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Benzodiazepines Safe in Chronic Obstructive Pulmonary Disease? Don't Hold Your Breath

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Benzodiazepine use in the United States has increased during the last several years, with an estimated 75 million prescriptions being written in 2008 (1), and outpatient clinic visits addressing benzodiazepine use have been increasing annually from 1999 to 2010 (2). Although useful for management of a variety of issues including anxiety and insomnia, clinical guidelines generally discourage long-term benzodiazepine use because of worse outcomes observed in the general population, including increased accidental overdose and suicidality (3, 4),

with worse outcomes seen in those who simultaneously take opioid medications (3). Up to 10% of patients with chronic obstructive pulmonary disease (COPD) are prescribed benzodiazepines (2), the use of which has been associated with higher rates of respiratory failure among those with COPD (5). As such, the medication class is often reserved for dyspnea in end-stage lung disease (6). However, clear evidence on the safety of both short- and long-term use of benzodiazepines in a large population with COPD has not previously been reported. Elucidating the etiology of a potential association between benzodiazepine use and mortality is difficult, given that those who are using benzodiazepines may have worse disease at the outset and may simply be sicker, leading to an increase in mortality, an example of confounding by indication, which occurs when the clinical indication for a treatment or exposure also affects the outcome (7).

In this month's issue of the *AnnalsATS*, Donovan and colleagues (pp. 82–90) address the difficulty of confounding by indication head-on in their retrospective review, using a national Veteran's Health Administration (VA) cohort with COPD and concomitant posttraumatic stress disorder (PTSD) (8). In an attempt to

address the multiple layers of potential confounding that cloud the relationship between benzodiazepine use and worse outcomes in COPD, the authors chose a study population with comorbid COPD and PTSD to examine the risks of long-term benzodiazepine use in a population likely to be using benzodiazepines for nonrespiratory indications.

The study revealed no difference in cause-specific mortality (COPD-related, suicide, or accidental overdose) or all-cause mortality; however, they did uncover an increased risk for death by suicide among those with COPD and PTSD receiving long-term benzodiazepines (≥ 90 days) compared with those without any use. Short-term users (< 90 days) also had increased risk for death by suicide compared with nonusers. Importantly, short-term benzodiazepine users with COPD and PTSD were also found to have an increased risk for all-cause mortality compared with those with either no use or long-term use of benzodiazepines. Combined use of long-term benzodiazepine and opioid medications was associated with increased risk for all-cause mortality and accidental overdose. These findings lead Donovan and colleagues to conclude that as there was no

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significant difference in mortality among long-term users, the long-term use of benzodiazepines does not confer the risk for respiratory compromise previously reported (5, 9); however, short-term users may still be at risk. Further, they note that increased risk for death by suicide associated with benzodiazepine use calls for additional studies.

The study was well-defined and was conducted using a large cohort, and had a multitude of data points for each of the 44,555 people included in the analysis. A rigorous analysis plan used propensity scores to match users and nonusers that accounted for medical and mental health comorbidities and included multiple sensitivity analyses. The results were consistent with previous literature on the risks for short-term benzodiazepine use in the general population (4, 9), and remained consistent after adjusting for covariates. Nonetheless, as the authors noted, this analysis is subject to survival bias, in that long-term use may not show mortality risk because those susceptible may have died during the period of short-term use. In addition, ascertainment and misclassification biases will always exist in retrospective studies, and here influence the diagnoses of COPD (lack of spirometry data) and PTSD, as well as the classification of cause of death; namely, suicide versus accidental overdose.

The population of COPD with comorbid PTSD was chosen with the stated goal of reducing confounding by indication by assuming a nonrespiratory reason for use; however, the indication for medication use (respiratory vs. nonrespiratory) was not reported and may be overlapping. COPD severity based on spirometry was not available, making this distinction more

difficult; thus, it is unclear whether the goal was achieved. Finally, the report of increased suicidality in short- and long-term benzodiazepine use prompts the following questions: What is the mechanism by which benzodiazepines lead to an increased risk for death by suicide? Is it independent of confounding by association with anxiety and depression? Benzodiazepines are commonly involved in drug overdose deaths, and are associated with increased risk for suicide through disinhibition and augmented aggression (4, 10, 11), and these findings are increased among those taking concurrent opioid medications (11). Further studies are needed to better understand the overlap of these disorders and suicidality as an outcome.

