified REPLACE study definition. Patients who transitioned from selexipag to oral treprostinil due to tolerability issues (30%) did not report intolerance after switching. Overall, transitioning from other prostacyclin therapies to oral treprostinil may improve prostacyclin class tolerability without the added limitation of a low dose ceiling.

2.4. Patient education and communication

Healthcare professionals (HCPs) should counsel patients on expected effects with oral prostacyclin therapy. Side effects are more common in the titration rather than maintenance phase, so patients should be educated accordingly and up-titrated slowly. HCPs should consider a proactive management plan, which should include recommendations for over-the-counter and/or prescription therapies as outlined in Table 1.

To optimize dose escalation and prevent patient discontinuation of oral treprostinil, we frequently advise patients to use these agents prophylactically, particularly in the 24- to 48-h period following up-titration. Once patients learn their side effect profile, they can de-escalate pharmacologic agents to manage the side effect as tolerated. Additionally, patients should receive ongoing education about side effect management and regular assessment of symptom burden. Patients should be counseled to contact their HCP's office or the specialty pharmacy when they have any questions about their therapy, dose titration, or side effect management.

3. Managing common side effects

Oral treprostinil has a known side effect profile that is consistent with other prostacyclin-class therapies, most commonly headache, diarrhea, and nausea [4,10,11,22,32]. Effective management of side effects may allow patients to achieve higher doses of oral treprostinil and potentially obtain a greater therapeutic response. Additionally, effective management can lead to increased tolerance and persistence on the drug [32].

3.1. Management of headache

Headache may be more likely to occur during dose up-titration [32]. Initial treatment for headache could consist of over-the-counter medications, such as acetaminophen [22,23]. Before increasing the dose of treprostinil, patients can take a pain reliever prophylactically. Also, HCPs should consider assessing blood pressure, as hypertension or hypotension may potentiate headache. Caution should be exercised when considering routine use of NSAIDs for headache due to the risk of bleeding and sodium retention with high NSAID doses. For chronic, severe headache that is refractory to common and alternative pain relievers, gabapentin, amitriptyline, and opioids are potential treatments. For refractory headache, some clinicians have had success with the combination therapy butalbital, acetaminophen, and caffeine (Fioricet), but others have expressed concern about the vasoconstrictive effects of caffeine in patients taking pulmonary vasodilators, as well as renal excretion of butalbital. Referral to neurology for secondary causes, including migraines, is often indicated [32].

3.2. Management of diarrhea

Diarrhea can usually be successfully managed with over-the-counter loperamide [32]. If diarrhea is refractory to first- and second-line therapies, consider decreasing the dose of oral treprostinil or slowing titration. Dietary measures that may be useful to manage diarrhea include changes to the diet, such as increasing fiber intake, decreasing fat intake, eating a gluten-free or BRAT (banana, rice, apple, and toast) diet, or adding a probiotic or concentrated peppermint oil (IBgard®) [4,22,23,32]. Specialty consultation with gastroenterology may be indicated in

Table 1
Management strategies for side effects of treprostinil therapy [4,22,23,29,32].

Side effect	First-line	Second-line	Refractory
Headache	Acetaminophen	• Tramadol • NSAID	• Gabapentin • Amitriptyline • Opioid if severe
Nausea, vomiting	Ondansetron	• Prochlorperazine • Proton pump inhibitors	• Metoclopramide • Promethazine
Diarrhea	Loperamide	• Diphenoxylate/atropine	• Dicyclomine
Dizziness, hypotension	Assess volume status	• Decrease dose of diuretic or BP medication	
Abdominal discomfort	Bismuth subsalicylate	• Loperamide • Dicyclomine • Acetaminophen	
Extremity pain	Acetaminophen	• Gabapentin • Pregabalin • Tramadol • Ibuprofen	• Duloxetine • Opioid • Massage
Jaw pain	Reassurance		
Flushing	Reassurance Cold packs		

Recommendations are based upon expert experience in PAH care and observations from the ADAPT registry.
BP, blood pressure; NSAID, non-steroidal anti-inflammatory drug.

cases of refractory diarrhea to rule out other causes such as infection due to *Clostridioides difficile*.[32]

3.3. Management of nausea

First-line therapy to treat nausea is prescription ondansetron [22,23,32]. If nausea is refractory to pharmacologic and non-pharmacologic methods, the dose of oral treprostinil can be decreased or titration can be slowed. If appetite loss or weight loss occur, supplement nutrients as needed and consider a referral to a dietary specialist [32]. Dietary methods to manage treprostinil-induced nausea include always taking the treprostinil dose with food, eating frequent small meals, and adding ginger-containing drinks or food to the diet. If nausea or weight loss continue, rule out any other possible causes, such as pregnancy or thyroid disorders, and consult a gastroenterologist if needed [32]. QT prolongation can occur with ondansetron or promethazine; consider monitoring QTc interval in patients receiving these medications.

