Antidepressants and Driver Impairment: Empirical Evidence From a Standard On-the-Road Test

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Background and Method: The current review summarizes the major results from all published studies from 1983 to 2000 (9 double-blind, crossover, placebo-controlled studies in healthy volunteers and 1 double-blind, baseline-controlled study in patients) that have determined the effects of antidepressants on actual driving performance using a standard test. That test measures driving impairment from vehicular "weaving" (i.e., standard deviation of lateral position [SDLP]) during 1 hour of on-the-road driving in normal traffic.

Results: Changes in SDLP after acute doses of sedating antidepressants (i.e., amitriptyline, imipramine, doxepin, and mianserin) were comparable to those seen in drivers conducting the same test with a blood alcohol concentration of 0.8 mg/mL or more. Driving performance of subjects returned to placebo levels after 1 week of treatment, except after treatment with mianserin, for which the impairing effect lasted unabated over treatment. Nocturnal doses of sedating antidepressants (i.e., dothiepin, mianserin, and mirtazapine), however, did not produce residual driving impairment when measured the next day. Nonsedating antidepressants (i.e., moclobemide, fluoxetine, paroxetine, venlafaxine, and nefazodone) generally did not affect SDLP. However, SDLP rose to unacceptable levels after administration of combinations of nonsedating antidepressants and benzodiazepines with incompatible pharmacokinetic profiles. Correlational analyses demonstrated that conventional tests of psychomotor performance or self-ratings of side effects did not strongly predict antidepressant effects on SDLP. Regression analysis revealed a strong linear relation between antidepressant effects in the standard driving test and the number of patients reporting somnolence in clinical trials with the same antidepressants.

Conclusion: Application of actual driving tests remains essential to conclusively defining the potential hazard of drugs for driving.

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Antidepressant drugs are an integral part of almost any medical treatment of depression. In relieving and curing this disease, they provide patients with a positive contribution to their quality of life. Besides this beneficial effect, antidepressants can also produce side effects such as sedation, lethargy, and sleep disturbances that can limit their clinical usefulness. At the behavioral level, these side effects may cause impairment of thought processing, attentional deficits, indecisiveness, and psychomotor impairment. In situations requiring antidepressant drug users to engage in potentially dangerous activities, i.e., operating a vehicle, these side effects may increase the risk of injury or death through performance-related accidents.[1]

Epidemiologic studies on the effects of antidepressants on driving performance are scarce, but have indicated that elderly users of tricyclic antidepressants (TCAs) are about 2 times more likely to become involved in traffic accidents as compared with a group of control subjects.[2,3] One survey reported no association between the use of TCAs or selective serotonin reuptake inhibitors (SSRIs) and road traffic accidents in people older than 18 years, or in a subset of elderly persons.[4] Yet, the authors attributed the latter finding to insufficient power of their study to detect any risk because of a limited number of cases in their study sample. For the same reason, none of the surveys were able to establish causal relations between individual antidepressants and road traffic accidents.

Experimental studies have proved very useful in determining separate drug effects on performance and are of great importance as the basis for decisions in the field of traffic safety. Results from experimental studies provide a reliable database for categorizing the potential hazard of individual drugs when the studies are based on a sound

methodology and when results of different studies are comparable. Several laboratory tests of psychomotor and cognitive functions related to driving have been developed that are sensitive to low levels of sedation and possess the degree of reliability to generate highly reproducible results. However, their predictive validity is sometimes questionable, for it is not always clear if performance in these tests can be converted into some real-life analog. Such transfer functions are not needed when measuring a safety-related performance parameter in an actual driving test conducted in normal traffic. Ideally, studies for establishing the driving hazard of medicinal drugs should thus not only include conventional laboratory testing but also proceed to sophisticated driving simulators and, finally, actual driving tests. A recent "Note for Guidance" on psychotropic drugs in the European Union[5] furthermore stressed that tests for assessing driver fitness should minimally last 1 hour, as motivational factors may affect the results of these tests. Only 1 actual driving test for measuring drug effects currently meets the latter criterion. That test was devised by 3 groups working at Dutch universities and was applied between 1983 and 2000 in 9 double-blind, crossover, placebo-controlled volunteer studies and in 1 double-blind, baseline-controlled patient study for determining the effects on driving of 14 antidepressants.

The aim of this review is to summarize and integrate results from these 10 experimental driving studies. Specific objectives are to show what driving impairment occurs after use of antidepressants and how this impairment compares with that caused by alcohol; to indicate whether antidepressant effects on driving are affected by duration of treatment, dosing regimen, and benzodiazepine comedication; and to compare antidepressant effects on driving as observed using this driving test with those observed using other experimental and clinical assessments.

THE STANDARD DRIVING TEST

Subjects perform the test in the company of a licensed driving instructor seated in the front passenger seat with access to redundant control. The test involves driving over a 100-km (62-mi) circuit on a primary highway in normal traffic while maintaining a constant speed of 95 km/h (59 mi/h) and a steady lateral position within the boundaries of the slower traffic lane. An electro-optical device mounted on the rear back of the car continuously records lateral position relative to lane-line delineation. These data are sampled at 4 Hz, stored on computer disk files, and edited offline to remove segments recorded during passing maneuvers or disturbances caused by roadway or traffic situations. The primary performance measure is standard deviation of lateral position (SDLP, measured in cm), an index of road tracking precision or "weaving."

