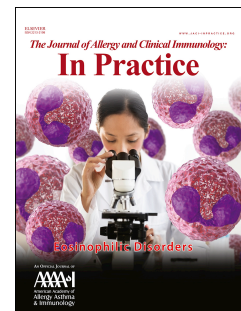


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Nebulizer Use by Black and Latinx Adults with Moderate to Severe Asthma

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Nebulizer Use by Black and Latinx Adults with Moderate to Severe Asthma INPRACTICE-D-21-00976 R1

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Conflicts of Interest

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Word Counts

Abstract: 235 words

Text: 3613 words

99 **Abstract**

100 **Background:** Generally, short-acting beta₂-agonist (SABA) delivered via metered dose
101 inhaler (MDI) is recommended for quick relief of asthma symptoms. However, in the
102 PeRson EmPowered Asthma RELief (PREPARE) pragmatic trial, 67% reported having
103 used a nebulizer for SABA administration.

104 **Objective:** To understand preferences, experiences, and decision-making regarding the
105 use of nebulizers in Black and Latinx adults with uncontrolled asthma.

106 **Methods:** We interviewed 40 of the 1201 PREPARE patients employing a matrix
107 analysis. Those interviewed were Black (n=20) and Latinx (n=20) adults with
108 uncontrolled asthma seeking primary or specialty care in clinics throughout the United
109 States. Data were analyzed using a Rapid Assessment Procedures (RAP) qualitative
110 methodology, informed by grounded theory.

111 **Results:** Sub-study participants, on average, reported using a nebulizer 3.5
112 times/week. Daily use was common, and frequency ranged from less than daily to up to
113 six times daily. Nearly all participants reported a longstanding history of nebulizer use.
114 Participants tended to use their nebulizer at home, and some shared it with others in the
115 home. Many reported preferring a nebulizer over an MDI for relief of severe symptoms
116 and to avoid ER visits or hospitalizations. The extent to which cost affected nebulizer
117 use varied among participants.

118 **Conclusion:** Despite asthma guideline recommendations that MDIs be used rather
119 than nebulizers for SABA administration, nebulizer use was common among PREPARE
120 study participants. Clinicians should explore patients' history and experiences with
121 nebulizer use as part of evaluation of asthma control.

Highlights Box

What is already known about this topic? Asthma guidelines recommend a metered-dose inhaler (MDI) rather than a nebulizer for short-acting beta₂-agonist (SABA) administration, except in the setting of severe asthma exacerbation. However, the real-world use of nebulizers may differ from guidelines.

What does this article add to our knowledge? This study adds to our understanding of the history, experiences, and preferences regarding the use of nebulizers in Black and Latinx adults with uncontrolled asthma.

How does this study impact current management guidelines? In order to adequately address asthma control and ensure that patients receive the most appropriate drug regimen, clinicians should routinely explore patients' use of nebulizers.

Key Words

Asthma
Nebulizer
Metered-dose inhaler
MDI
Rescue inhaler
SABA
Black adults
Latinx adults
Uncontrolled asthma

Abbreviations

ACT: Asthma Control Test
AIDS: Acquired Immunodeficiency Syndrome
ASUI: Asthma Symptom Utility Index
CDC HRQOL-4: Healthy Days Core Module
COPD: chronic obstructive pulmonary disease
COREQ: Consolidated Criteria for Reporting Qualitative Studies
HIV: Human Immunodeficiency Virus
ICS: inhaled corticosteroid
IRB: Institutional Review Board
LABA: long-acting beta₂-agonist
LAMA: long-acting muscarinic antagonist
LTRA: leukotriene receptor antagonist
MDI: metered-dose inhaler
PCORI: Patient-Centered Outcomes Research Institute
PREPARE: PeRson EmPowered Asthma RELief
RAP: Rapid Assessment Procedures
SABA: short-acting beta₂-agonist
SAMA: short-acting muscarinic antagonist
SD: standard deviation
US: United States

Introduction

Short-acting beta₂-agonists (SABAs), such as albuterol, are often used for quick relief of asthma symptoms. SABAs may be delivered by a metered-dose inhaler (MDI) plus holding chamber or spacer, or a nebulizer. MDIs provide the same or better delivery, are less likely to cause aerosol spread, have fewer adverse effects, and may cost patients less than a nebulizer, depending on insurance coverage.^{1,2} Despite potential advantages of MDIs, we lack understanding of patient preference, experiences, and decision-making about the use of nebulizers versus inhalers for rapid symptom relief.