3.4. Diet modification

Addressing dietary considerations before and during treatment, especially the timing of eating, is helpful in managing gastrointestinal side effects and improving oral treprostinil absorption [32]. Consuming food, with a moderate calorie intake that includes protein, at the same time as taking an oral treprostinil dose can be beneficial in managing side effects. Patients can keep a food diary and record the timing of oral treprostinil doses in relation to recent meals to determine if there is an improvement in side effects.

4. Managing less common side effects

Patients taking oral treprostinil may experience other side effects that include dizziness related to hypotension, flushing, appetite/weight loss, abdominal discomfort, jaw pain, or extremity pain. These less common side effects can be managed reactively with non-pharmacological, over-the-counter, and prescription medications, as well as reassurance that the symptoms may lessen over time (in the case of flushing and jaw pain). Referrals to specialists, as needed, can also be a resource.

5. Patient and healthcare professional resources

Patient support and encouragement can be key to maintaining a patient on oral treprostinil therapy. Specialty pharmacy providers play an important role in patient education, titration, and side effect management. During the referral process, patient support programs are available from the manufacturer at no cost [33]; these can provide timely support and education for the patient and their care team. Regular communication between the specialty pharmacy and the PAH care team will help to refine individual treatment plans over time.

Predicting which patients will tolerate and persist on oral treprostinil is challenging. Utilizing the 90-day trial program for PAH patients new to treprostinil therapy can help assess initial therapy tolerance without a financial burden to the patient. In 2023, a 3-month titration kit became available, which contains dosing guidance, reminders for patients, and daily TID dose packs to match the prescription. This may help simplify the initial dosing process for patients and lessen the support needed from the care team, while encouraging greater medication adherence.

6. Real-world side effect management: analysis of patient-reported outcomes from ADAPT

ADAPT was a US-based, multicenter, prospective, real-world, observational registry (ClinicalTrials.gov identifier: NCT03045029) following patients with PAH up to 78 weeks after initiating oral treprostinil (ORENITRAM; United Therapeutics Corp.). Adults aged ≥18 years were eligible if they were newly prescribed oral treprostinil or had been receiving oral treprostinil for ≤182 days for PAH from their treating HCP. Dosage, titration, and transitions were at the discretion of the prescribing physician (see online appendix for full details). In ADAPT, patients reported their medications, side effect burden, and effectiveness of side effect treatment. We used these reports to examine the utility of side effect management over time.

A total of 139 participants in ADAPT completed at least one weekly side effect survey, with a median (interquartile range [IQR]) time since diagnosis of 1.9 (0.8–4.4) years (Table A1). At Month 6, the median TDD of oral treprostinil was 10.3 mg (IQR 6.8–16.1; Fig. A1).

During Months 1–5 (defined as the 'early therapy' timeframe), 91 % of patients (126/139) filled out at least one weekly side effect survey. Of these patients, 62 % (78/126) reported headache, 40 % (50/126) reported nausea, 62 % (78/126) reported diarrhea, 46% (58/126) reported extremity pain, and 48% (61/126) reported flushing in at least

one weekly survey. This reporting is in the range of what has been observed in clinical trials [10,11,20,21].

To assess the potential change in patient burden of specific side effects, we compared each patient's earliest weekly report (Months 1–5) of specific side effects to their Month 6 side effects report. A subset (n = 98) of the registry population had sufficient data (an early report and a Month 6 report) in their daily diary to report on the longitudinal burden of their side effects. To understand the efficacy of common treatments, we reviewed patient-reported effectiveness over time. In examining three common side effects, we found that patients' bothersome scores improved over time and that side effect management was at least somewhat effective for most patients (Fig. 3).

In the population of patients who reported any side effect during the ADAPT study, of the 56 % (78/139) of patients reporting headache during early therapy, 44 had a side effect report at Month 6 for comparison. Of those, 61 % (27/44) reported improvement at Month 6 (Fig. 3a). Acetaminophen was the most common treatment for headache, and 97 % and 100 % of patients at Months 3 and 6, respectively, reported it to be at least somewhat effective (Fig. 3b).

Among the 36 % (50/139) of patients reporting nausea during early therapy, 27 had a side effect report at Month 6 for comparison. Of those, 70 % (19/27) reported improvement at Month 6 (Fig. 3c). Ondansetron was the most common treatment for nausea and was reported as at least somewhat effective in 92 % and 100 % of patients reporting its use at Months 3 and 6, respectively (Fig. 3d). At Month 6, 29 % of patients reporting nausea were left untreated.