The results presented by Donovan and colleagues are notable, yet provoke several residual uncertainties (8). First, the study included VA patients who were 89% white and 96% men. Such a population may have different symptoms, resources, and outcomes from other groups with COPD. Next, exposure to different types of benzodiazepines (i.e., long-acting vs. short-acting) may result in variable outcomes (11); VA patients may be prescribed relatively uniform types of benzodiazepines via the national VA formulary, whereas prescribing practices in the non-VA population may vary according to individual insurance. Further, it is unclear what differences may exist between a VA versus a non-VA population with comorbid COPD and PTSD. Individuals with military-related PTSD may be unique in a variety of factors, which may have influenced study results, and whether these findings translate to a non-PTSD/general COPD population is unknown. Taken together, the generalizability of these results may be questioned.

The article by Donovan and colleagues adds to existing literature on a very important and relevant topic as the U.S. population faces increased mortality rates because of medication-induced accidental overdose in the opioid crisis (3), which can be extended to include benzodiazepine use (8). Benzodiazepines are often found associated with opioid overdose (12), and outpatient clinic visits addressing the concomitant use of both medications are increasing in the United States (13). Although these unfortunate consequences do exist, there are medically indicated uses of benzodiazepines, and these medications play a helpful role in managing anxiety, insomnia, and refractory respiratory symptoms in COPD (6, 14). Therefore, it is imperative to better understand who, specifically, will benefit from this treatment, and who is at risk for adverse harm. Prospective cohorts must be established to collect longitudinal data on COPD, comorbid psychiatric disease, and respiratory symptoms with rigorous data collection of both objective and subjective data points at brief intervals. Confounding is a major concern in this topic, with significant symptom overlap between diagnoses, and strategies such as development of a composite symptom score could be considered to better identify the groups most at risk for mortality and suicidality. These findings, combined with future studies, have the potential to affect clinical practice and influence the prescribing patterns for benzodiazepines in the COPD population. ■

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It's Time to Rehabilitate Pulmonary Rehabilitation

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Chronic obstructive pulmonary disease (COPD) is associated with substantial morbidity. A severe exacerbation necessitating hospitalization is a sentinel event in the life course of patients with COPD. Each exacerbation is followed by a prolonged period of pulmonary and systemic inflammation, worsened symptoms, functional limitation, skeletal muscle dysfunction, frailty, and debility. In the long run, these severe exacerbations are associated with a greater decline in lung function, and the 2-year survival rate after hospitalization is only 50% (1). Currently available inhaled medications are associated with a modest reduction in exacerbation frequency and an even smaller effect on hospitalizations (2).

Now imagine that a new therapy is brought to the market that results in a significant improvement in respiratory quality of life, with a change in the St. George's Respiratory Questionnaire score of 7 units, a change in the 6-minute walk distance of 44 m, improvement in dyspnea, and a 56% reduction in hospitalizations (3, 4). The therapy is also considerably more cost effective than existing inhaled therapies (5). This therapy would be an immediate blockbuster! Such a therapy, however, already exists, is supported by Medicare, and is recommended by every major respiratory society for patients with COPD. It is the often-underappreciated

cousin of pharmacotherapy, pulmonary rehabilitation (PR). Despite the many established benefits, patients who present with stable COPD but debilitating symptoms are infrequently offered PR. Indeed, it is not uncommon for patients with severe COPD to go a lifetime having never even heard of PR. In a national survey of patients with COPD and a high symptom burden, 57% were not aware of PR (6).

Multiple recent studies underscore the post-hospital discharge vulnerability of patients to decompensation and rehospitalization. To arrest the downward spiral in pulmonary and skeletal muscle function experienced after a severe exacerbation, the initiation of PR is recommended soon after hospital discharge (7). Recent studies have also highlighted the very poor referral rates for PR after hospitalization, with rates as low as 10% (8), and it is not surprising that even fewer patients eventually receive PR.

In a study presented in this issue of *AnnalsATS*, Spitzer and colleagues (pp. 99-106) analyzed 223,832 individuals who had been hospitalized for a COPD exacerbation, using a Medicare administrative claims database in a single calendar year, and determined that only 1.9% received PR within 6 months of hospital discharge (9). This number increased marginally to 2.7% when follow-up was extended to 12 months after hospitalization. The authors found striking disparities in rehabilitation participation by age, sex, race, and socioeconomic status. Those who lived 10

miles or more from a rehabilitation center were considerably less likely to receive PR, and half the patients lived within 5 miles of a rehabilitation provider. Those with prior hospitalizations, and thus the very patients expected to benefit the most, were less likely to receive PR. These sobering data are a stark reminder that we need to do more to improve our abysmal record of referral and enrollment in a therapy with proven benefits.

There are a few limitations to the study that should be considered. First, because of the design of the study and the use of administrative data, it is not possible to determine whether the low participation in PR was due to poor referral rates or the inability or refusal of patients to enroll. Previous studies suggest it is very likely a combination of these factors. Second, by excluding patients who had previously received PR, the authors did not account for those who may not have been referred due to exhaustion of lifetime limits on the number of sessions covered by payers. This,

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