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RESEARCH LETTER

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Using a knowledge translation program to facilitate guideline- and evidence-based patient management: the PAH-QuERI Extension Program

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Abstract

The Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative Extension Program was designed to support physicians' adherence to pulmonary arterial hypertension (PAH) guidelines. Guidelines were followed in >95% of patients with functional class (FC) II/III, but for only 28.6% of FC IV patients (Month 36). Low adherence was driven by FC IV patients' preference to avoid parenteral treatment.

KEYWORDS
educational gaps, guidelines, NYHA/WHO functional class, patient management, pulmonary arterial hypertension

Delayed or inadequate diagnosis and treatment contribute to poor prognosis of patients with pulmonary arterial hypertension (PAH).[1–3] The Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative (PAH-QuERI) captured data from 2005 to 2010 and demonstrated significant gaps in the diagnosis and treatment of patients with PAH.[3] Here, we report findings from the PAH-QuERI Extension Program, a US-based, prospective, multicenter, knowledge translation program tracking patient management, which investigated reasons for this care gap and whether an educational intervention improves physician adherence to evidence-based guidelines (NCT01389206).

Physicians participating in the PAH-QuERI Extension Program received automatically generated educational interventions in response to information provided on electronic case report forms for eligible patients, that is, those aged ≥18 years with a documented PAH diagnosis within 3 years. Patient management was at the treating physician's discretion. There were no protocol-mandated visits, tests (except New York Heart Association/World Health Organization [NYHA/WHO] functional class [FC] assessment), or treatments.

Retrospective and current data were collected at enrollment. Prospective study data were captured every 6 ± 2 months for up to 36 months (study end) or until consent withdrawal, loss to follow-up, death, atrial septostomy, lung transplant, or referral to another center (for intravenous therapy mainly, but not only, due to PAH worsening). Physicians were given guidelines/evidence-based recommendations and steps to help optimally manage their patients with PAH (Figure 1).[4–6] Program endpoints were the proportion of patients receiving a guideline-recommended treatment at each documented visit (primary endpoint), utilization of system reminders and reasons given by physicians about why guideline-based therapy was not utilized, and proportion of patients on PAH therapies relative to FC. Based on previous PAH registries and studies,[7,8] it was determined that a sample size of 800 patients with PAH would be sufficient to explore differences in demographic and clinical data (the study was not powered to determine the statistical significance of comparisons).

Overall, data from 797 eligible patients were captured in the PAH-QuERI Extension Program from 71 centers in the United States: mean age was 56 years; 78.9% were female; 38.2% and 49.9%, respectively, were NYHA/WHO FC II and III. Most patients had idiopathic PAH (49.2%), 49.7% were incident cases (new PAH diagnosis within 3 months of enrollment), and 50.3% were prevalent (PAH diagnosis >3 months before enrollment). Overall, 348 patients (43.7%) completed the study, 251 (31.5%) died before study completion, and 149 (18.7%) were lost to follow-up.

Most patients were receiving PAH-specific medications at baseline (91.6%) and at Month 36 (96.6%). At baseline, 90.1% and 92.2% of FC II and III patients, respectively, received PAH medications, including a prostacyclin analog in 24.3% of FC II patients (parenteral in 14.8%; inhaled/oral in 9.5%) and 31.9% of FC III patients (parenteral in 22.2%; inhaled/oral in 10.1%). At Month 36, prostacyclin analogs were being received by 36.1% of FC II patients (parenteral in 18.5%; inhaled/oral in 18.1%) and 56.4% of FC III patients (parenteral in 23.6%; inhaled/oral in 33.6%). In the FC II and III groups, agents acting on the nitric oxide (NO) pathway (sildenafil, tadalafil, riociguat) were the most common treatment at all visits (baseline > 60% of patients; Month 36 ~80% of patients). In the small group of FC IV patients ($N = 58$ at baseline), prostacyclin analogs were most commonly prescribed. At Month 36, 85.7% received a prostacyclin analog or an NO pathway agent. Parenteral prostacyclin analogs were prescribed for 65.5% and 71.4% of FC IV patients at baseline and Month 36, respectively, including intravenous epoprostenol (55.2% [32/58 patients] at baseline; 28.6% [2/7 patients] at Month 36). Among the