This gap in understanding became apparent during work on the PeRson EmPowered Asthma RELief (PREPARE) Study, a randomized, open-label, pragmatic study funded by the Patient-Centered Outcomes Research Institute (PCORI).³ In this study, participating adults were randomized to either an additional puff of the inhaled corticosteroid (ICS) beclomethasone (80 mcg/puff) with each as-needed puff of their MDI containing SABA (intervention), or to enhanced usual care (control). If a patient in the intervention group used nebulized SABA, we recommended five puffs of ICS be used with each nebulization. We expected little use of nebulizers yet were surprised to discover that many participants reported owning and using a nebulizer. This prompted us to explore nebulizer usage in our population.

The primary objective of this study is to describe the history, experiences, and preferences regarding nebulizer use among Black and Latinx adults with uncontrolled asthma. The secondary objectives are to understand what types of symptoms and

193 situations prompt nebulizer use, and how nebulizer use compares/contrasts with the
194 use of an MDI, in Black and Latinx adults with asthma. Answers to these questions will
195 help improve our understanding of the experience of people with asthma, support their
196 self-management, and optimize treatment recommendations.

Methods

As mentioned, this is a sub-study of the PREPARE Study,³ which was funded by PCORI (PCS-1504-30283) and received approval from Mass General Brigham Institutional Review Board (IRB). The PREPARE study design and methods have been published previously.³

We report our sub-study methods here per the Consolidated Criteria for Reporting Qualitative Studies (COREQ)⁴ for rigor in qualitative research.

Study design

We used a Rapid Assessment Procedures (RAP) qualitative methodology for our analysis,^{5,6} informed by grounded theory.⁷⁻¹⁰ Rapid qualitative analysis techniques have been used previously in health services research and related fields.^{6,11-13}

Eligibility criteria

To be eligible, individuals had to be enrolled in the PREPARE study. That is, they were 18–75 years of age, self-identified as African American/Black or Hispanic/Latinx, had a history of asthma for at least one year, were prescribed daily ICS therapy and had a baseline Asthma Control Test (ACT) score of ≤ 19 or an asthma exacerbation in the past year. To be eligible for this qualitative sub-study, PREPARE participants were required to 1) be from one of the PREPARE sites that ceded to Mass General Brigham's IRB (12 of the 19 PREPARE sites met this criterion), and 2) have indicated

use of a nebulizer at least once in the past month on both their baseline survey and at least one additional monthly survey.

Participant sampling strategy

The study team mailed letters to 252 participants at 12 participating sites explaining the sub-study and inviting their participation. Of this group, 105 participants, representing 11 of the 12 sites, expressed interest in the study. A study team member contacted interested individuals to schedule a phone call, obtain informed consent, and conduct the interview. The team interviewed the first 40 individuals of the 105 who responded on a first-come-first-served basis. The following targets were pre-defined and achieved, divided equally between intervention and control participants: 20 Black, 10 Latinx English-speaking, and 10 Latinx Spanish-speaking individuals. The pre-defined targets were chosen based on feasibility, cost, and ability to collect sufficient data for the domains of interest.

Informed consent process and patient remuneration

Three study team members (AT, VF, CG) obtained informed consent and conducted interviews. One was bilingual in Spanish and English. All had backgrounds in pulmonary medicine and research and were trained in qualitative interviewing. The study team member called each individual at their scheduled time, obtained verbal informed consent, and conducted the interview. Interviews were conducted from September 2019 through April 2020 and were approximately 30 minutes in duration. Participants received \$25 in remuneration upon completion of the interview.

242

243 Data source/interview domains

244 The data sources used for this sub-study consisted of English and Spanish transcripts
245 from the recorded phone interviews and descriptive data from the baseline survey. The
246 interview domains were: asthma medication use, nebulizer characteristics, nebulizer
247 history and use, rescue inhaler history and use, insurance/copay/medication cost
248 issues, and important events or advice received regarding asthma. The **Online**
249 **Repository Text** shows the interview guide. We tested interview questions with four
250 PREPARE patient partners, two Black (both English-speaking) and two Latinx (one
251 English-speaking and one Spanish-speaking). The patient partners provided feedback
252 on the questions, process, and overall flow of the interview which was used to modify
253 the interview guide and questions.