The test was first applied in a pilot study for showing the effects of diazepam, 10 mg.[6] The test was standardized shortly thereafter and has since been repeatedly applied for measuring drug effects on actual driving. SDLP is a very reliable characteristic of an individual's normal driving behavior. Test-retest reliability coefficients measured from unmedicated young and middle-aged individuals are generally higher than $r = 0.75$.[7] SDLP is very sensitive to sedative drug effects, indicating that the standard driving test possesses high construct validity. Whether drug-induced changes in SDLP also predict accident involvement in real life is more difficult to establish. It is impossible to validate the driving test, or any other experimental test, against the criterion of actual accident involvement. However, it is possible to validate the test against a secondary criterion that itself is highly correlated with accident risk, i.e., blood alcohol concentration (BAC). To this end, an alcohol calibration curve was established on the basis of the performance of social drinkers who conducted the standard driving test on 5 separate occasions while their BACs were controlled in equal steps between 0.00 and 0.15 mg/mL.[8] The calibration curve demonstrated that the drinkers' mean SDLP rose exponentially with BAC. A similar quantitative relationship has previously been found in epidemiologic research showing that BAC > 0.50 mg/mL is associated with an exponential rise in the relative risk of fatal traffic accidents.[9] Similarity of both equations does not necessarily confirm the accident-related validity of the standard driving test, but the absence of any similarity certainly would have implied its invalidity.[7] In any case, results from the alcohol calibration study can certainly be used for describing drugs' effects on SDLP in terms of respective BAC equivalencies. The change in SDLP at a BAC of 0.5 mg/mL, i.e., 2.4 cm, is taken as the lowest criterion value defining a relevant impairing drug. The standard driving test has not changed substantially in more than 70 studies spanning about 2 decades.

METHOD

Subjects and Study Procedures

The effects of antidepressants on actual driving have been assessed in 9 crossover, double-blind studies in healthy volunteers[10–18] and 1 parallel, double-blind, randomized study in depressed outpatients.[19] Crossover designs always involved at least 3 treatment conditions, i.e., the primary drug under investigation, placebo, and an active control for assuring the validity of the testing procedure. Driving tests were always conducted on the first day of treatment to assess the acute effects of a particular drug and generally also after 1 or several weeks of treatment to capture the subchronic effect as well. The parallel design involved 2 treatment legs, i.e., fluoxetine and moclobemide, preceded by a stable driving performance and

symptomatology at baseline. Driving tests were then conducted throughout 6 weeks of antidepressant therapy. All studies were approved by the standing Medical Ethics Committee of each institution and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject prior to participation after study procedures had been fully explained. Antidepressants were administered using normal therapeutic dose regimens.

Volunteers were screened on the basis of a medical history, physical examination, blood chemistry analysis, electrocardiogram, and urine drug screening. Subjects participating in the studies with healthy volunteers were generally between 21 and 40 years of age, although a subgroup of elderly subjects, aged 60 to 72 years, was also included in 1 study.[14] Subjects participating in the patient study were between 27 and 56 years of age. Their symptom severity as assessed using the Hamilton Rating Scale for Depression ranged between 17 and 32 at study entrance. All volunteers had held their drivers' license for at least 3 years and had a minimum driving experience of 5000 km (3125 mi)/year. Major exclusion criteria pertaining to both healthy volunteers and patients were as follows: alcohol and drug abuse; unusual sensitivity to antidepressant drugs; renal, hepatic, sensory, or neurologic disease; history of cardiovascular disease; and pregnancy. For healthy volunteers, exclusion criteria also included any chronic mental disorder.

Statistical Analyses

Sample sizes in the driving studies were determined by difference power calculations. These calculations revealed that a sample of 16 subjects was sufficient for providing a power > 90% for detecting a critical mean difference of 2.4 cm in SDLP at the p = .05 level of significance. Statistical procedures in the separate driving studies were virtually identical. SDLP was analyzed using multivariate analysis of variance or analysis of variance for the overall effect of treatments, followed by mean contrast test (drug vs. placebo) for measuring the contributions of individual drugs to the overall treatment effect.

RESULTS

A total of 14 antidepressants have been assessed for their effects on actual driving performance. Three of those never entered the market, i.e., oxaprotiline, levoprotiline, and brofaromine, and need no particular mention to date. It suffices here to say that none had any detrimental effect on driving.[10–12] The effects of the remaining 11 antidepressants on driving are described in Figures 1 through 4 that follow. Mean changes in SDLP from the same group's corresponding placebo or baseline levels are shown on the ordinates. Information given along the abscissa identifies antidepressants and the conditions of testing with respect to the following: dosing regimen, days or weeks after the beginning of treatment, hours since drug ingestion, number of divided doses taken prior to driving, use of comedication (when applicable), and sample size. Horizontal grid lines indicate changes in SDLP at BACs of 0.5, 0.8, and 1.0 mg/mL, the most common legal limits for driving under the influence. BAC equivalents are taken from the alcohol calibration curve described above. Levels of significance of antidepressant effects shown in the figures are reproduced from the original articles.