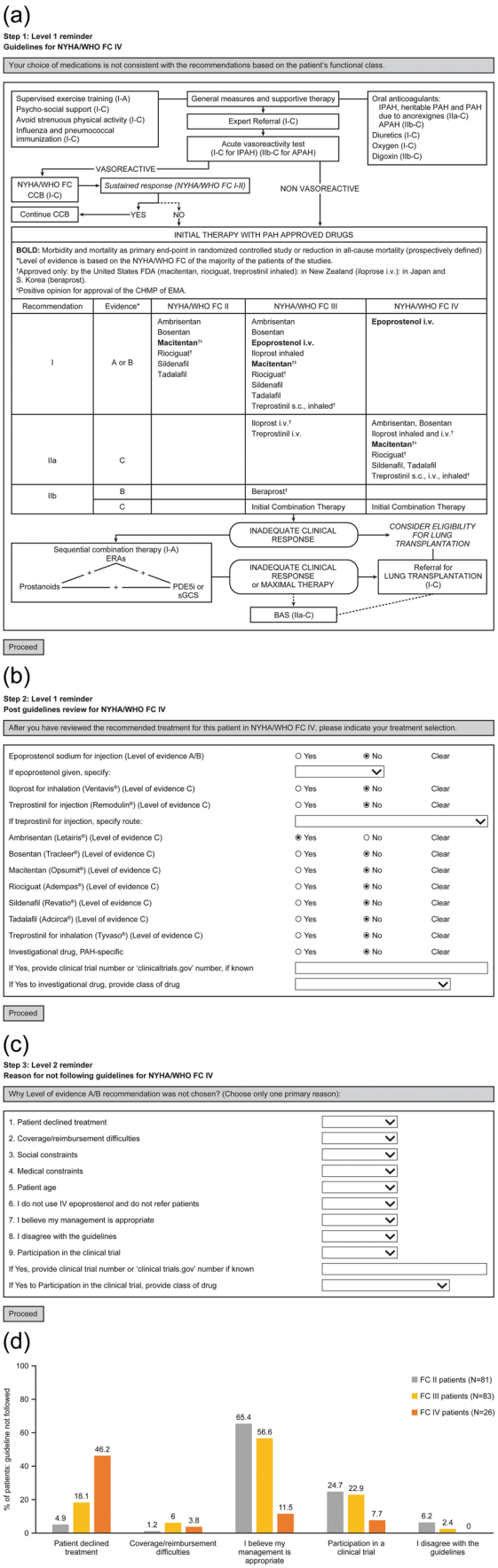

FIGURE 1 (See caption on next page)

138 patients in FC IV at one or more visits from baseline to Month 36, 88 (64.7%) were not prescribed intravenous epoprostenol at any point.

At baseline (study entry), physicians adhered to treatment guidelines for 73.4%, 79.1%, and 55.2% of patients in FC II, III, and IV, respectively. At Month 36, physicians adhered to treatment guidelines for 96.3% and 99.3% of patients in FC II and III, respectively, but only for 28.6% of FC IV patients. Findings in the FC IV group are limited by the small sample size. The most common reasons for prescribing an alternative treatment at baseline were the belief that management was appropriate (FC II, III) and the patient declined treatment (FC IV). Prescription of intravenous or subcutaneous treprostinil, instead of the guideline-recommended intravenous epoprostenol, was considered nonadherent ($n = 6$ at baseline; $n = 1$ at Month 36).

Physicians were asked why they diverged from recommended treatments (Figure 1a–c). At baseline, guidelines were not followed for 81 patients in FC II (27%) and 83 patients in FC III (21%), and the most common reason identified was "I believe my management is appropriate" (Figure 1d). This reason was cited less frequently when guidelines were not followed for FC IV patients ($n = 26$ patients) (Figure 1d). Note that the interpretation of these findings is limited due to the small size of the FC IV group.