254

255 Data preparation and management

256 A medical transcription company transcribed all interviews. Transcriptions were
257 completed in May 2020. Professional translation was performed for interviews
258 conducted in Spanish. One team member (VF) reviewed all transcripts to remove any
259 personal information (e.g., name, location) before review by other analysis team
260 members.

261

262 Data analysis

263 We assembled an analysis team with attention to team composition and diversity in
264 several ways: gender, racial and ethnic identities, roles on the PREPARE project,

professional background, and level of experience with qualitative research. Roles on the PREPARE study were: patient partners (AC, WM), research coordinator (AT), co-investigator and expert stakeholder (RC), asthma educator (JRL), pulmonary physician assistant (VF), asthma specialist physicians (AA, JCC, RC, CG), and family physician (JKC). Two team members (AA, JKC) conducted team training to orient the group to overall goals, timeline, work plan, qualitative research, RAP methods, and other project logistics. Next, the team identified and reached a consensus on the critical domains to serve as the basis for understanding participants' nebulizer use: nebulizer characteristics, nebulizer history, reasons for nebulizer use, preferences for nebulizer versus inhaler use, and overall preference. All members of the analysis team were blinded to identifying participant information.

For the data reduction phase, the team prepared summary templates. Two team members read each of the 40 transcripts and designed a summary template for each transcript, noting their findings for the domains mentioned earlier.

When the summary templates were completed, the team chose two participant characteristics, race/ethnicity (Black or Latinx) and primary language (English or Spanish), for the matrix development phase. These characteristics were chosen for two reasons. First, the team felt these characteristics would provide an insightful lens to explore themes and interpretations of the domains of interest. These characteristics are also the focus of other analyses for the PREPARE study. Second, distribution across

these characteristics was balanced, which permitted an analysis of the findings based on these characteristics.

Following other published methods for matrix development,^{5,6} the team prepared matrices and critically appraised the matrices based upon guiding questions for interpretation. Each team member was paired with 1–2 other team members to conduct matrix analyses on sets of ten each of the total sample of 40 transcripts. Then, the entire team met to discuss findings from the matrix analyses and prepare the narrative account of the findings. Throughout the analytic process, and consistent with central practices of grounded hermeneutic research,¹⁴ corroborating and legitimizing findings occurred via inclusion of the patient partners' and clinicians' perspectives as members of the research team. The principles of grounded theory and hermeneutics (i.e., the interpretive process) research that we adopted were that 1) the narrative accounts and experiences of the participants have meaning; 2) meaning is not just verbalized, but expressed in actions, behaviors, and experiences; 3) human behavior is rarely fixed, clear, and unambiguous; and 4) interpretation is necessary to understand human behavior.¹⁴

Data saturation

Saturation was defined in two ways. First, we obtained verbal consensus from the analysis team that we had reached redundancy in the findings. Second, two analysis team members (AA, JKC) reviewed the matrix analysis materials which also indicated

redundancy of themes across all four analysis sub-groups and their associated data sources and matrix documents.

The analysis began in August 2020 and was completed in January 2021.

Results

Patient characteristics

Demographic and health characteristics of the overall PREPARE population and the sub-study participants are described in **Table 1**. The sub-study participants represented 11 of the 19 PREPARE study sites.

Sub-study participants were 50 years old on average, mostly female, primarily residing in the Northeast, and with baseline ACT scores indicating poorly controlled asthma (≤ 19).¹⁸ Sub-study participants reported nebulizer use of about 3–4 times per week at baseline. The majority of participants had multiple chronic conditions (e.g., diabetes, hypertension, obesity). Sixty percent of Black and 80% of Latinx participants reported their general health to be fair or poor.

Of the 1201 participants in the PREPARE study, 61% (n=371) of Black and 72% (n=433) of Latinx participants reported using a nebulizer for quick relief of their asthma symptoms.

Domains

We describe the key themes and findings in each domain.

Nebulizer characteristics

Most participants had a plug-in nebulizer that they kept in a consistent location at home, typically their bedroom. Nearly all participants were able to describe the exact location where they stored their nebulizer. Most left their nebulizer at home when they went out; the few that did take it did so for significant travel or extended time away from home. Only one participant indicated she took it with her to work regularly.

