The Interface

DRIVING ON ANTIDEPRESSANTS: Cruising for a Crash?

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

Antidepressants are commonly prescribed medications that carry an imprecise risk of driving impairment. In this edition of The Interface, we explore the relationship between antidepressant medications and driving impairment. We conclude that while there may be a small risk of driving impairment with these medications, this risk is considerably heightened under particular clinical conditions. These conditions include the advanced age of the driver, initial dosing and start-up of the antidepressant, rapid escalation of antidepressant doses, high-dose antidepressants, presence of active and severe depressive symptoms (i.e., the antidepressant is merely functioning as a pharmacological marker for severe depressive illness), and/or coadministration of other psychotropic medications, especially benzodiazepines. Clinicians need to be mindful of these specific clinical conditions when prescribing antidepressants to patients.

KEY WORDS

antidepressants, driving, psychotropic medications, motor vehicle

INTRODUCTION

Approximately 1.2 million people die on the world's roads each year, some as drivers and others as passengers or pedestrians.[1] For example, during the year 2004, motor vehicle crashes accounted for more than 37,000 deaths in the US; an additional three million individuals were treated for associated injuries.[2] Sadly, for the years 1979 through 2004, motor-vehicle-related accidents have consistently ranked as the number one cause of death by injury.[3] In this edition of The Interface, we explore the possible contributory role of antidepressant medications to driving impairment and motor vehicle accidents.

THE PREVALENCE OF ANTIDEPRESSANT PRESCRIPTIONS

Antidepressants are universally prescribed medications in the US. According to the Centers for Medicare and Medicaid Services, between the years 1991 and 2005, the total number of antidepressant prescriptions among those insured through Medicaid increased by 380 percent, from 6.8 to 32.7 million.[4] In addition to these data, findings from the third National Health and Nutrition Examination Survey

(NHANES), a nationally representative cross-sectional health examination survey, indicate that between the 1988–1994 and 1999–2002 surveys, antidepressant use increased more than three-fold.[5] According to the NHANES data, the observed increase in antidepressant use was higher than any other class of psychotropic medication. Clearly, antidepressant prescription and usage in the US is prevalent and growing.

DRIVING WARNINGS TO PATIENTS ON ANTIDEPRESSANTS

Like all medications, antidepressants have a number of potential risks. These include cognitive and/or psychomotor impairment, which may affect an individual's ability to operate a motor vehicle. This precaution is clearly acknowledged in the Clinical Psychopharmacology Database, which states, "Because any psychoactive drug may impair judgment, thinking, or motor skills, patients should use caution when driving or operating machinery."[6] Given this warning, is there genuine evidence for risk?

MOTOR VEHICLE ACCIDENTS AND ANTIDEPRESSANT USE

A number of studies have examined the potential relationship between antidepressants and impaired driving skills/motor vehicle accidents. Not surprisingly, the findings have been mixed.

The evidence for tricyclic antidepressants. We will first review the data for tricyclic antidepressants (TCAs). In a retrospective study of TCA use among elderly individuals ages 65 to 84 years in the Tennessee Medicaid program, Ray et al[7] found a greater relative risk for motor vehicle accidents (relative risk=2.2; 95% CI=1.3–3.5). This risk increased with increasing TCA dose.[8] Leveille et al[8] examined older drivers in a Seattle-based health maintenance organization and found that for those participants taking TCAs, there was an increased relative risk for a motor vehicle accident of 2.3 (95% CI=1.1–4.8). In a Japanese study, Iwamoto et al[9] examined the effects of amitriptyline among healthy men through performance assessment on a driving simulator; four hours after initial dosing, participants demonstrated significantly impaired road-tracking and car-following performance as well as somnolence and reduced vigilance. Finally, in a Norwegian study by Bramness et al,[10] researchers divided participants into two groups—those on sedating versus those on nonsedating antidepressants. Drivers prescribed sedating antidepressants, which included TCAs and mirtazapine, demonstrated an increased risk of being in a traffic accident, with a standardized incidence ratio of 1.4 (95% CI=1.2–1.6).

As one might expect, not all studies of TCAs have demonstrated deleterious effects on driving. For example, in a study from the UK, Barbone et al[11] examined the association between TCAs and motor vehicle accidents and found no increased risk.[11] In a prospective controlled Dutch study by Movig et al,[12] there was no association between TCA use and driving difficulty, although the number of study cases was extremely small. Finally, in a literature review by Ramaekers,[13] participants taking TCAs were only susceptible to motor vehicle accidents when taking the more sedating drugs and only during the initial phases of treatment.

The findings for non-TCA antidepressants. As for studies entailing the newer nontricyclic antidepressants, again, the existing data demonstrate mixed results. For example, in a Spanish study, De las Cuevas et al[14] electronically assessed five driving skills in patients taking antidepressants. As for the types of antidepressants, the majority were prescribed either selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). Nearly half of the sample was taking two or more psychotropic drugs. On assessment, 84 percent failed at least one of the required driving skills. At the study's end, nearly 80 percent of participants demonstrated impairment to the degree that they would not be able to obtain a driver's license in Spain.

