# Antidepressants and Driving Ability: Results From a Clinical Study

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**Objective:** Psychomotor disturbances can frequently be found in depressed patients and may have an important influence on the ability to drive. Additionally, effects of sedation, as seen with some antidepressants, probably impair driving performance. The present study was designed to evaluate the effects of antidepressant monotherapy on psychomotor functions related to cardriving skills in depressive patients in a routine clinical setting.

*Method:* Inpatients (N = 100) who met the ICD-10 and DSM-IV criteria for major depressive disorder were tested under steady-state plasma level conditions prior to being discharged to outpatient treatment. The study ran from January 2004 through March 2005. All patients participated voluntarily and gave informed consent. According to the German guidelines for road and traffic safety, data were collected with the computerized Act & React Testsystem ART-90 and the Wiener Testsystem, measuring visual perception, reaction time, selective attention, vigilance, and stress tolerance. Psychopathologic symptoms were rated with the Hamilton Rating Scale for Depression.

Results: Before discharge to outpatient treatment, 24% of the patients tested were without clinically relevant psychomotor disturbances. In 60% of the cases, mild to moderate impairments could be seen, and about 16% of the patients were considered as severely impaired in psychomotor functions related to car-driving abilities. Data show that patients treated with selective serotonin reuptake inhibitors (SSRIs) or the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine had an altogether better test performance in comparison with patients receiving tricyclic antidepressants (TCAs). Differences were most pronounced in measures of reactivity, stress tolerance, and selective attention. Statistically significant differences between patients treated with TCAs or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine could not be found. Among the newer antidepressants there is an advantage for patients treated with mirtazapine, especially in tasks with high multi-channel perception and output demands.

*Conclusion:* About 16% of depressive patients discharged from hospital to outpatient treatment must be considered unfit to drive. In 60% of the

cases, patients performed at a questionable level of fitness for driving, and it seems justified to counsel patients individually, taking into account compensational factors. Data point to an advantage for patients treated with SSRIs or mirtazapine when compared with TCAs or venlafaxine. However, causal relationships cannot be drawn from our data.

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slowing of motor and cognitive functions can frequently be found in depressed patients,<sup>1-3</sup> and increasing evidence suggests that deficits within the chain of cognitive functions are likely to be a key factor in psychosocial rehabilitation efforts.<sup>4</sup> An outstanding example of daily life functioning is driving. There have been relatively few attempts to determine what proportion of road traffic accidents involve drivers with a known history of psychiatric illness treated with psychotropic medication. It does seem that psychiatric patients have a higher than expected rate of involvement in road traffic accidents.<sup>5</sup> According to a study by Ray and coworkers,<sup>6</sup> treatment with tricyclic antidepressants (TCAs) is associated with a 2.2 times greater relative risk of accidents in elderly drivers. The intake of amitriptyline at doses  $\ge 125$ mg/day increases the risk of road accidents by 6 times. Although there were a number of confounding factors like health status of the individuals or concomitant use of alcohol, data suggest that these drugs may have contributed to traffic accidents.

Depressed patients may have impaired driving behavior because of the pathology itself, with concentration and

Table 1. Mean Dosages of Antidepressants							
Antidepressant	No. of Patients	Dosage, mg/d <sup>a</sup>					
TCAs							
Amitriptyline	19	128.2 (37.2)					
Doxepin	11	138.6 (45.2)					
Maprotiline	3	133.3 (28.9)					
Trimipramine	7	107.1 (37.4)					
SSRIs							
Citalopram	10	37.5 (7.1)					
Paroxetine	15	38.9 (42.3)					
NaSSA							
Mirtazapine	20	40.7 (9.2)					
SNRI							
Venlafaxine	15	208.9 (78.8)					

<sup>a</sup>Values are shown as mean (SD).

Abbreviations: NaSSA = noradrenergic and specific serotonergic antidepressant, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

attention disturbances and mnemonic and executive function deficits. In addition, adverse effects of antidepressant treatment, such as sedation, agitation, sleep disturbances, and central anticholinergic effects, may be detrimental. Most TCAs and selective serotonin reuptake inhibitors (SSRIs) in use are comparable in their therapeutic efficacy. Newer antidepressants seem to be more effective with patients who are more severely depressed,<sup>7</sup> whereas SSRIs cause less impairment in tests of cognition and psychomotor functioning.<sup>8,9</sup>

The effects of antidepressants on actual driving performance were investigated in various studies of healthy volunteers. Driving performance was affected after acute doses of sedating antidepressants but returned to placebo levels after 1 week of treatment. Nonsedating antidepressants generally did not affect driving ability but had a serious impact on driving when combined with benzodiazepines with incompatible pharmacokinetic profiles (for a review see Ramaekers<sup>10</sup>).