Several participants shared a nebulizer or received nebulizer solution from a family member. For example, one English-speaking Latinx participant (ID 25) stated, “I live in a household full of nine people and eight of us have asthma. So really, you know, we never run out of asthma medication.” The most prominent themes for this domain were that participants 1) consistently described a specific habit and routine for their nebulizer storage and patterns of use, and 2) tended to use their nebulizer at home and some shared it with others in the home.

History of nebulizer use

Nearly all participants reported a longstanding history of nebulizer use. No participant in this sample had used a nebulizer for fewer than two years; most had used one for several years or, in some cases, decades. Many individuals described a history of asthma beginning at a young age and had used nebulizers since childhood or early adult years. Many could recall and describe a specific context, illness experience,

and/or interaction with their physician or medical team associated with nebulizer prescription and subsequent use. Nebulizers were prescribed by allergists, emergency department or hospital physicians, pediatricians, pharmacists, primary care physicians, and pulmonologists. Frequently, the prescription for a nebulizer was related to an attempt to avoid ER visits or hospitalizations. As one Black participant (ID 14) explained, “My asthma was not under control. I needed to have [a nebulizer] at home because I was constantly in the emergency room all the time. So, if you're at home, if you have a nebulizer, at least you can try it at home before you go to the hospital.”

There was variation in the frequency of nebulizer use. Daily use was common, and frequency ranged from less than daily to up to six times daily. As one Black person (ID 5) commented, “When I have [asthma] under control, I don't have to take many [nebulizers]...I could just take it as needed. But when I catch a cold or the pollen [is heavy] or I'm walking or I'm trying to do some activities with the kids, ...then up to 6 times a day...” Most participants acknowledged trying their inhaler first, and then using the nebulizer as second-line or as a “last resort” if inhaler therapy proved ineffective. One Spanish-speaking Latinx participant (ID 33) explained, “When I use the... pump. I see that it doesn't help me much, well, then I go use the machine [nebulizer].” There was some variation in this general pattern in that some individuals, often those who had had a nebulizer since early childhood, reported that they typically used the nebulizer first. A few participants described using a nebulizer without symptom severity or progression, generally because the individual anticipated exposure to triggers known to cause exacerbations in the past, or as prophylaxis before exercise or work. For

example, an English-speaking Latinx person (ID 23) talked about a nebulizer “night cap” to ensure a good night’s sleep.

There was variation among participants in the extent to which cost affected their nebulizer use. Some participants reported that price was problematic for all of their asthma medications, including their nebulizer solution, and that copays were significant and burdensome. One Black participant (ID 11) reported a \$35 copay for inhaler refills, stating “If I don’t have the money, they don’t give it to me.” Some patients that shared nebulizers with family members mentioned cost of drugs as a reason. But, generally speaking, nebulizer medication tended to be less expensive. Some participants stated that their nebulizer medication was fully covered by their insurance or available at no cost via other means (i.e., a charity program).

Participants frequently described having reasonably large quantities of nebulizer medication dispensed at a time. Consequently, they required less frequent refills of the nebulizer medication, which was convenient, especially if running low on other asthma medications. One patient tried to extend the interval of asthma medications; when asthma worsened due to extending the interval, s/he would use a nebulizer.

For these reasons, participants for whom cost was problematic tended to prefer the nebulizer over the inhaler.

Reasons for nebulizer use

All participants described similar symptoms that led them to use the nebulizer: cough, wheezing, chest tightness, and shortness of breath with difficulty breathing. The severity and progression of these symptoms that resulted in nebulizer use were consistently described and usually indicated significant functional impairment, such as difficulty walking or speaking. Less frequently, a participant would use a nebulizer in anticipation of an exposure such as to an allergen.

While participants understood that both the nebulizer and the inhaler were rescue therapies, most described using the nebulizer as the next step if the inhaler was ineffective. Symptoms that were either refractory to the inhaler or escalating despite use of the inhaler were the predominant scenarios leading to nebulizer use.

Another theme described under this domain was the use of nebulizers to prevent emergency department visits or hospitalization. As described previously, a desire to stay out of the hospital, attempt to manage asthma exacerbations at home, and replicate treatment given in the emergency department or hospital were all frequently mentioned by participants.

Comparison of nebulizer versus inhaler

Participants noted several advantages and disadvantages for both nebulizer and inhaler use.

