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Reply

From the Authors:

We appreciate the important data presented by Dr. Hawley and colleagues regarding occupational exposure to carbon monoxide (CO) in a number of work settings, including coffee processing facilities. As highlighted by Hawley and colleagues, CO is the most frequent cause of acute chemical exposure fatality in the workplace, and although there are myriad sources of CO, the most common exposure is from motor vehicles (1). Generators are also a very common cause of CO poisoning in the occupational setting, accounting for 13% of occupational CO-related deaths from 1992 to 2008 in one study (1–3). Of note, generators, along with gas grills and heaters operated inappropriately indoors, are the main contributors to the increase in CO poisoning during storm-related and natural disaster-related power outages (3).

Fire is one of the most common sources for CO, and perhaps the most lethal (2, 4). In one study looking at risk factors for acute mortality, more than half of CO deaths occurred from a fire source of CO (4). The National Fire Protection Association reports that in 2015, there were 1,345,000 fires reported in the United States, causing 15,700 civilian injuries and 3,280 deaths (5). Inhalational injury occurs concomitantly in more than two-thirds of lethal cases (2).

Almost 15,000 individuals suffer CO poisoning intentionally each year. Between 1999 and 2014, more than 70% of CO related deaths were from intentional versus unintentional poisonings (6). Intentional CO poisoning deaths declined in the past decade, thought to be partially a result of improving regulations for vehicle CO emissions (6), which make it more difficult to asphyxiate in a sealed environment with a motor vehicle running. More than 25% of occupational fatalities from non-fire-related CO poisoning from 1992 to 2008 were a result of intentional poisoning (1).

Education and prevention efforts are critical to controlling CO exposure (1–3). The catalytic converter has reduced CO emissions

by automobiles by 75% since 1975, which has reduced unintentional motor vehicle-related CO death rates by more than 80% (2). Although there have been multiple public campaigns and regulatory measures to increase the placement of CO alarms, there has been no study demonstrating the efficacy of CO alarms to reduce the morbidity or mortality of CO poisoning (2). Although preventing CO exposure is of critical importance, after exposure there remains no quickly administered, widely available, portable antidote for CO poisoning available (2).

For severe cases, in addition to hyperbaric oxygen therapy, discussed in detail in our review, aggressive interventions have been tested in humans, such as extracorporeal membrane oxygenation (2, 7). An ideal treatment would be a portable, quickly administered antidotal agent that could be given immediately at the site of rescue or at the emergency department (2). Roderique and colleagues have presented work in which intravenous hydroxycobalamin can increase the clearance of CO from the bloodstream (2, 8). Our group recently demonstrated a mutationally engineered recombinant neuroglobin molecule that binds to CO avidly, scavenging CO from hemoglobin (2, 9). CO scavenging may have applicability in very severe CO poisoning exposures, as recombinant neuroglobin infusion improved survival significantly by reversing hemodynamic collapse in a lethal model of severe poisoning in mice (2, 9).

The many known and new emerging sources of CO exposure, such as coffee processing facilities, demonstrate the global burden of CO poisoning. Despite increasing safety regulations and public awareness, more than 1,200 individuals die each year from CO poisoning of any source in the United States alone (6). ■

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FULFIL an Unmet Need in Chronic Obstructive Pulmonary Disease

To the Editor:

We read with interest the recent data from the FULFIL (Lung Function and Quality of Life Assessment in COPD with Closed Triple Therapy) trial, which showed that for both coprimary end points, triple therapy consisting of inhaled corticosteroid (ICS) with long-acting β -agonist (LABA) and long-acting muscarinic antagonist (LAMA) was superior to twice-daily dual therapy (ICS/LABA) after 24 weeks in patients with chronic obstructive pulmonary disease (1), confirming the known benefits of dual versus single long-acting bronchodilator therapy (2). It was nonetheless impressive that for trough FEV₁ at 24 weeks, the mean difference of 171 ml was not only statistically significant but also exceeded the minimal clinical important difference of 100 ml (3), suggesting that the impact of single-inhaler triple therapy was clinically relevant. However, the same was not true for the St. George's Respiratory Questionnaire score, where the mean difference of 2.2, while statistically significant, was less than the minimal clinical important difference of 4.0. Nonetheless, a 35% significant reduction in exacerbations was observed at the same time point. A real-life observational study with time-dependent analysis in 2,853 patients with chronic obstructive pulmonary disease over 4.65 years showed a 29% significant reduction in exacerbations requiring oral corticosteroids and 15% significantly fewer hospital admissions conferred by administering once-daily tiotropium in addition to twice-daily ICS/LABA as separate inhalers (4). Moreover, such triple therapy was associated with a significant reduction (35%) in all-cause mortality. The question remains as to whether equally impressive differences would be seen when comparing single inhalers containing ICS/LABA/LAMA and LABA/LAMA, particularly considering that LABA/LAMA has been shown to be superior to ICS/LABA (5). This will be important to know because combinations containing ICS are more likely to be associated with pneumonia, and this is especially true for combinations including fluticasone furoate, which has prolonged lung retention (6). ■

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Triple Therapy in Chronic Obstructive Pulmonary Disease

To the Editor:

In an article by Lipson and colleagues published in the *Journal* (1), the authors state that the TRILOGY study (2) showed that triple therapy with beclomethasone dipropionate (BDP)/formoterol fumarate (FF)/glycopyrronium bromide compared with BDP/FF “had a modest benefit with a reduction in exacerbations and an improvement in health-related quality of life; however, this appeared to wane as the study continued.” Furthermore, they stated that “in FULFIL, the benefits of [fluticasone furoate/umeclidinium/vilanterol] over [budesonide/formoterol] seem substantially greater and more persistent than those seen in the comparison of beclomethasone dipropionate/formoterol/glycopyrronium bromide with beclomethasone dipropionate/formoterol [2]” (1).

In our opinion, comparisons between the FULFIL (Lung Function and Quality of Life Assessment in COPD with Closed Triple Therapy) and TRILOGY studies are inappropriate owing to relevant differences in the enrolled populations and study designs. There are three important differences between the patient populations:

First, patients in the TRILOGY study were required to have FEV₁ < 50% predicted, whereas in the FULFIL study, patients with FEV₁ ≥ 50% could be recruited. This resulted in a lower mean FEV₁ predicted at baseline in TRILOGY (36.5% vs. 45.3% in FULFIL).

Second, there were substantial differences between the enrolled populations with regard to the patients' exacerbation history in the year before study entry. All of the TRILOGY patients had

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