The Benzodiazepine Stigma Persists

To the Editor: I read with interest the article "Benzodiazepine Use and Driving: A Meta-Analysis," by Rapoport et al.[1] This is a well-written, comprehensive review of the literature regarding the association between the acute use of benzodiazepines and motor vehicle accidents and driving ability. In the conclusion section, however, the authors made recommendations that are overreaching, stigmatizing, and not consistent with public policy in the United States. They stated, "Given the large numbers of drivers prescribed benzodiazepines, and the significant increase in MVC

[motor vehicle collision] risk found in this meta-analysis..., calls to limit prescriptions for benzodiazepines…are warranted."[1(p671)]

Limiting the prescription of a certain class of medication or making "legislative changes…to better deal with drivers under the influence of drugs such as benzodiazepines,"[1(p671)] which, later in the article, the authors stated may be required, would dramatically change the landscape regarding how driving is regulated in the United States. It would be difficult to imagine what limiting prescriptions for substances on a legislative level would look like.

The laws in the United States vary by state but impose penalties on drivers who operate a motor vehicle while under the influence of alcohol or other substances. (In Massachusetts, the law reads, "…while under the influence of intoxicating liquor, or marijuana, narcotic drugs, depressants, or stimulant substances."[2]) The criteria used to determine impairment are the road safety test administered by the police and/or the police officer's judgment as to whether a driver is operating a vehicle in an impaired manner.

The number of medications that have been associated with impaired driving and an increase in motor vehicle accidents is large and includes mirtazapine, amphetamines, opioids, antihistamines, selective serotonin reuptake inhibitors (SSRIs), nonbenzodiazepine hypnotic agents, oral hypoglycemic agents, all antidepressants, various antipsychotics, and carbamazepine.[3–13] Some of these medications have been associated with impairment in on-the-road driving tests and psychomotor tests in addition to being associated with motor vehicle accidents.

The question that naturally follows is where the line would be drawn regarding which medications would be legislatively regulated and what criteria would be used. This would also apply to whether new medications would meet the threshold for being restricted. The authors noted the high lifetime prevalence of nonprescription use of benzodiazepines among US college students (7.8%) as being a major reason why "clinical approaches will…not be sufficient"[1(p671)] and why legislative changes would be required. However, the lifetime prevalence of nonmedical prescription opioid and stimulant use among US college students was 12% and 6.9%, respectively, in the same study[14,15] the authors cite. Clearly, there is widespread abuse of many prescription drugs in this country. Both stimulants and opioids have been associated with impaired simulated driving and an increase in fatal traffic accidents.[4,5] Thus, the list of medications subject to legislative regulation could be quite large.

It is clear that benzodiazepines can impair driving ability; however, it is not clear that there is a specific dose or serum level associated with impairment. To this author's knowledge, there are no studies looking at this question. In addition, no studies have looked at whether patients who are maintained on long-term benzodiazepine treatment and have developed physiologic tolerance are less likely to show impaired driving ability. Some data indicate that long-term benzodiazepine use (average = 5 years) is not associated with psychomotor impairment.[16]

Data on long-term benzodiazepine use are important, as these agents have been recommended for the long-term treatment of panic disorder[17] and in combination with SSRIs for treatment-refractory panic disorder.[18] In addition, a large prospective, longitudinal study involving 443 patients with panic disorder found that benzodiazepines were the most commonly used psychotropic medication for this condition.[19] The authors were uncertain as to the reason for this, but the robust efficacy of these medications in the treatment of panic disorder in combination with a tolerable side effect profile for most patients may play a large role.[20] Of note, when benzodiazepines are used in the treatment of panic disorder, they maintain their efficacy, and the dosage tends not to increase over long periods of time.[20,21] The use of benzodiazepines in the long-term treatment of panic disorder makes sense on the basis of studies demonstrating reduced γ-aminobutyric $acid_A$–benzodiazepine binding sites in the insular cortex bilaterally in patients with panic disorder.[22] Because of this very important place of benzodiazepines in the treatment of anxiety disorders, panic disorder in particular, we should not be so cavalier about calling for legal restrictions on their use.

Although benzodiazepines and other potentially sedating medications should be prescribed with caution, the call for legislative action and limitations on prescription is not warranted. Rather, enhanced practitioner and patient education regarding the pharmacodynamic and pharmacokinetic effects of all sedating medications is preferable. It is unfortunately all too common for benzodiazepines to be associated with addiction and psychomotor impairment without being given due respect for their impressive efficacy in certain conditions. As described above, this is the case with many other medications: impressive efficacy but high rates of sedation or in other cases addiction and abuse. There are simply too many potentially hazardous drugs available to legislate restrictions on their use in a way that would produce more benefit than harm.