Setting and convenience were mentioned as factors. As nebulizers were infrequently taken outside of the home, participants would more commonly use their nebulizer while at home and the inhaler outside the home.

Most participants felt that the nebulizer was more effective than the inhaler. For example, one Black participant (ID 16) stated that nebulizer medication was “more powerful”, “stronger” medicine, which “goes deeper” and “settles in the lungs” compared to the inhaler. Another Spanish-speaking Latinx individual (ID 33) remarked, “The nebulizer changes the outcome [...] because it's like I feel that it goes further in. Cause I breathe deeply and it's more than just two pumps”. While opinions were mixed as to whether the time to onset of relief of symptoms was faster for the nebulizer versus the inhaler, most felt that relief of symptoms was more complete and longer lasting with the nebulizer compared to the inhaler. Several participants mentioned the unpleasant side effects of feeling anxious and jittery, both as indications that the nebulizer medication was more potent, and as reasons why they limited the nebulizer use to only severe or escalating symptoms.

Overall preference

Overall preference for the nebulizer versus inhalers was not always explicitly stated. When symptoms were severe, progressive, and refractory to other asthma medications, nearly all participants preferred the nebulizer. The general preference for the nebulizer was that it worked faster, provided more complete and long-lasting relief, and in some cases was less expensive and in more ready supply. Those who preferred the inhaler

stated that it was effective for milder symptoms, had quick onset, was convenient (i.e., portable and easier to administer, especially when outside the home), and did not have the adverse effects of the nebulizer.

Similarities and differences based on patient characteristics

In examining our matrices by the pre-determined patient characteristics of interest (race/ethnicity, Black vs Latinx; and language spoken, Spanish vs English), we found that the overall results for the key domains were more similar than different. The few differences noted, and infrequently so, were that two Spanish-speaking Latinx participants mentioned using the nebulizer prophylactically; this finding was not observed with the other groups. Secondly, Latinx participants tended to comment more universally that the nebulizer was lower-cost and more convenient. While this was also expressed among Black participants, views about cost and convenience were more variable.

Impact of COVID-19 on Nebulizer Use

Due to the timing of this study relative to the onset of the COVID pandemic, our interview guide was not designed to elicit COVID-specific discussion and did not contain any COVID-specific questions. We reviewed the transcripts of interviews that were conducted in March and April 2020 and did not identify any spontaneous COVID-related discussion among participants.

Discussion

This qualitative study found that many patients use nebulizers to control refractory symptoms. Approximately 70% of the overall PREPARE cohort owns a nebulizer. Most of our sub-study participants had had nebulizers for many years. Some patients revealed that they use nebulizers intermittently and may receive prescriptions from various clinicians and health care systems. Considering the long duration of nebulizer use for many participants, the possibility that a different clinician may have prescribed a nebulizer, and the practice of sharing nebulizer solutions, it is possible that use of a nebulizer may not always be known to patients' current clinicians. Patients may not think to discuss their use with their current clinician, and clinicians may not consider asking about it. Findings from this study suggest that it is essential for clinicians to ask about the history, frequency, and context of nebulizer use to get a clear picture of the patient's asthma control. Further, many of our participants characterized their general health to be poor, placing them at a higher potential risk for COVID-19–related complications. While asthma exacerbations decreased during the COVID-19 pandemic,²¹ nebulization has been identified as a high-risk activity due to the generation of respiratory droplets and airborne particles. Thus, considering the frequent use of nebulizers in this population, it would be important to warn patients that nebulization may increase the risk of COVID-19 spread to those in their immediate area.

Many patients described side effects from using the nebulizer (e.g., feeling “shaky”). Whether the shakiness is simply an adverse effect or has other clinical significance is not clear and worthy of further study. However, patients uniformly reported that

nebulizers tended to work faster and better than inhalers. Thus, it seemed most patients felt the nebulizer provided some benefit.

