Potentially Driver-Impairing Medications: Risks and Strategies for Injury Prevention

Abstract: *Impaired driving is a major cause of motor vehicle accidents, injury, and fatality. Several classes of medication have been found to affect a driver's cognition, judgment, and reaction time and may put patients at increased risk for accidents and injury. This article will explore medications with side effects posing a potential threat to drivers, including anxiolytics, sedative hypnotics, antihistamines, and antidepressants, as well as describe potential strategies for mitigating or minimizing such risks.*

Keywords: driver impairment; motor vehicle accidents; benzodiazepines; sedative hypnotics; antihistamines; antidepressants

Background

Driving is an intricate behavior, requiring a precise sequence of physical and cognitive function to be carried out safely. Impaired driving is a major cause of motor vehicle accidents, injury, and fatality. Several classes of medication have been found to affect a driver's cognition, judgment, reaction time, and other essential driving skills and may put patients at increased risk for accidents and injury. In 2008, a study by the United

States Department of Transportation and National Highway Traffic Safety Administration (NHTSA) found that drivers who took potentially driver-impairing medications were 1.2 to 7.5 times more likely to be involved in a motor vehicle accident.¹ In all, there are

These drug classes were selected based on their prevalence in therapy and associated odds ratio for motor vehicle crashes as reported by the NHTSA.¹ It is important to note that many illicit drugs can also impair driving; however, this discussion will cover only those

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90 pharmacological classes of drugs that are considered potentially driver impairing.¹ The impairing effects differ based on the agent's mechanism of action but often fall under one of the following categories: sedation, hypoglycemia, blurred vision, hypotension, syncope, and ataxia. This article will focus on the evidence to date regarding the potentially driver-impairing effects of anxiolytics, antidepressants, sedative hypnotics, and antihistamines.

substances that can be prescribed legally in the United States.

Benzodiazepines (BZDs)

BZDs, although effective in the treatment of anxiety, insomnia, and panic disorders (among others), can have unwanted side effects that are potentially dangerous when driving. Common driver-impairing side effects of BZDs include sedation, dizziness, blurred

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vision, double vision, and weakness.^{2,3} A 2011 meta-analysis found that BZDs were associated with a 60% to 80% increase in the risk of traffic accidents.⁴ The risk seems to be greater when using BZDs with long half-lives and at high doses, and in the initial weeks of BZD therapy.⁵

BZDs with effects (intended and not intended) lasting longer than 9 hours are classified as long half-life BZDs. Commonly prescribed long-half-life BZDs include alprazolam, lorazepam, and diazepam.² Two studies examined the association of long-half-life BZDs with the risk of traffic accidents.^{6,7} The first study found that long, but not short, half-life drugs were associated with increased accident risk in elderly individuals (>65 years of age).⁶ The second study found that new users of long-half-life BZDs were at significantly greater risk of accident responsibility, whereas those on short-acting BZDs displayed accident responsibility risk similar to that of controls.⁷

There seems to be a dose-response relationship between BZDs and motor vehicle accidents, with higher BZD doses conferring greater risk.^{8,9} The duration of BZD use also seems to play a role. In a systematic review of the relationship between BZDs and traffic accidents, the highest risk of accidents occurred within the first weeks of the initial BZD prescription.⁵ The study authors hypothesized that patients were more prone to accidents in the first weeks of therapy because of uncertainty of the drug's effect on driving and the lack of developed tolerance to the medication's effects.

Interestingly, recent laws in other countries have called for restrictions and limitations to BZD use before driving. Sweden and Finland both list BZDs in their zero tolerance laws regulating traffic safety.^{5,10} Although no such restrictions exist in American legislation, there are some precautions that can be taken when prescribing BZDs to ambulatory patients who intend to drive. At minimum, providers should explain the increased risk of driver impairment and emphasize that this risk appears to be greatest in the first weeks of BZD

therapy while patients are getting used to how the medications will affect them. Patients should be encouraged to temporarily cease driving when initiating BZD therapy or titrating doses. Therapy with short half-life BZDs and at the lowest dose possible should also be considered.

Sedative Hypnotics

Sedative hypnotics known for the treatment of insomnia pose a serious threat to the typical driver because of their sedating properties. Patients are often unaware of sedative hypnotics' long half-lives and lasting effects on the central nervous system. Administration of sedative medications in the middle of the night has raised a concern for the driver's performance the following morning. A study by the US Department of Transportation and NHTSA found impairments in coordination, cognition, and reaction time in individuals subjected to a driving test within the first 4 to 5 hours of administration of therapeutic doses of zolpidem.¹¹ No significant effects were seen when driving tests were given 10 to 12 hours after zolpidem administration. Interestingly, findings from a similar study indicated that sublingual forms of zolpidem 3.5 mg and zaleplon, both 10 mg and 20 mg, had no effect on driving performance 4 hours after administration.¹²

Duration of use also seems to play a role. In 2015, a cohort study found an association between the new use of sedative hypnotics and risk of crash.¹³ The peak incidence of crash risk for individuals treated with zolpidem occurred between 31 and 120 days (hazard ratio [HR] = 5.69; 95% confidence interval [CI] = 3.14, 10.29). The risk decreased as the length of exposure increased; however, there was a significant ongoing increased crash risk among zolpidem users after 1 or more years of continuous therapy (HR = 1.76; 95% CI = 1.21, 2.55). The study authors hypothesized that the waning crash risk may be a result of tolerance to the sedative properties of the medications.