Sedating Antidepressants

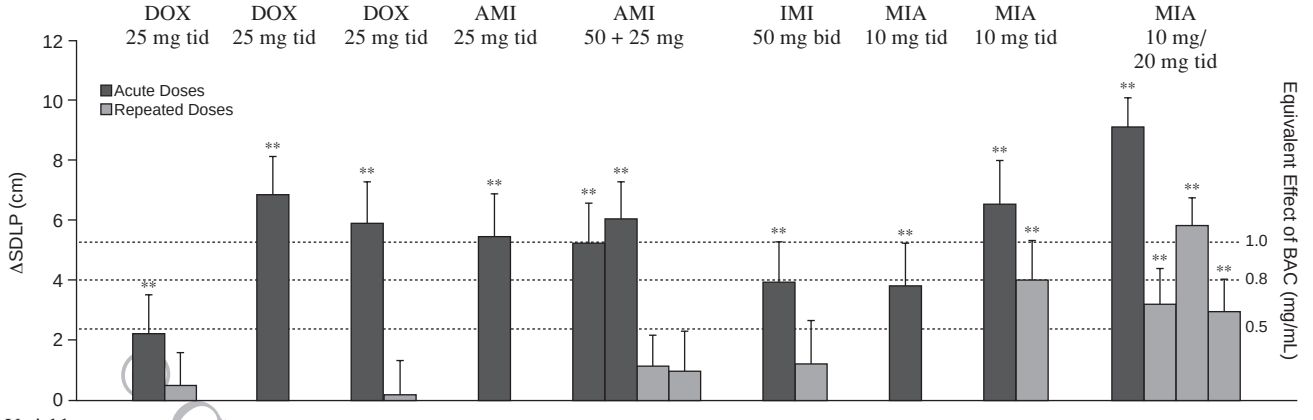
TCAs have been most frequently used as active control in volunteer studies because of their well-known potential to cause cognitive impairment and sedation by their antagonistic activities at cholinergic, adrenergic (α_1) and histaminergic (H_1) receptors. Daily doses of amitriptyline, 75 mg,[10,13] doxepin, 75 mg,[11,12] and imipramine, 50 mg,[14] all produced highly significant elevations of SDLP on the first day of treatment. Changes in SDLP after acute doses of TCAs were comparable to those seen in drivers operating the vehicle with a BAC of 0.8 mg/mL and higher. However, after 1 week of treatment with TCAs, change in SDLP was only minimal as a result of tolerance. A comparison of effects of imipramine in adult (N = 12) and elderly (N = 12) volunteers revealed little difference between the groups' mean SDLPs, although impairment was more prominent in the former group after a single dose.[14]

Mianserin is an α_2 antagonist that may also produce sedation by blocking α_1 and H_1 receptors. The drug drastically impaired the subjects' driving performance on the first day of treatment.[10,15,16] Elevations in mean SDLP were greater than those seen after BACs of 1.0 mg/mL. Between 10% and 50% of the subjects receiving acute doses of mianserin were unable to complete the driving test in 3 studies in which it was employed. Driving performance of subjects improved somewhat over time, but was still significantly impaired after 1 week of treatment with 10 mg 3 times a day. Driving further deteriorated when doses were doubled at the beginning of a second treatment week.[16] At the end of the second treatment week, the subjects' performance was still worse than that at the same time during placebo treatment. Mean changes in SDLP after administration of TCAs and mianserin are shown in Figure 1. Change scores for imipramine are included for the middle-aged and elderly subjects combined.

Nocturnal Doses of Sedative Antidepressants

Dothiepin is another TCA that is well known to produce sedation and performance impairment. Mirtazapine is an α_2 antagonist that also has strong binding affinities for serotonergic 5-HT_2 and 5-HT_3 and histaminergic H_1 receptors. In contrast to mianserin, it has little affinity for

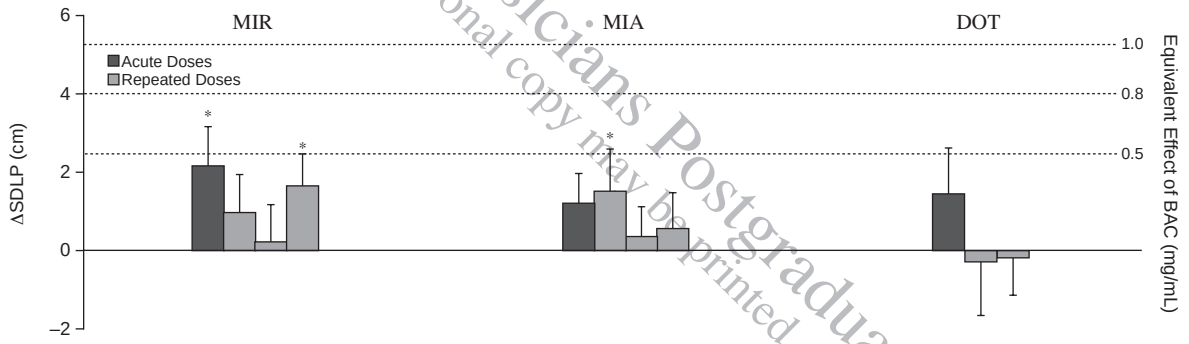
Figure 1. Mean ± SE ΔSDLP After Acute and Repeated Doses of Doxepin, Amitriptyline, Imipramine, and Mianserin When Given Divided Over the Day[a]



Variable																								
Day	1	8	1	1	8	1	1	1	8	8	1	7	1	1	8	1	7	8	15
Time post dose (h)	1.5	1.5	2	3	3	2	1.5	5	1.5	5	1.5	1.5	2	2.5	2.5	2	2	2	2
Divided doses prior to driving	3	3	3	3	3	2	2	2	2	2	1	1	3	3	3	1	1	1	1
N	16		20	16		20	16				24		16	18		22			
Reference	11		10	12		10	13				14		10	15		16			

[a]Abbreviations: AMI = amitriptyline, BAC = blood alcohol concentration, DOX = doxepin, IMI = imipramine, MIA = mianserin, SDLP = standard deviation of lateral position.
**p ≤ .01 vs. placebo.