We observed considerable variation in participants' reports of costs of their asthma medication, and their level of concern about the costs. Asthma medication costs vary regionally and by insurance coverage, and clinicians may be unaware of the costs of medications or their patients' level of concern about cost. Nebulizer costs can be variable depending on whether covered by Medicare, Medicaid, or commercial insurance. Nebulizer devices are billed as durable medical equipment. Thus, Medicare, Medicaid, and commercial insurance cover the cost of the machine. Some nebulizer solutions can be relatively inexpensive (e.g., albuterol, budesonide, ipratropium, and DuoNeb cost \$15–20 per month's supply); others (e.g., formoterol, arformoterol, glycopyrrolate and revefenacin) cost over \$1000/month and are therefore unaffordable for patients without supplemental plans. Inhalers, on the other hand, are billed through prescription benefits, and may have expensive copays. For patients with Medicare Part D, inhalers (which cost \$300–600 per device) can become unaffordable when reaching the "donut hole", when a 25% copayment is required. Our findings suggest that cost is an issue affecting AA/B and H/L patients' decision-making about asthma medication use to some extent; a recommendation for clinicians is that they be aware of this and consider asking about cost as part of their discussions with patients.

This study's findings should be considered in the context of its limitations and strengths. First, this is a sub-study of a more extensive study with a sample size of 40 participants.

Qualitative research involves relatively small sample sizes to provide a detailed description of patients' thoughts, beliefs, and experiences. The aim of qualitative research is to capture the array of responses, not to count how many of each type. At 40 patient interviews, we had reached saturation; that is, we were no longer seeing new answers to our interview questions. Second, this paper reports on a specific population and it is not clear how these findings apply to other groups of asthmatic patients. Finally, we did not ask about spacer use, which could have affected participants' perceptions of MDI effectiveness compared to nebulizer use.

Strengths of this study include the diversity of the analysis team, robust engagement with several patient partners, use of rigorous and established qualitative methods, and participants from 11 sites in the US including Puerto Rico.

Conclusion

This study adds to our understanding of the real-world use of nebulizers in asthma. In this study, nebulizer use was common, and for many, preferable to MDI therapy. In order to adequately address asthma control and ensure that patients receive the most appropriate drug regimen, clinicians should routinely explore patients' use of nebulizers.

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References

1. Camargo CA, Jr., Rowe BH. Emergency Treatment and Approach to the Patient with Acute Asthma. In: Burks AW, Holgate ST, O'Hehir RE, et al., eds. *Middleton's Allergy Principles and Practice*. 9th ed: Elsevier; 2020:895-896.
2. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev*. 2013;2013(9):Cd000052.
3. Israel E, Cardet JC, Carroll JK, et al. A randomized, open-label, pragmatic study to assess reliever-triggered inhaled corticosteroid in African American/Black and Hispanic/Latinx adults with asthma: design and methods of the PREPARE trial. *Contemporary Clinical Trials*. 2021;101, 106246.
4. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19(6):349-357.
5. Averill JB. Matrix analysis as a complementary analytic strategy in qualitative inquiry. *Qual Health Res*. 2002;12(6):855-866.
6. Beebe J. *Rapid assessment process: an introduction*. Walnut Creek, CA: AltaMira Press; 2001.
7. Glaser BG, Strauss AL. *The discovery of grounded theory; strategies for qualitative research*. Chicago: Aldine Pub. Co.; 1967.
8. Glaser B. *Theoretical sensitivity: Advances in the methodology of grounded theory*. Mill Valley, CA: Sociology Press; 1978.
9. Glaser BG. *Basics of grounded theory analysis: Emergence vs. forcing*. Mill Valley, CA: Sociology Press; 1992.
10. Strauss A, Corbin J. *Basics of qualitative research: Grounded theory procedures and techniques*. Newbury Park, CA: Sage Publications; 1990.
11. Burgess-Allen J, Owen-Smith V. Using mind mapping techniques for rapid qualitative data analysis in public participation processes. *Health Expect*. 2010;13(4):406-415.
12. Neal JW, Neal ZP, VanDyke E, Kornbluh M. Expediting the Analysis of Qualitative Data in Evaluation: A Procedure for the Rapid Identification of Themes From Audio Recordings (RITA). *American Journal of Evaluation*. 2015;36(1):118-132.