In a US sample, Dannewitz and Petros[15] studied 60 individuals using a driving simulation test. Nearly half of the sample was taking no psychotropic medications and these participants functioned as controls; the remainder was taking at least one antidepressant, which included SSRIs as well as nonSSRIs (e.g., bupropion). The antidepressant subsample was not restricted to just one psychotropic drug. Importantly, in comparison with controls, those on antidepressants with high depression scores performed significantly worse on the driving simulation test whereas those on antidepressants with depression scores in the normal range performed no differently than controls.

In the previously noted Norwegian study, Bramness et al[10] also reviewed the effects of nonsedating antidepressants on driving, including SSRIs and venlafaxine. Again, there was a slightly increased risk of being involved in an automobile accident, with a standardized incidence ratio of 1.6 (95% CI=1.5–1.7).

In contrast to the preceding studies, a number of studies of nonTCAs have concluded that there is no significant association between

these newer antidepressants and impaired driving ability. For example, Barbone et al[11] found no driving risks with SSRIs in their UK study. During a review of the literature, Ramaekers[13] found no evidence for impaired driving with fluoxetine, paroxetine, and venlafaxine, and minimal effects with mirtazapine (i.e., there was only a first-dose effect, which was equivalent to a blood alcohol level of 0.5mg/mL). In the study by Iwamoto et al,[9] paroxetine did not impair driving ability. Finally, in a German study, Brunnauer et al[16] examined the effects of mirtazapine in depressed patients and found that after 14 days of treatment, the antidepressant actually improved driving ability.[16]

TABLE 1. Factors that may increase the risk of impaired driving while taking antidepressants

Increasing age of the patient
Initial start up of/adjustment to the antidepressant
Rapid dose escalation or higher doses of antidepressants
First week of antidepressant treatment
Active depressive symptoms (i.e., depressive illness)
Comorbid administration of other psychotropic medications, especially benzodiazepines

INTERPRETATION OF FINDINGS

Clearly, there are some divergences in the findings in this area. However, these divergences are readily explainable when comparing the nuances of the studies. Explicitly, among the studies with TCAs, specific risk factors for impaired driving ability appear to be (1) advanced age, (2) rapid escalation and/or high doses of TCAs, and (3) the initial dose as well as the initial treatment period with TCAs (i.e., first week). Studies with the newer antidepressants suggest that active depressive symptoms (i.e., the depressive illness, itself) and the administration of comorbid psychotropic drugs, especially benzodiazepines, heighten the risk for motor vehicle accidents. These tentative conditions for risk probably apply to all antidepressants to some degree and are summarized in Table 1.

It is also important to note that these studies have a number of methodological variances. These include participants being on one versus numerous psychotropic medications, varying ages of participants, varying exposure times to antidepressant medications (i.e., variation in the time for participants to adjust to the potential side effects), and different measures of outcome (e.g., retrospective reports of automobile accidents versus driving simulation tests). In some studies, the potential role of coadministered medications was not accounted for. These factors are likely to influence findings from study to study.

WHAT MIGHT EXPLAIN ANTIDEPRESSANT-RELATED DRIVER IMPAIRMENT?

There may be a number of pharmacological properties of the antidepressants that account for potential driver impairment. Some antidepressants have antihistaminic and/or anticholinergic effects, particularly the TCAs. These effects may initially cause somnolence or sedation,[9] resulting in cognitive difficulties, attentional deficits, indecisiveness, and psychomotor impairment.[13] However, most individuals appear to adapt to these side effects if (1) given low initial doses, (2) maintained on stable and routine doses, (3) there is no evidence of hepatic dysfunction, and (4) the individual is not elderly.

Antidepressants may also contribute to cognitive dysfunction and hazardous driving through their potential effects on other drugs via cytochrome P-450 system. As a general rule, antidepressant drugs may potentially inhibit various enzymes, depending on the drug. When coadministered drugs are metabolized through affected enzymes, they experience a slowing in their clearance, resulting in an elevated serum level and an enhancement in their overall effects. A practical example would be a patient who is taking alprazolam and then receives a prescription for fluoxetine; through the cytochrome P-450 2D6 enzyme, fluoxetine may increase alprazolam levels, resulting in enhanced benzodiazepine side effects, including psychomotor impairment.

Finally, as we previously noted, depressive illness itself may impair judgment with driving.[17] In these cases, the antidepressants merely function as a marker of that illness, rather than as a cause of impairment.

CONCLUSION

In examining the literature on the relationship between antidepressants and impaired driving, there are conflicting data. It seems safe to conclude that there may be a potential risk—one that depends on

a number of factors, including the prescription of more sedating antidepressants, advanced age of the patient, type of antidepressant, phase in antidepressant treatment, dosing strategy of the antidepressant, intensity of concurrent depressive symptoms, and presence or not of coadministered psychotropic drugs. Clinicians in both psychiatric and primary care settings need to caution patients about the risks of driving while taking antidepressants, but these risks may only be truly evident under specific clinical conditions.

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