At Month 6, among the 56 % (78/139) of patients reporting diarrhea during early therapy, 41 had a side effect report for comparison. At 6 months, 44 % (18/41) of those noted an improvement (Fig. 3e). Loperamide was the most common treatment for diarrhea, and 100 % of patient reports noted it was at least somewhat effective at Months 3 and 6 (Fig. 3f). At Month 6, 26 % of patients reporting diarrhea were left untreated.

Limitations of the the ADAPT Registry study include the self-reported nature of the data, limited follow-up data for some patients, and variable times at which the data were collected.

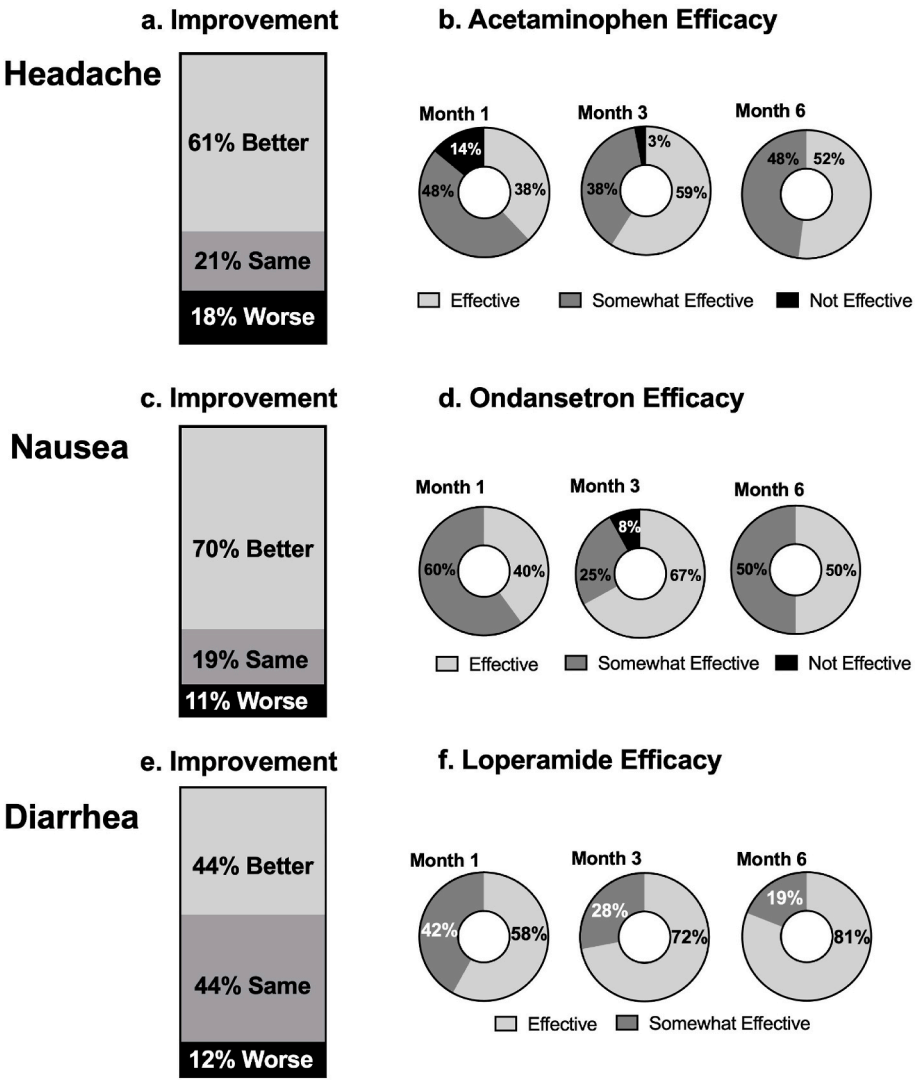

Fig. 3. Real-world outcomes of common side effects of oral treprostinil therapy and common over-the-counter and prescription medication management. Patient-reported incidence and treatment of common side effects associated with oral treprostinil therapy were collected prospectively in ADAPT to better understand side effect management and tolerability. Left column (a, c, e) shows calculated improvement of the bothersome score. This was calculated by comparing the earliest report to Month 6 report. If a previously reported side effect was not reported in Month 6, it was considered 'better'. Patients missing an early or a Month 6 report were not included in these analyses. For headache, n = 44; nausea, n = 27; and diarrhea, n = 41.The right column (b, d, f) shows all patient-reported effectiveness of common over-the-counter and prescription medications given to a portion of those patients reporting the side effect. Early therapy was defined as ≤5 months in this analysis and represents the first reported data from the patient during this period. Month 6 is defined as Weeks 22–25. At Months 1, 3, and 6, respectively, for acetaminophen, n = 21, 32, 33; ondansetron, n = 10, 12, 10; and loperamide, n = 12, 18, 26.