13. Taylor B, Henshall C, Kenyon S, Litchfield I, Greenfield S. Can rapid approaches to qualitative analysis deliver timely, valid findings to clinical leaders? A mixed methods study comparing rapid and thematic analysis. *BMJ Open*. 2018;8(10):e019993.
14. Addison RB. Grounded hermeneutic research. In: Crabtree BF, Miller WL, eds. *Doing Qualitative Research*. 2nd ed. Newbury Park, CA Sage Publications, Inc.; 1992:110-124.
15. Fuseini H, Newcomb D. Mechanisms driving gender differences in asthma. *Curr Allergy Asthma Rep*. 2017;17(3):19. doi: 10.1007/s11882-017-0686-1
16. Colombo D, Zagni E, Ferri F, et al. Gender differences in asthma perception and its impact on quality of life: a post hoc analysis of the PROXIMA (Patient Reported Outcomes and Xolair® In the Management of Asthma) study. *Allergy Asthma Clin Immunol*. 2019;15:65. doi: 10.1186/s13223-019-0380-z. eCollection 2019.
17. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: A survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65. doi:10.1016/j.jaci.2003.09.008
18. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Accessed February 14, 2021. www.ginasthma.org
19. Revicki DA, Kline Leidy N, Brennan-Diemer F, Sorensen S, Togias A. Integrating Patient Preferences Into Health Outcomes Assessment. *Chest*. 1998;114(4):998-1007. doi:10.1378/chest.114.4.998
20. Health-Related Quality of Life (HRQOL). CDC HRQOL-14 “Healthy Days Measure.” Published October 31, 2018. Accessed March 11, 2021. https://www.cdc.gov/hrqol/hrqol14_measure.htm
21. Salciccioli JD, She L, Tulchinsky A, Rockhold F, Cardet JC, Israel E. Effect of COVID-19 on asthma exacerbation. *J Allergy Clin Immunol Pract*. 2021;9(7):2896-2899.e1. doi:10.1016/j.jaip.2021.04.038.

Table 1. Participant Characteristics

Characteristic	Nebulizer Substudy (N=40)		PREPARE Population (N=1201)	
	African American/ Black (n=20)	Hispanic/ Latinx (n=20)	African American/ Black (n=603)	Hispanic/ Latinx (n=598)
Age (yrs), mean (SD)	49.8 (12.6)	50.4 (11.6)	48.6 (13.4)	47.7 (14.0)
Sex reported at birth, n (%) ^a				
Female	19 (95%)	16 (80%)	508 (84%)	497 (83%)
Male	1 (5%)	4 (20%)	95 (16%)	101 (17%)
Language, n (%)				
English	20 (100%)	10 (50%)	603 (100%)	331 (55%)
Spanish	0 (0%)	10 (50%)	0 (0%)	267 (45%)
Region, n (%)				
Northeast	9 (45%)	11 (55%)	185 (31%)	301 (50%)
Ohio Valley Central	5 (25%)	1 (5%)	128 (21%)	45 (8%)
Puerto Rico	0 (0%)	4 (20%)	0 (0%)	102 (17%)
Southeast	6 (30%)	4 (20%)	290 (48%)	80 (13%)
Southwest	0 (0%)	0 (0%)	0 (0%)	70 (12%)
Age at asthma diagnosis (years), n (%)				
<5	7 (35%)	6 (30%)	132 (25%)	156 (27%)
5–12	1 (5%)	3 (15%)	101 (19%)	111 (20%)
13–18	1 (5%)	2 (10%)	46 (9%)	58 (10%)
19–40	7 (35%)	4 (20%)	152 (29%)	167 (29%)
41–60	3 (15%)	5 (25%)	84 (16%)	73 (13%)
>60	1 (5%)	0 (0%)	12 (2%)	4 (<1%)
Missing	0	0	76	29
Baseline asthma medication use, n (%)				
Short-acting bronchodilator rescue inhaler (SABA, SAMA, SABA/SAMA)	20 (100%)	20 (100%)	603 (100%)	598 (100%)
Inhaled corticosteroid (ICS) ^b	9 (45%)	6 (30%)	218 (36%)	235 (39%)
ICS/LABA ^b	13 (65%)	15 (75%)	430 (71%)	429 (72%)
Long-acting bronchodilator (LABA, LAMA, LAMA/LABA)	6 (30%)	2 (10%)	61 (10%)	88 (15%)
Leukotriene receptor antagonist (LTRA)	13 (65%)	15 (75%)	282 (47%)	316 (53%)
Biologic	1 (5%)	2 (10%)	11 (2%)	25 (4%)
Ever use of a nebulizer for shortness of breath or for SABA administration, n (%)	20 (100%)	20 (100%)	371 (61%)	433 (72%)
Baseline reported frequency of nebulizer use per week, mean (SD)	3.7 (5.1)	3.4 (4.0)	3.0 (5.1)	2.7 (4.3)