Figure 2. Mean ± SE ΔSDLP After Acute and Repeated Doses of Mirtazapine, Mianserin, and Dothiepin When Given in the Evening[a]



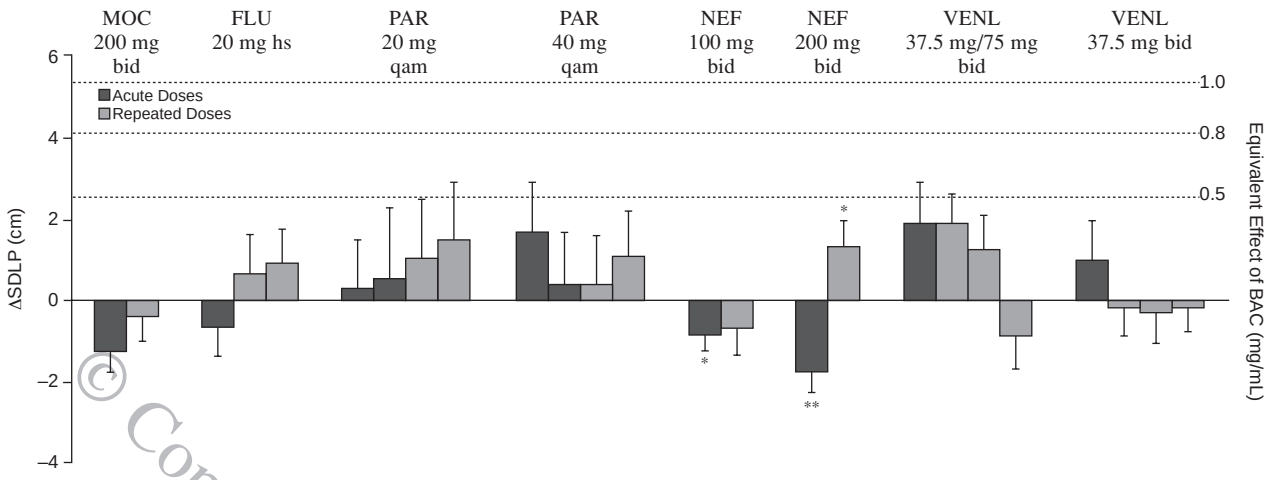
Variable												
Dosing regimen	15 mg/30 mg hs				30 mg/60 mg hs				75 mg/150 mg hs			
Day	1	7	8	15	1	7	8	15	1	8	22	
Time post dose (h)	17	17	17	17	17	17	17	17	16	16	16	
N	18				18				18			
Reference	18				18				17			

[a]Abbreviations: BAC = blood alcohol concentration, DOT = dothiepin, MIA = mianserin, MIR = mirtazapine, SDLP = standard deviation of lateral position.
*p ≤ .05 vs. placebo.

the α_1 receptor. Dothiepin, mianserin, and mirtazapine all share a strong binding affinity for the postsynaptic H_1 receptor that is thought to play a major role in the development of sedation. Their detrimental effects on performance are well established when given in divided doses over the day, but little is known about the effects of sedating antidepressants on performance when administered at night.

The residual effect of dothiepin, mianserin, and mirtazapine on daytime driving performance has been assessed in 2 studies employing healthy volunteers.[17,18] In both studies, antidepressants were administered in the evening.

Figure 3. Mean ± SE ΔSDLP After Acute and Repeated Doses of Moclobemide, Fluoxetine, Paroxetine, Nefazodone, and Venlafaxine[a]



Variable																												
Day	1	8	1	8	22	1	1	8	8	1	1	8	8	1	7	1	7	1	7	8	15	1	7	8	15
Time post dose (h)	2.5	2.5	15	15	15	1.5	5	1.5	5	1.5	5	1.5	5	1.5	1.5	1.5	1.5	2	2	2	2	2	2	2	2
Divided doses prior to driving	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
N	18		18			16				16				24		24		22				22			
Reference	15		17			13				13				14		14		16				16			

