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Benzodiazepine Safety: Mortality Risk or Multiple Chronic Disease Comorbidity?

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Several studies in recent years have suggested increased mortality among patients diagnosed with schizophrenia and treated with benzodiazepines. In this issue, Fontanella et al¹ add to this literature with the first US study of this kind, examining data from more than 18,000 Ohio Medicaid patients diagnosed with schizophrenia who were treated between 2006 and 2013. Patients treated with benzodiazepines without a co-prescribed antipsychotic showed a 3-fold greater risk of dying (hazard ratio [HR] = 3.08), but, curiously, patients treated with benzodiazepines with antipsychotics showed a notably lower risk of about half the magnitude (HR = 1.48). The authors conclude from these data that benzodiazepine use is associated with increased mortality risk in schizophrenia and that “given unproven efficacy, physicians should exercise caution in prescribing benzodiazepines to schizophrenic patients.”^{1(p661)} While they express appropriate methodological restraint in specifying that the observed increase in mortality risk is associational and does not justify causal attribution of mortality risk to benzodiazepines, their conclusion that clinical caution is warranted in the care of patients diagnosed with schizophrenia is reasonable only if one assumes that this association in fact may reflect a causal relationship. If benzodiazepines are not causally involved, no change in the clinical use of these agents is warranted and an alternative explanation of the findings is needed.

While we fully agree that benzodiazepines should be used cautiously and only for sound indications in any population, we think several notable details in the results of this report deserve attention and that it must be viewed in the context of the much broader pharmacologic and clinical literatures on risks associated with benzodiazepines. We particularly think this article deserves further consideration because of what it may reveal about the care of patients with what has been called “multiple chronic conditions” rather than because we have any doubts about the need for caution in the use of benzodiazepines as specific pharmacologic agents, regardless of mortality risks.

It is first of all notable that the authors offer no theoretical explanation for the observed increase in mortality risk. The

absence of a plausible causal mechanism, one of the widely accepted Bradford Hill criteria for causation,² especially important in an observational study, leaves the possibility of a causal relationship difficult to justify. For example, the risk of death presented for benzodiazepines in this article is almost twice that observed for the risk of cardiovascular events (not necessarily involving death) with rofecoxib (1.5% vs 0.78%; relative risk = 1.92, $P < .008$) in a clinical trial,³ an effect that resulted in the removal of rofecoxib from the market and the addition of a boxed warning for another COX-2 inhibitor, celecoxib. The far more urgent response to the cardiovascular risks of COX-2 inhibitors, as compared to that of benzodiazepines, presumably reflects the fact that the risk from COX-2 inhibitors emerged in a long-term randomized clinical trial (RCT) and that a plausible mechanism was available, two additional criteria for causation noted by Hill.² Statistical associations that are identified in observational studies, and in the absence of either RCT data or a plausible causal mechanism, should be regarded with an especially high degree of skepticism.

Polypharmacy might have been a suggested risk mechanism in the study by Fontanella et al,¹ but the fact that the risk of death was greater in patients treated with benzodiazepines alone than it was among patients treated with benzodiazepines in combination with antipsychotics makes this explanation implausible. The hazard ratio for patients treated with both benzodiazepines and antipsychotics (1.48) falls completely outside and below the 95% confidence interval of mortality risk for patients prescribed benzodiazepines without an antipsychotic (2.61–3.61). If polypharmacy was the culprit, one would have expected the opposite relationship, with greater risk among patients prescribed both antipsychotics and benzodiazepines. The authors offer no interpretation of this paradoxical finding, which suggests that some unidentified or unmeasured factor explains the greater risk of mortality with benzodiazepines alone than with benzodiazepines and antipsychotics. Examination of potential risk factors in Table 1 of the article by Fontanella et al¹ reveals no psychiatric or medical comorbidity among patients taking benzodiazepines alone that would help account for the observed differential risk. Most strikingly, patients who were exposed to both benzodiazepine and antipsychotic medications also had far greater exposure to all other classes of psychotropic medication, with 2 to 3 times greater rates of exposure to antidepressants, mood stabilizers, antiparkinsonian agents, and even other hypnotic agents. It is also notable in Table 1 that 26.1% of patients not taking

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J Clin Psychiatry 2016;77(5):e591–e593
dx.doi.org/10.4088/JCP.15com10472

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antipsychotics were prescribed anticholinergics, suggesting that some patients may have received antipsychotics (and perhaps other medications) that were not documented in the Medicaid database.