Dr Rapoport was shown this letter and declined to comment.

REFERENCES

1. Rapoport MJ, Lanctot KL, Streiner DL, et al. Benzodiazepines and driving: a meta-analysis. *J Clin Psychiatry.* 2009;70(5):663–673.
2. Mass Gen Laws, ch 90, §24
3. Wingen M, Bothmer J, Langer S, et al. Actual driving performance and psychomotor function in healthy subjects after acute and subchronic treatment with escitalopram, mirtazapine, and placebo: a crossover trial. *J Clin Psychiatry.* 2005;66(4):436–443.
4. Silber BY, Papafotiou K, Croft RJ, et al. The effects of dexamphetamine on simulated driving performance. *Psychopharmacology (Berl).* 2005;179(3):536–543.
5. Drummer OH, Gerostamoulos J, Batziris H, et al. The incidence of drugs in drivers killed in Australian road traffic crashes. *Forensic Sci Int.* 2003;134(2–3):154–162.
6. Gibson JE, Hubbard RB, Smith CJ, et al. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *Am J Epidemiol.* 2009;169(6):761–768.
7. Reidy L, Gennaro W, Steele BW, et al. The incidence of zolpidem use in suspected DUI drivers in Miami-Dade Florida: a comparative study using immunalysis zolpidem ELISA KIT and gas chromatography-mass spectrometry testing. *J Anal Toxicol.* 2008;32(8):688–694.
8. Skurtveit S, Strom H, Skrivarhaug T, et al. Road traffic accident risk in patients with diabetes mellitus receiving blood glucose-lowering drugs. Prospective follow-up study. *Diabet Med.* 2009;26(4):404–408.
9. Bramness JG, Skurtveit S, Neutel CI, et al. Minor increase in risk of road traffic accidents after prescription of antidepressants: a study of population registry data in Norway. *J Clin Psychiatry.* 2008;69(7):1099–1103.
10. Soyka M, Winter C, Kagerer S, et al. Effects of haloperidol and risperidone on psychomotor performance relevant to driving ability in schizophrenic patients compared to healthy controls. *J Psychiatr Res.* 2005;39(1):101–108.
11. Ramaekers G, Lamers J, Verhey F, et al. A comparative study of the effects of carbamazepine and the NMDA receptor antagonist remacemide on road-tracking and car-following performance in actual traffic. *Psychopharmacology (Berl).* 2002;159(2):203–210.
12. Verster JC, Volkerts ER. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann Allergy Asthma Immunol.* 2004;92(3):294–303.
13. Theunissen EL, Vermeeren A, Ramaekers JG. Repeated-dose effects of mequitazine, cetirizine and dexchlorpheniramine on driving and psychomotor performance. *Br J Clin Pharmacol.* 2006;61(1):79–86.
14. McCabe SE, Teter CJ, Boyd CJ, et al. Nonmedical use of prescription opioids among US college students: prevalence and correlates from a national survey. *Addict Behav.* 2005;30(4):789–805.
15. McCabe SE, Knight JR, Teter CJ, et al. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a

national survey. *Addiction.* 2005;100(1):96–106.
16. Lucki I, Rickels K, Geller AM. Chronic use of benzodiazepines and psychomotor and cognitive test performance. *Psychopharmacology (Berl).* 1986;88(4):426–433.
17. Pollack MH, Allgulander C, Bandelow B, et al. WCA recommendations for the long-term treatment of panic disorder. *CNS Spectr.* 2003;8 (8 suppl 1):17–30.
18. Mathew SJ, Coplan JD, Gorman JM. Management of treatment-refractory panic disorder. *Psychopharmacol Bull.* 2001;35(2):97–110.
19. Bruce SE, Vasile RG, Goisman RM, et al. Are benzodiazepines still the medication of choice for patients with panic disorder with or without agoraphobia? *Am J Psychiatry.* 2003;160(8):1432–1438.
20. Pollack MH, Otto MW, Tesar GE, et al. Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol.* 1993;13(4):257–263.
21. Worthington JJ 3rd, Pollack MH, Otto MW, et al. Long-term experience with clonazepam in patients with a primary diagnosis of panic disorder. *Psychopharmacol Bull.* 1998;34(2):199–205.
22. Cameron OG, Huang GC, Nichols T, et al. Reduced gamma-aminobutyric acid(A)-benzodiazepine binding sites in insular cortex of individuals with panic disorder. *Arch Gen Psychiatry.* 2007;64(7):793–800.

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