Physicians selecting "I believe my management is appropriate" were asked to select reasons for this. For FC II patients, options were "in higher FC responded to treatment," "did not tolerate therapy but tried," "believe safety concern," and "believe strength is appropriate." At the baseline visit, the most common reason was "believe strength is appropriate" (for 16/81 [19.8%] patients); by Month 36, the most common reason was "in higher FC responded to treatment" (for 6/8 [75%] patients). For FC III patients, options for explaining why management was appropriate were "safety concern," "believe treatment is appropriate," and an option to select one of several parameters (hemodynamic, 6-min walk distance [6MWD], biomarkers, echocardiogram) that suggested a patient is more stable than the FC indicates. From baseline to Month 36, physicians most commonly selected that 6MWD, echocardiogram, or hemodynamic parameters showed that the patient was more stable than was indicated by FC.

The PAH-QuERI Extension Program is the first knowledge translation program evaluating physician adherence to PAH treatment guidelines and the reasons for nonadherence. Automated reminders presented physicians with guideline-based treatment recommendations. Electronic reminders have been shown to improve the adoption of clinical guidelines[9] and reduce medical errors.[10] While most physicians in this study adhered to the guidelines, many did not. Adherence to guidelines appeared to be lower when treating the sickest patients (FC IV) than those with less severe PAH (FC II and III), as decisions could be influenced by the presence of comorbidities or other factors indicating that the patient is not a candidate for parenteral treatment. Adherence appeared to increase over time when physicians were making decisions for their FC II and III patients. This is possibly due to the incorporation of the Fifth WSPH guidelines (from December 2013), which provided updated guidance on tadalafil use and additional treatment options, and may reflect the lag between the adoption of these treatment options in clinical practice versus the time taken to update the guidelines.[4,6] For FC III patients, physicians most commonly indicated that their current treatment was appropriate, based on results of 6MWD, echocardiogram, or hemodynamic parameters that suggested PAH was more stable than indicated by FC. These findings highlight the importance of a multiparametric approach to risk assessment as best practice in PAH management.[1,2]

Before the PAH-QuERI Extension Program, little was known about treatment guidelines' nonadherence. The most frequent reason in the FC IV group was patient refusal. Our study did not capture the specific reasons for patient refusal of parenteral therapy or physician engagement in discussions about treatment. Understanding these reasons will be important for overcoming this

FIGURE 1 Example of a Level I and Level 2 reminder applicable to any patient. The scenario shown is for NYHA/WHO FC IV patients (a–c). (a) Step 1, Level 1 reminder: PAH treatment algorithm shown. (b) Step 2, Level 1 reminder: list of medications shown to reconsider the PAH recommended treatment. (c) Step 3, Level 2 reminder: shown if no changes were made following the Level 1 reminder. This Level 2 reminder asks for a reason why recommendations were not followed. As the scenario shows for NYHA/WHO FC IV (see panel b), ambrisentan was selected for NYHA/WHO FC IV; since intravenous epoprostenol was not selected, physicians were to indicate the reason(s) for not following the recommended guidelines. (d) Most common physician-cited reasons at baseline for diverging from practice guidelines by not prescribing the recommended treatment to PAH patients in NYHA/WHO FC II, NYHA/WHO FC III, and NYHA/WHO FC IV. APAH, associated pulmonary arterial hypertension; BAS, balloon atrial septostomy; CCB, calcium channel blocker; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; ERA, endothelin receptor antagonist; FDA, US Food and Drug Administration; IPAH, idiopathic pulmonary arterial hypertension; i.v., intravenous; NYHA/WHO FC, New York Heart Association/World Health Organization functional class; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; s.c., subcutaneous; sGCS, soluble guanylate cyclase stimulator.

barrier through patient education, enhanced physician–patient communication, and identifying ways to ease the burden of parenteral therapy on patients. Optimizing physician–patient communication and shared decision-making are paramount because taking parenteral therapy for PAH is a complex and life-altering decision. Beyond patient choice, reasons for physician nonadherence to PAH guidelines include clinical judgment guided by patient assessments and comorbidities,[11] lack of resources, and cost constraints.[12]

The limitations of our study include basing treatment recommendations on NYHA/WHO FC, which has wide interobserver variability[13] and may not be indicative of PAH severity.[14] Other risk calculators, including REVEAL and COMPERA, may support informed treatment decisions and earlier recognition of disease progression, but the use of these tools is low in clinical practice.[15] Another limitation is that the findings only relate to the healthcare provision of the participating US centers and may not be relevant to or reflect other healthcare systems.