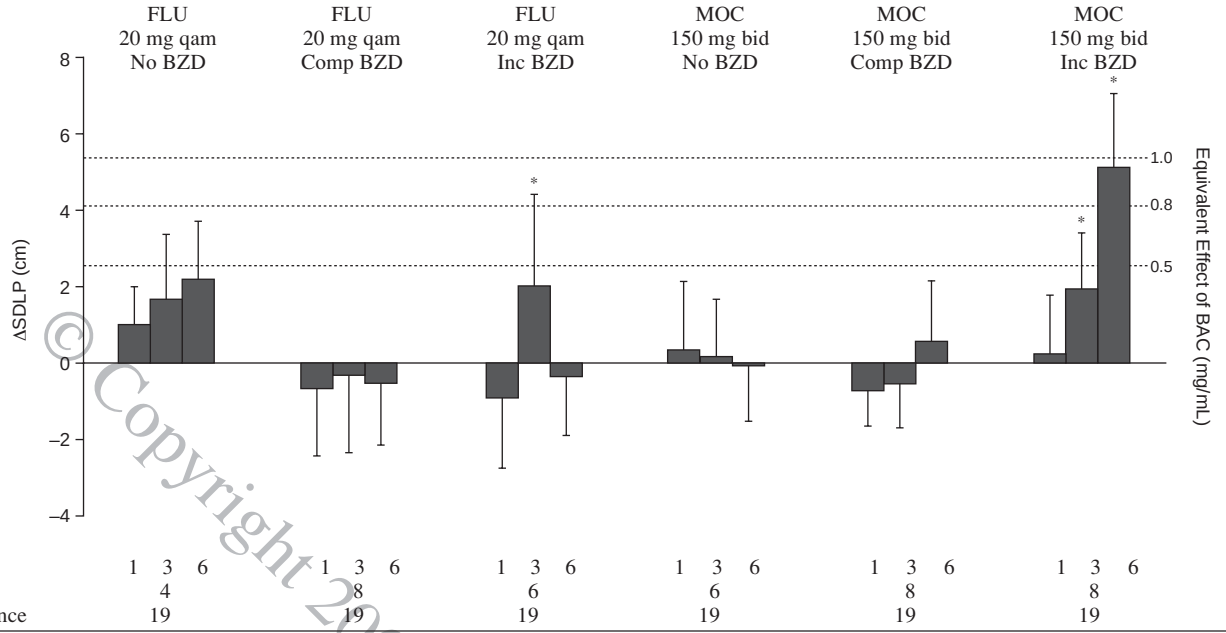
[a]Abbreviations: BAC = blood alcohol concentration, FLU = fluoxetine, MOC = moclobemide, NEF = nefazodone, PAR = paroxetine, SDLP = standard deviation of lateral position, VENL = venlafaxine.
*p ≤ .05 vs. placebo.
**p ≤ .01 vs. placebo.

The standard driving test was conducted the next day between 16 and 18 hours following the evening dose. SDLP of subjects receiving dothiepin, 75 mg, did not differ from that during placebo after 1 and 8 days of treatment. Additional treatment with dothiepin, 150 mg, for another 2 weeks also did not significantly affect SDLP when measured on the last day. Mianserin and mirtazapine, respectively, were given at doses of 15 mg and 30 mg h.s. for 7 days and in doses of 30 mg and 60 mg h.s. for another 8 days. Relative to placebo, mirtazapine increased SDLP after a single dose and on the last day of treatment; mianserin significantly increased SDLP on the last day of treatment with the lower dose. Yet, mean changes in SDLP after administration of both drugs were always less than that after a BAC of 0.5 mg/mL. Mean changes in SDLP after administration of dothiepin, mianserin, and mirtazapine are shown in Figure 2.

Nonsedating Antidepressants

Novel antidepressants whose effect on actual driving have been assessed in healthy volunteers conducting the standard test include: a reversible inhibitor of monoamine oxidase A, i.e., moclobemide[15]; SSRIs, i.e., fluoxetine and paroxetine[13,17]; a serotonin receptor antagonist and reuptake inhibitor, i.e., nefazodone[14]; and a serotonin-norepinephrine reuptake inhibitor, i.e., venlafaxine.[16] These antidepressants generally have no or little affinity for histaminergic, adrenergic, and cholinergic receptors. This is generally why therapeutic doses of these drugs have never been shown to seriously affect driving performance in the standard test after acute doses or after 1 to 3 weeks of repeated dosing. Figure 3 shows that mean changes in SDLP after these antidepressants were generally close to 0. Only nefazodone, 200 mg, produced a significant increase in SDLP after repeated doses. The magnitude of impairment, however, was well below the criterion level of BAC = 0.5 mg/mL. Several novel antidepressants showed a tendency to improve the subjects' driving performance relative to placebo. These stimulating effects, however, never approached statistical significance, except in 1 study,[14] in which SDLP significantly decreased after single doses of 100 and 200 mg of nefazodone. The sample size in that particular study was relatively high, which may have contributed to the study's statistical power to detect changes in SDLP below the criterion level. Stimulating effects, however, were short-lived and proceeded to modest impairment after repeated dosing. The dualistic effect of nefazodone is assumed to result from its antagonistic effects at α_1 and 5-HT_2 receptors known to produce somnolence, and from *m*-CPP

Figure 4. Mean ± SE ΔSDLP for Patients Receiving Compatible Benzodiazepine (BZD), Incompatible BZD, or no BZD Comedication During 6 Weeks of Treatment With Fluoxetine or Moclobemide[a]



[a]Abbreviations: BAC = blood alcohol concentration, Comp = compatible, FLU = fluoxetine, Inc = incompatible, MOC = moclobemide, SDLP = standard deviation of lateral position.
*p ≤ .05 vs. baseline.

(*m*-chlorophenylpiperazine) metabolite formation causing activation, agitation, and insomnia. The improving effect of nefazodone on driving performance was not significantly different between groups of adult and elderly volunteers.[14]

Combined Use of Nonsedating Antidepressants and Benzodiazepines

The effects of the combined use of antidepressants and benzodiazepines (BZDs) have been assessed in 1 experimental driving study with outpatients suffering from major depression.[19] These patients were tested for driving ability twice at baseline and then randomly assigned to 2 groups for double-blind treatment with fluoxetine, 20 mg, and moclobemide, 150 mg b.i.d., lasting 6 weeks. Clinical assessments, e.g., the Hamilton Rating Scale for Depression and the Montgomery-Asberg Depression Rating Scale, and the standard driving test were repeated after 1, 3, and 6 weeks of treatment. Doses were doubled for those patients who failed to improve. About 80% of the patients were also on long-term treatment with BZDs and were allowed to continue taking them as comedication. Moclobemide and fluoxetine are known to inhibit different cytochrome P450 (CYP) isozymes that are responsible for the metabolism of many BZDs. The greatest inhibitory action of moclobemide is at CYP2C19, whereas fluoxetine is a potent inhibitor of CYP2D6 as well as CYP3A3/4.