As with all potentially driver-impairing prescription medications, providers should counsel patients on crash risk, especially in patients new to sedative hypnotic therapy. In addition, prescribers may want to consider use of shorter-acting agents, such as zaleplon, especially for patients who wish to have a sleep aid that can be administered on waking in the middle of the night. When using zolpidem, patients should be encouraged to devote an entire night to sleep following administration.

Antihistamines

Antihistamine use is prevalent and indicated in the treatment of a variety of ailments. Because antihistamines cross the blood-brain barrier, they have the potential to cause sedation and, thus, impair high-level functions, such as driving.¹⁴ First-generation antihistamines are much more likely to cause sedation because they readily cross the blood-brain barrier. Second-generation antihistamines are more selective for peripheral histamine receptors and are generally associated with less sedation secondary to this characteristic. Third-generation antihistamines such as fexofenadine, desloratadine, and levocetirizine claim to be devoid of central nervous system effects, including sedation. A review of double-blind placebo controlled trials analyzed the effects of antihistamines on driving ability. First-generation antihistamines such as diphenhydramine or dexchlorpheniramine were found to significantly impair driving ability with one-time administration.¹⁴ Although some tolerance develops after repeated daily administration, residual sedation and anticholinergic effects are observed, and driving may continue to be impaired. Verster et al¹² compared the driving impairment observed after consuming alcohol to that observed after immediate administration of diphenhydramine.¹⁴ The study found that impairment with use of this first-generation antihistamine was comparable to a blood alcohol level between 0.05% and 0.10%.

Second-generation antihistamines such as cetirizine were also found to impair driving performance, especially at higher doses, but to a lesser extent than first-generation agents. Third-generation antihistamines such as fexofenadine or levocetirizine seem to be free of sedative properties and have not been shown to have potential for driver impairment.¹⁴

Many antihistamines are available over-the-counter and can be used without physician supervision. As such, it is important for pharmacists to counsel patients purchasing over-the-counter antihistamines about the risk of sedation and potentially impaired driving. Physicians should also ensure that all nonprescription medications are accounted for in the patient's chart. This ensures the opportunity to counsel patients about the risks associated with driving and find alternative therapy options, as applicable. Third-generation antihistamines appear to pose the least risk and should be recommended when driving impairment is a concern.

Antidepressants

Antidepressants are highly prevalent and can have a positive impact on a patient's quality of life. However, many antidepressants also cause unwanted side effects that can be potentially impairing to drivers. Side-effect profiles vary by the type of antidepressant. Tricyclic antidepressants (TCAs) such as nortriptyline or amitriptyline are known to cause sedation, dizziness, double vision, blurred vision, tachycardia, and tremors.^{1,2} This class of antidepressants has been associated with a 41% increased risk of motor vehicle accidents.¹ A study by Ramaekers evaluated the effects of TCAs on driving. The study found that same-day doses were associated with poor performance as measured by lane-keeping ability.¹⁵ The impairment was comparable to a driver with a blood alcohol level of 0.08%, the current upper limit for legal driving in the United States. However, when the TCA was taken the evening before performance testing or the patient had been on TCA therapy for longer than

1 week before performance was measured, no significant changes in driver impairment were found.¹⁵

Serotonin-2 antagonist and reuptake inhibitors such as trazodone or nefazodone have been linked to impaired driving with repeated dosing.¹⁶ A dose-response relationship seems to exist between this class of medications and driver reaction time.¹⁶

Mirtazipine, an α -2 receptor antagonist antidepressant and sleep aid, has been shown to cause significant sedating effects in the hours immediately following dosing. Prescribing information warns about sedation and it has been recommended to avoid this medication, whenever possible, in individuals who wish to continue driving.¹⁷

Bupropion, a dopamine and norepinephrine reuptake inhibitor, is used to treat depression and aid in smoking cessation. In a study done by the NHTSA, bupropion was found to have the lowest odds ratio for increased crash rates of all the antidepressants reviewed. The study found that drivers taking bupropion experience a 19% increased risk for accident (OR = 1.19; $P = 0.27$, NS) compared with drivers not taking the medication.¹ Still, drug information states that patients on bupropion should only continue to drive when they are certain of how it will affect them.¹⁸

The impact of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on a patient's ability to drive have conflicting data. Some researchers have found that SSRIs and SNRIs are well tolerated and have minimal to no effect on driving ability.^{17,19} Still others found that patients on SSRIs are 59% more likely to be involved in a motor vehicle collision, and for patients using SNRIs, it is 78% more likely than for case-control comparators.¹

Additional research is needed to further elucidate confounding factors and driver impairment risk with the commonly prescribed SSRIs and SNRIs. Bupropion seems to carry the lowest risk for driver impairment among the antidepressants. For all classes of antidepressants, it is

prudent for providers to advise patients of potential driver-impairing effects and encourage patients to cease driving during medication initiation and dosage increases.

Conclusion

Although medication offers amelioration from disease, it may also cause unintended side effects. The aforementioned medications are used to treat ambulatory patients who are expected to carry out their activities of daily living in a manner similar to unmedicated individuals. However, it is clear that certain medications can adversely affect an individual's ability to function at a level adequate for safe driving. Sedation, dizziness, blurred vision, and other unwanted side effects can lead to cases of preventable motor vehicle collision. Patient education plays an important role in minimizing risk. Prescribers should remind patients of the risk of impaired driving, help patients identify driver-impairing effects, and encourage patients to see how potentially impairing medications affect them before getting behind the wheel. Prescribers should also consider strategies to reduce driver-impairing side effects, such as dose limitation, avoidance of prescribing multiple potentially impairing medications, and use of agents within the therapeutic class with low known risk for impairment. **AJLM**

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