Baseline reported frequency of nebulizer use per week by category, n (%)				
0	4 (20%)	5 (25%)	124 (33%)	138 (32%)
1–2	8 (40%)	8 (40%)	140 (38%)	167 (39%)
3–4	4 (20%)	1 (5%)	46 (12%)	47 (11%)
≥5	4 (20%)	6 (30%)	62 (17%)	81 (19%)
Missing	0	0	231	165
Baseline ACT ^c score, mean (SD)	14.6 (3.6)	13.1 (4.4)	15.0 (4.4)	14.3 (4.5)
Baseline ASUI ^d score, mean (SD)	0.69 (0.17)	0.55 (0.24)	0.68 (0.21)	0.65 (0.22)
Baseline history of asthma hospitalization in past year, n (%)				
0	18 (90%)	10 (50%)	496 (82%)	476 (80%)
1	0 (0%)	7 (35%)	63 (10%)	69 (12%)
2	0 (0%)	1 (5%)	23 (4%)	27 (5%)
3+	2 (10%)	2 (10%)	21 (3%)	26 (4%)
Baseline history of corticosteroid bursts in the past year, n (%)				
0	5 (25%)	1 (5%)	226 (37%)	211 (35%)
1	7 (35%)	10 (50%)	159 (26%)	169 (28%)
2	3 (15%)	2 (10%)	102 (17%)	80 (13%)
3+	5 (25%)	7 (35%)	116 (19%)	138 (23%)
Baseline number of comorbidities ^e , n (%)				
0	4 (20%)	7 (35%)	151 (25%)	206 (35%)
1	3 (15%)	3 (15%)	148 (25%)	128 (21%)
2	5 (25%)	3 (15%)	155 (26%)	97 (16%)
3	3 (15%)	6 (30%)	75 (12%)	92 (15%)
4+	5 (25%)	1 (5%)	74 (12%)	75 (13%)
General health (CDC HRQOL-4) ^f , n (%)				
Excellent	1 (5%)	2 (10%)	13 (2%)	9 (2%)
Very Good	0 (0%)	1 (5%)	54 (9%)	74 (12%)
Good	7 (35%)	1 (5%)	216 (36%)	178 (30%)
Fair	9 (45%)	12 (60%)	261 (43%)	268 (45%)
Poor	3 (15%)	4 (20%)	59 (10%)	69 (12%)
Days per month physical health not good, mean (SD)	11.4 (12.3)	12.5 (11.5)	10.0 (10.6)	11.7 (10.6)
Days per month mental health not good, mean (SD)	7.6 (9.0)	10.3 (11.0)	7.4 (10.1)	9.2 (10.3)

^a Gender disparities in asthma prevalence¹⁵ and perceptions of asthma control¹⁶ may have influenced recruitment for prepare, and thus this substudy, resulting in greater enrollment of women than men.

^b The Asthma Control Test (ACT) is a patient self-administered tool for assessing level of asthma control.¹⁷ The ACT is a validated, 5-item questionnaire that assesses asthma symptoms, rescue medication use, daily functioning, and overall perception of asthma control, with a 4-week recall. Scores on each item range from 1 to 5 and the total score

669 ranges from 5 to 25. ACT scores of 20-25 are classified as well-controlled asthma; 16-19 as not well-controlled; and
670 5-15 as very poorly controlled.¹⁸

671 ^c The Asthma Symptom Utility Index (ASUI), which assesses preference-based quality of life, is a validated, 10-item
672 questionnaire designed to assess four asthma symptoms (cough, wheeze, dyspnea, and nocturnal awakening) and
673 side effects from asthma medications over a 2-week recall period. The frequency and severity of each item are
674 assessed on a 4-point Likert scale. The items are then weighted according to patient preferences, and the summary
675 score is a continuous scale ranging from 0 (worst possible symptoms) to 1 (no symptoms).¹⁹

676 ^d Some participants were taking both ICS and ICS/LABA.

677 ^e Comorbidities included heart disease, cancer, stroke, diabetes, chronic kidney disease, chronic obstructive
678 pulmonary disease (COPD), Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS),
679 and hypertension.

680 ^f General health was assessed using question 1 from the Healthy Days Core Module (CDC HRQOL-4).²⁰