Some BZDs used by these patients were substrates of CYP2C19, i.e., nordiazepam; some were substrates of CYP3A3/4, i.e., alprazolam and bromazepam; and some were substrates of none of the isoenzymes inhibited by moclobemide or fluoxetine. Patients using BZDs that are known substrates of an isoenzyme inhibited by their particular antidepressant were defined as taking incompatible BZDs, and patients using other BZDs or none were defined as taking compatible BZDs or none. A post hoc multiple regression analysis revealed that patients taking incompatible BZDs drove progressively worse over the course of treatment, whereas the others continued to drive in about the same manner, relative to baseline. In the moclobemide group, the mean SDLP of patients taking an incompatible BZD rose throughout the 6 weeks of treatment and reached a maximal elevation comparable to that seen for drivers operating with a BAC > 0.8 mg/mL. In the fluoxetine group, the mean change in SDLP of patients taking incompatible BZDs was maximal in the third week and comparable to the effect of a BAC just below 0.5 mg/mL. Interestingly, depression severity as measured using clinical rating scales did not correlate with SDLP. Mean changes in SDLP of patients in the moclobemide and the fluoxetine groups taking incompatible, compatible, or no BZDs are shown in Figure 4.

Correlations Between SDLP, Psychomotor Performance, and Subjective Assessments in Experimental Studies

Most driving studies currently under review also included a variety of laboratory tests of psychomotor per-

Table 1. Mean, Minimum, Maximum, and Percentage of Significant ($p < .05$) Individual Intrasubject Correlations Between Changes in SDLP and Psychomotor Task Performance/Subjective Assessments Across Treatment Conditions as Assessed in 2 Separate Studies Showing Mild Drug Effects[11] and Strong Drug Effects[13a]

		SDLP (mild drug effects[11])				SDLP (strong drug effects[13])			
Variable	Dependant Variable	Mean r	Min	Max	% With $p < .05$	Mean r	Min	Max	%With $p < .05$
Psychomotor tasks									
Critical Flicker Fusion frequency task	Flicker/fusion threshold	–0.37	–0.88	0.54	13	–0.32	–0.63	0.06	31
Critical Tracking task	Tracking (lambda-c)	…	…	…	…	–0.45	–0.80	0.35	44
Memory task	Reaction time	…	…	…	…	…	…	…	…
Divided Attention task	Tracking (error)	0.23	–0.62	0.67	0	0.45	0.06	0.87	25
	Reaction time	0.26	–0.28	0.88	6	0.33	–0.42	0.88	31
Choice Reaction Time task	Reaction time	…	…	…	…	…	…	…	…
Finger Tapping Test	Timing ability	…	…	…	…	0.30	–0.34	0.72	25
Vigilance test	Correct detections	…	…	…	…	…	…	…	…
	False alarms	…	…	…	…	0.30	–0.31	0.79	31
Subjective assessments									
Visual analogue scale	Drowsiness	0.27	–0.43	0.92	25	0.39	–0.47	0.47	38
Bartenwerfer scale	Mental activation	…	…	…	…	–0.23	–0.98	0.72	19

[a]Only significant mean correlations with 2-tailed $p < .05$ are shown. Abbreviations: Max = maximum, Min = minimum, SDLP = standard deviation of lateral position.

formance and subjective assessments of side effects in addition to the standard driving tests. These task batteries typically included tests to measure sedation or drowsiness, divided attention, perceptual motor coordination (tracking), sustained attention (vigilance), and cognitive functions such as working memory. A total of 7 conventional psychomotor tasks were employed over the course of all driving studies, although most studies used only a selection. The full battery was applied in 2 studies. Their driving data sets contained mild drug effects of doxepin, 75 mg, in 1 study,[11] and strong drug effects of amitriptyline, 75 mg, in the other.[13] These studies were selected for correlating changes in SDLP with changes in psychomotor task performance and subjective ratings, in order to determine the latter's predictive validity of antidepressant effects on actual driving. Intrasubject coefficients of correlation were calculated for every subject between each pair of variables, i.e., change in SDLP and change in performance in 1 of the psychomotor tests or subjective ratings. Individuals' correlations were based on the total number of test repetitions across treatment conditions, i.e., between 8 and 16. Individual intrasubject correlations were averaged across subjects. This mean was tested for a significant deviation from 0 by t tests. Significant mean intrasubject correlations are shown in Table 1. SDLP was significantly correlated with some psychomotor performance measures and subjective ratings of drowsiness, but these correlations were relatively modest. The highest intrasubject correlations were found between SDLP and tracking performance.