7. Discussion

Oral prostacyclin receptor agonists are suggested by current guidelines as add-on therapy to reduce the risk of morbidity/mortality events in patients with PAH [19,34]. Oral treprostinil is a prostacyclin analogue that has shown benefits for clinical worsening, disease progression, hemodynamics, risk scores, and exercise capacity in a heterogenous group of patients with PAH with characteristics of intermediate risk status [4,10,11,32] Although titrating to higher doses of oral treprostinil is correlated with greater treatment benefit [14–16], this may be challenging due to expected side effects of prostacyclin-class therapies. Here, we provide an overview of treatment strategies, patient selection, and side effect management supported by expert consensus, anecdotal evidence, and the literature. The importance of side effect management is demonstrated by our analysis of the ADAPT Registry's patient-reported outcomes, which supports the effectiveness of common treatments and the lessening of side effect burden for oral treprostinil therapy over time.

Oral treprostinil dosing should ideally be three times a day, with an initial goal of $\geq$3 mg TID at 6 months. A prostacyclin-naïve patient can receive oral treprostinil as de novo therapy or parenteral treprostinil induction (prostacyclin-experienced patients can utilize a transition strategy). This choice is partly determined by patient characteristics including the time available to titrate, the disease characteristics, the risk profile, and patient preferences. Patients transitioning to oral treprostinil using parenteral induction can achieve a target TDD of oral treprostinil faster than patients using a de novo dosing scheme. HCPs may need to adjust the frequency of up-titration to the individual needs and experience of each patient.

Proactive management and prophylactic treatment of expected prostacyclin-related side effects may be beneficial, aiding in titration and persistence on therapy and allowing the patient with PAH an opportunity to obtain optimal therapeutic benefit from oral treprostinil. From the ADAPT prospective registry data, we note that side effects improved over time, and patients reported that common over-the-counter treatments were effective in managing their side effects. Of note, over one-quarter of patients reporting diarrhea or nausea in the ADAPT Registry were left untreated, indicating an opportunity for HCPs to support their patients with PAH. These data are supported by a Delphi consensus project, indicating the need to proactively manage oral treprostinil-associated effects and prescribe medications as appropriate [23].

Initial counseling and continued assessment with collaborative, multidisciplinary care from the PAH clinic and specialty pharmacy care team is important to ensure proper management of patients receiving oral treprostinil. During up-titration, patients may need more frequent contact with the PAH clinic for support in managing any effects of therapy. Adherence to therapy may be improved with education on expected effect management and diet, medication reminders, and regular assessment and dialogue with the treating team.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: JC reports research funding from United Therapeutics Corporation. CK reports consulting and speaking fees from United Therapeutics; consulting fees from Merck & Co Inc.; and speaking fees from Altavant Sciences. JK reports consulting fees, speaking fees, grant funding, and travel reimbursement from United Therapeutics Corporation and Janssen Pharmaceuticals Inc; grant funding from Acceleron Pharma and Gossamer Bio; consulting fees and speaking fees from Bayer Corporation; and speaking fees and travel reimbursement from Actelion Pharmaceuticals Inc. MEW reports consulting fees, speaking fees, and travel reimbursement from United Therapeutics Corporation. MW reports consulting fees, speaking fees, and travel reimbursement from United Therapeutics and Actelion Pharmaceuticals Inc; consulting fees and speaking fees from Bayer Corporation; and consulting fees from Janssen Pharmaceuticals Inc. SS reports consulting fees, speaking fees, and grant funding from United Therapeutics Corporation and Janssen Pharmaceuticals Inc; consulting fees and grant funding from Bayer Corporation, Gossamer Bio, and Altavant Sciences Inc.; consulting fees from Merck & Co Inc., and Liquidia Corporation Inc; and grant funding from Keros Therapeutics Inc. SS is an associated editor for pulmonary vascular diseases at *Respiratory Medicine*. VL reports speaking fees and travel reimbursement from United Therapeutics Corporation; and consulting and speaking fees from Bayer Corporation. AA reports consulting fees from United Therapeutics Corporation. AR reports speaking fees from United Therapeutics Corporation; and consulting and speaking fees from Janssen Pharmaceuticals Inc. CM reports consulting fees and speaking fees from United Therapeutics Corporation and Janssen Pharmaceuticals Inc.; speaking fees from Bayer AG; and consulting fees from Merck Pharmaceutical (HK) Ltd. JB reports consulting fees and speaking fees from United Therapeutics Corporation; and speaking fees from Janssen Pharmaceuticals Inc. AK, MB, DL, NP are employees of United Therapeutics Corporation, and may own stock in United Therapeutics Corporation. AS has no declarations of interest.

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Appendix A. Supplementary data

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