It is further notable that the risk associated with benzodiazepine use was significant and of similar magnitude regardless of whether the death was accidental, self-inflicted, or due to natural causes including infectious diseases or diseases of the respiratory and digestive systems. Thus, neither psychiatric comorbidities, additional polypharmacies, nor specific causes of death suggest an explanation for the increased risk of death associated with benzodiazepine use among people diagnosed with schizophrenia. In the absence of any such explanation, the association must be treated with considerable scientific caution. In the era of big data, highly publishable associations between risk factors and adverse outcomes can be easily identified, but caution is needed when statistical associations cannot be explained by plausible mechanisms. The 1996 edition of the Goodman and Gilman textbook of pharmacology (the most recent edition available to us) stated that “Even huge doses [of benzodiazepines] are rarely fatal unless other drugs are taken concomitantly.”^{4(p371)}

One might imagine that there is some specific interaction between schizophrenia and the pharmacology of benzodiazepines that produces this increased mortality risk—a risk that is especially high in the absence of antipsychotic drugs. One scenario that can be imagined is that without antipsychotics, patients diagnosed with schizophrenia are far less stable and more vulnerable to the increased impulsivity and reduced behavioral inhibition resulting from benzodiazepine use. However, the lack of even greater risk of death due to suicide or accidental causes detracts from the plausibility of this explanation.

While other studies^{5,6} have also found an increased risk of mortality among patients with schizophrenia treated with benzodiazepines, they also fail to suggest any convincing causal mechanism or any plausible explanation. One study⁵ found a significantly greater risk of suicidal death among patients diagnosed with schizophrenia as compared to other causes, perhaps suggesting some support for the increased impulsivity hypothesis. That study also found the greatest risk to be observed among patients who also received drugs used to treat addictive disorders, perhaps suggesting that severe substance-abuse comorbidity may be the central mediating factor for both mortality risk and suicidality. Another study of patients with schizophrenia⁶ failed to find a statistically significant increase in mortality among patients diagnosed with schizophrenia who used benzodiazepines but did find a greater risk specifically with use of benzodiazepines with long elimination half-lives, although the risk here was associated with death from natural causes and predominantly involved middle-aged patients.

While these recent studies^{1,5,6} focus exclusively on patients with schizophrenia, the study of the association of benzodiazepines with mortality that has received the widest notice in recent years involved over 100,000 patients in 273 primary care practices in the United Kingdom.⁷ This

study found a hazard ratio for mortality associated with benzodiazepines of 3.46 during a follow-up period that averaged 7.6 years and was able to identify dose response associations for 3 different subclasses (benzodiazepines, Z-drugs [zaleplon, zolpidem, and zopiclone], and other hypnotic drugs). Although this study, like all of the studies cited above, found increased comorbidity with sedative hypnotic use, including smoking, cancer, respiratory disorders, and other psychiatric disorders, it controlled for these factors in multivariate analyses. Of particular note is that the increased risk persisted even for patients who stopped taking sedative hypnotics after no more than 1 year of use, and the authors suggest that such comorbidities may have acted as “classic confounders,” ie, the cause of death may have been a comorbidity rather than the sedatives.

Some studies of mortality associated with benzodiazepine dependence⁸ have also suggested that they key element associated with increased mortality is comorbid addictive or psychiatric disorder rather than excessive use of benzodiazepines itself. Similarly, studies of poor outcomes among patients in methadone maintenance treatment who use benzodiazepines^{9–11} suggest that it is greater severity of addiction rather than the benzodiazepines that result in poorer outcomes. Finally, a review¹² of 6 studies of benzodiazepine-related mortality found mixed results, with some evidence that mortality may be associated with being elderly.

Taken together, these studies all point to the central importance of multimorbidity as a key factor in mortality associated with benzodiazepine use. They are thus consistent with a burgeoning literature on patients with multiple chronic conditions.^{13,14} This literature points out that patients with a single acute or even a single chronic condition are increasingly a rarity and that the typical patient presenting for care in the 21st century has multiple chronic conditions, each complicating the presentation and optimal treatment of the others. Not uncommonly, it has been observed, one of these comorbid conditions is a psychiatric or addictive disorder.¹⁵ While there has been extensive attention paid to the special challenges of treating the dually diagnosed patient with both mental health and addiction problems in psychiatry, studies increasingly draw attention to the multiplicity of medical and psychiatric illnesses that complicate mental health care.^{16,17} With these diverse considerations in mind, we suggest that studies on benzodiazepine risk in schizophrenia may point more strongly to the risks imposed by multiple comorbidities, as well as by multiple pharmacotherapies, than to a specific risk of benzodiazepines in the treatment of schizophrenia. Clinical practice increasingly requires broad peripheral vision and demands an orchestral perspective rather than that of a solo specialist.

Submitted: October 19, 2015; accepted October 21, 2015.

Potential conflicts of interest: None reported.

Funding/support: None reported.

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