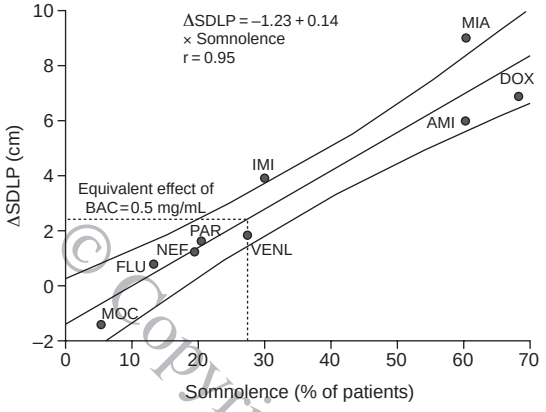
Correlation Between SDLP and Somnolence Ratings in Clinical Trials

One of the most common adverse events reported after the use of antidepressant drugs is somnolence. The percentage of patients experiencing this particular side effect varies greatly between individual antidepressants, but may be very large with TCAs. It is assumed that somnolence or sedation is by far the most important cause of driver impairment in patients treated with antidepressant drugs. Regression analyses of elevations in SDLP observed in experimental driving studies and the number of patients complaining of somnolence in clinical trials with the same antidepressants[20–29] strongly supported this notion. Elevations in SDLP caused by antidepressants administered over the day strongly increased as a linear function of the percentage of depressed patients complaining of somnolence ($r = 0.95$). This linear relation between ΔSDLP and somnolence for antidepressant drugs is depicted in Figure 5A, which shows that antidepressants that produce marginal sedation have only mild effects on driving performance, whereas antidepressants that produce somnolence in most of its users are associated with severe driving impairment.

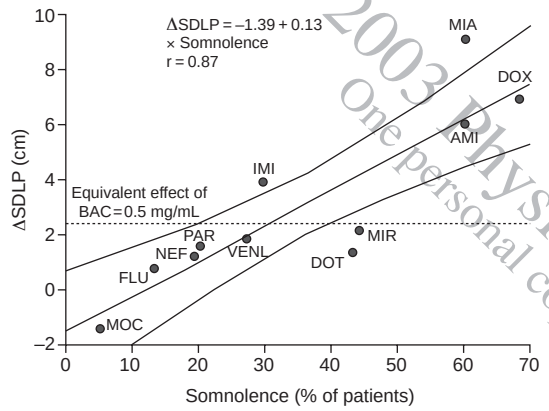
Given the very strong correlation between SDLP and somnolence, it is even possible to establish a minimum criterion of somnolence above which performance in the standard driving test was always impaired, i.e., the percentage of somnolence associated with a change in SDLP that is equivalent to the effect produced by a BAC of 0.5 mg/mL. Figure 5A shows that this minimal criterion of somnolence is close to an incidence of 30%. However, validity of this criterion depended on the dose regimen as well. The strength of association between SDLP and somnolence diminished when nocturnal dose regimens of antidepressants were also included in the equation (Figure 5B). Evening doses of sedative antidepressants such as dothiepin and mirtazapine produced complaints of somnolence in a large proportion of patients, i.e., exceeding the minimal somnolence criterion, but their mean effects

Figure 5. Linear Regression (95% confidence interval) Between Maximum Mean ΔSDLP Observed for Antidepressant Drugs in Experimental Driving Studies and the Number of Depressed Patients Complaining of Somnolence in Clinical Trials With the Same Drugs[a]

A. Antidepressants Recommended to Be Given Over the Day



B. Antidepressants Recommended to Be Given Either Over the Day or as an Evening Dose



[a]For abbreviations, see Figures 1–4.

on driving performance were mild and below the threshold of clinically relevant driving impairment when subjects taking these antidepressants were tested the next day. Consequently, the somnolence criterion cannot be automatically applied to antidepressants when given at night.

DISCUSSION

Driving impairment observed for sedating antidepressants in experimental driving studies is in accordance with epidemiologic data showing that sedating antidepressants such as TCAs may increase the risk of becoming involved in traffic accidents. Experimental studies furthermore demonstrated that many novel antidepressants that have been introduced on the market over the last decade are free of detrimental effects on driving when given in therapeutic doses. In general, these should be preferred over TCAs or other sedating antidepressants when choosing between equally effective antidepressants for treating ambulant patients.

Yet, an important message from the experimental studies is also that sedating antidepressants do not necessarily produce driver impairment under any circumstance. Detrimental effects of TCAs that were assessed in tests conducted immediately after acute doses were given mitigated over time and were no longer measured in tests conducted after 1 week of dosing. The implication would be that for patients taking TCAs, driving should be contraindicated only during the starting phase of treatment. An exception, however, should be made for the α_2 antagonist mianserin. The subjects' driving performance remained impaired over 2 weeks of treatment, although the magnitude was considerably less than on the first day.

The impairing effects of sedating antidepressants on driving performance could also be overcome by administering them in the evening. None of the 3 sedative antidepressants that were studied after nocturnal doses, i.e., dothiepin, mianserin, and mirtazapine, had any great effects on SDLP when subjects were tested the next day during 2 to 3 weeks of treatment. Mirtazapine is currently recommended to be taken at night, but others are not. Since there is no particular medical reason why antidepressants need to be taken in divided doses during the day, prescribing physicians should consider nocturnal dosing regimens for all potentially sedating antidepressants to minimize the patients' risk for traffic injuries.

The nonsedating antidepressants that were studied in the standard test failed to produce serious driving impairment at therapeutic doses. Yet, caution should be taken when these antidepressants are used in combination with BZDs. Results from the patient study demonstrated how driving performance of patients treated with moclobemide or fluoxetine decreased over time when they were taking incompatible BZDs. In particular, the combination of moclobemide and nordiazepam led to serious driving impairment. This difference in effect is possibly related to the respective sites of the pharmacokinetic interaction. The only known BZD substrates of CYP2C19, diazepam and nordiazepam, are slowly metabolized under normal circumstances. Benzodiazepine substrates of CYP3A3/4, on the other hand, are all more rapidly metabolized. Supposing moclobemide and fluoxetine selectively inhibit the respective isoenzymes to similar degrees, it would take longer for substrates of CYP2C19 to reach a new steady state than substrates of CYP3A3/4.