Most physicians in the PAH-QuERI Extension Program followed PAH guidelines for FC II and III patients, with lower adherence for FC IV patients. Parenteral prostacyclin pathway agents are underutilized in FC IV patients. Patient refusal was the most common reason driving a physician's decision not to use parenteral prostacyclin analogs; physicians therefore need strategies to overcome patients' hesitancy regarding treatments that optimize their outcomes.

AUTHOR CONTRIBUTIONS

Concept and design: Vallerie V. McLaughlin, Ronald J. Oudiz, and Mona Selej. *Acquisition, analysis, or interpretation of data*: Vallerie V. McLaughlin, Richard N. Channick, Karimah S. Bell Lynum, Ronald J. Oudiz, Mona Selej, Victor F. Tapson, and Lewis J. Rubin. *Drafting of the manuscript*: Vallerie V. McLaughlin, Ronald J. Oudiz, and Karimah S. Bell Lynum. *Administrative, technical, or material support*: Karimah S. Bell Lynum and Mona Selej.

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CONFLICTS OF INTEREST

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Vallerie V. McLaughlin has served as a consultant for Janssen Pharmaceutical Companies of Johnson & Johnson, Acceleron Pharma, Altavant, Arena Pharmaceuticals, Bayer, Caremark, CiVi Biopharma, Gossamer Bio, and United Therapeutics, and has received research funding from Acceleron Pharma, Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer, Reata Pharmaceuticals, SoniVie, and United Therapeutics. Richard N. Channick has received research grants from Actelion Pharmaceuticals US, Inc., and Bayer Corporation, and is a consultant to Actelion Pharmaceuticals US, Inc., Bayer Corporation, ZappRx, Inc., and ThirdPole. Karimah S. Bell Lynum and Mona Selej are employees of Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson. Ronald J. Oudiz has received grants and personal fees from Actelion Pharmaceuticals US, Inc., Bayer Corporation, Gilead Sciences, Inc., Lung Biotechnology PBC, and United Therapeutics, and grants from Ikaria, Inc., Janssen Pharmaceuticals, Inc., Pfizer, Inc., and Reata Pharmaceuticals, Inc. Victor F. Tapson is a consultant for Bayer Corporation, Actelion Pharmaceuticals US, Inc., Gilead Sciences, Inc., and United Therapeutics Corporation. Payment for speaking engagements (Actelion Pharmaceuticals US, Inc., Bayer Corporation) has been paid to Cedars-Sinai Medical Center. Cedars-Sinai Medical Center has received research funding from Actelion Pharmaceuticals US, Inc., Arena Pharmaceuticals, Bayer Corporation, and Reata Pharmaceuticals, Inc. Lewis J. Rubin reports receipt of personal fees (outside of the submitted work) from Actelion Pharmaceuticals US, Inc., Arena Pharmaceuticals, Karos Pharmaceuticals, SoniVie Ltd, Gilead Sciences, Inc., Pfizer, Inc., and MannKind Corporation.

DATA AVAILABILITY STATEMENT

Due to the sensitive nature of the questions asked in this study, survey respondents were assured that raw data would remain confidential and would not be shared.

ETHICS STATEMENT

The study protocol was approved by the Western Institutional Review Board (study number 1123636) and was conducted in accordance with the Declaration of Helsinki, Good Pharmacoepidemiology Practices, and the International Conference on Harmonisation Good

Clinical Practice (ICH E6). Patients provided written informed consent.

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