Fluoxetine and moclobemide are certainly not the only antidepressants that are potent inhibitors of the cytochrome P450 system. Most SSRIs are potential inhibitors of CYP2D6 and CYP3A3/4, and other antidepressants such as venlafaxine and nefazodone inhibit either one or

the other of these isoenzymes as well.[30–32] The likelihood of potential interactions between antidepressants and comedication should therefore always be determined in order to choose or adjust treatment combinations.

The repeated application of the standard driving test in experimentally controlled studies has provided a number of clear and consistent results. Yet, the clinical value of these findings largely depends on their generalizability to patients with depression who drive. An evaluation of the strengths and weaknesses of the driving studies at hand seems appropriate, particularly regarding the validity of the healthy volunteer model and the standard driving test itself.

Most studies reviewed here have employed healthy volunteers for predicting antidepressant effects in patients. It could be argued that healthy volunteers respond differently to antidepressant treatment than depressed patients and that one response does not predict the other. The obvious example is that depressed patients may respond favorably to antidepressant treatment whereas healthy volunteers do not. However, the rationale for studying antidepressant effects in healthy volunteers is that they experience side effects just like patients do. This is certainly so at the beginning of therapy and in the minority of patients who do not respond to antidepressant treatment. Whether driving performance of depressed patients would also change, i.e., improve, as a consequence of successful treatment with antidepressants is largely unknown. Results from the only driving study in depressed outpatients indicated that there exists no causal relation between the relief of depressive symptoms and patients' driving ability.[19] More important, however, might be the practical notion that a therapeutic response to antidepressant treatment does not occur within the first week of treatment, but develops slowly over 3 to 6 weeks. Healthy volunteer studies demonstrated that the potential for driving impairment of sedating antidepressants is largely confined to the first week of treatment. It thus seems evident that patients will also experience the same impairment at the beginning of antidepressant therapy when a therapeutic response is not yet present or complete.

A possible cause for bias in the driving studies is the limited age range of the subjects included. Most volunteers were (young) adults, and only 2 studies included the middle-aged or elderly. Yet, it is thought that elderly patients are generally at greater risk for adverse drug reactions than their younger counterparts. The amount of drugs prescribed, as well as age-related changes in pharmacokinetics and pharmacodynamics of the drugs, is often cited as the underlying cause of adverse drug reactions.[33] This general notion, however, could not be confirmed in the only comparative study of antidepressant effects on actual driving performance in adults and elderly subjects.[14] That study showed that the antidepressant effects on SDLP were generally the same in both groups, although a small treatment-by-age interaction was found on the first day of treatment, which indicated that the impairing effect of imipramine on driving performance was more pronounced in younger adults than in elderly subjects. It should be noted, however, that the age groups comprised only 12 volunteers each. More systematic research with larger subject populations is needed before a reliable conclusion about antidepressant effects on driving performance in the elderly can be drawn. For the moment, it seems wise to generalize results from the experimental driving studies to the elderly patient population with caution. The magnitude of driving impairment observed in adult volunteers might be only a conservative estimate of a drug's activity in elderly individuals who appear extra sensitive to pharmacologic treatment, particularly in the case of sedating antidepressants.

Although it is clear that the primary measure of the standard driving test reflects a realistic and fundamental aspect of driving, i.e., road tracking control, it should not be taken as a measure of overall driving performance. The latter also includes understanding of traffic, decision making, risk assessment, responses to changes in traffic control devices, and interaction with other road users and involves higher-level driving skills demanding effortful processing and attention. Thus, a more complex driving test might provide a better prediction of overall driving performance as compared with the current standard driving test that measures highly automated performance at an operational level.

Nonetheless, performance in the standard driving test seems highly relevant, as it was shown to strongly correlate with an external variable of undoubted clinical relevance, i.e., the proportion of patients suffering from antidepressant-induced somnolence in clinical trials. Moreover, the standard driving test provides a degree of realism that is difficult to approximate with laboratory tests of psychomotor function. Correlational analyses demonstrated that performance changes as measured in psychomotor tasks and subjective side effect ratings were at best only moderately related to those in the standard driving test. The lack of any strong correlation between actual driving and performance at psychomotor tests suggests that the latter possess only little construct validity. That is, the tasks may not be relevant to driving or may not be sensitive to drug effects.

The use of psychomotor tests for measuring drug effects has been criticized because test duration is generally too short to detect any drug-by–time-on-task interaction.[34] Driving is often performed for prolonged periods, often with decreasing proficiency due to fatigue or inattention. It is important to establish whether a drug can enhance such tendency toward poorer performance. Psychomotor tasks or subjective ratings of side effects cannot achieve this goal and should not be used to replace the standard driving test for predicting drug effects on actual driving.

This is not to say that they are of no use in the determination of a drug effect on performance. They often provide the earliest evidence of a drug's potential to affect driving. However, unless better predictive psychomotor tasks are developed for assessing driver fitness, the application of actual driving tests remains imperative to conclusively assessing and categorizing the potential hazard of drugs for driving.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), diazepam (Valium and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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