There is little research available about patients' fitness to drive while receiving clinically relevant dosages of antidepressive treatment. Gerhard and Hobi<sup>11</sup> demonstrated a significant improvement between the acute and chronic phase of pharmacologic treatment with TCAs, although patients performed worse than normal control subjects on all tests. Polydrug treatment with antidepressants did not reveal differences between patients taking TCAs, SSRIs, or monoamine oxidase inhibitors (MAOIs).<sup>12</sup> However, antidepressant monotherapy with newer antidepressants had more salutary effects on driving ability compared to treatment with TCAs.<sup>13,14</sup>

To sum up, there is a paucity of patient studies to evaluate the effects of antidepressants on fitness to drive. The aims of this study were to explore, in depressive patients prior to being discharged to outpatient treatment, (1) what proportion of patients meets the requirements for ability to drive according to the German guidelines for road and traffic safety and (2) whether newer antidepressants compared with TCAs have more salutary effects on psychomotor function related to driving skills. According to the German guidelines for road and traffic safety, we focused on psychomotor functions that are thought to be critical for an assessment of driving ability.

### **METHOD**

## Subjects

We conducted a nonrandomized, comparative clinical study from January 2004 through March 2005 at the District Hospital Gabersee with 100 depressive inpatients. Subjects completing the study included 42 men and 58 women who met the ICD-10 and DSM-IV criteria for major depressive disorder. Additionally, patients were rated with the Hamilton Rating Scale for Depression (HAM-D)<sup>15</sup> on the day of psychomotor assessment. The mean  $\pm$  SD age was 46.8  $\pm$  13.6 years (range, 20–78 years). Forty patients received TCAs, 25 received SSRIs, 20 received the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, and 15 received the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Table 1). All patients participated voluntarily in the study and gave their informed consent. The study was approved by the medical ethics committee of our institution and was conducted in accordance with the Declaration of Helsinki.

Dosage and choice of antidepressants were selected on an individual clinical basis by the treating psychiatrist. Subjects with a history of neurologic illness, substance abuse, or mental retardation were excluded. Inclusion criteria for the study were (1) antidepressant monotherapy, (2) steady-state pharmacologic conditions (all patients were considered for discharge within at least 3 days), and (3) possession of a valid driver's license.

### Procedure

The study followed a naturalistic, nonrandomized design. After informed consent was given, a baseline assessment was carried out, which included HAM-D ratings and collection of sociodemographic and clinical data. All subjects were tested at approximately 9:00 a.m. with computerized psychomotor tests administered by a technician in individual sessions. Complete testing lasted about 2.5 hours for each person and was administered in the same sequence for each study subject.

## **Psychomotor and Visual Perception Tests**

According to the German guidelines for road and traffic safety (described in detail in Laux<sup>16</sup>), various domains were assessed—visual perception, selective attention, vigilance, and reactivity and stress tolerance—which are thought to be critical for an assessment of driving ability. According to these regulations, a test has to be considered

Table 2. Demographic Variables, Diagnoses, and HAM-D Scores of Depressive Patients									
Variable	TCAs $(N = 40)$	SSRIs (N = 25)	$\begin{array}{l} \text{Mirtazapine} \\ (\text{N} = 20) \end{array}$	Venlafaxine (N = 15)	Significance (p < .05)				
Age, mean (SD), y	46.4 (12.4)	44.7 (12.4)	43.5 (13.6)	53.4 (15.7)	Venlafaxine > TCAs Venlafaxine > SSRIs Venlafaxine > mirtazapine				
Gender, N					NS				
Male	17	11	8	6					
Female	23	14	12	9					
Education, mean (SD), y	11.3 (1.4)	11.5 (1.9)	11.4 (1.3)	10.9 (1.4)	NS				
Days since admission, mean (SD)	61.8 (36.4)	61.2 (31.6)	58.4 (20.9)	59.4 (34.5)	NS				
Diagnosis, N									
Bipolar affective disorder (F31 <sup>a</sup> )	5	2	1	4					
Depressive episode (F32 <sup>a</sup> )	25	18	12	11					
Recurrent depressive episode (F33 <sup>a</sup> )	10	5	7	0					
HAM-D score, mean (SD)	10.6 (4.1)	9.9 (4.1)	10.2 (3.2)	10.4 (2.2)	NS				

<sup>a</sup>ICD-10 code.

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, NS = not significant, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Symbol: ... = not applicable.

as failed if a patient falls short of the threshold of 1 standard deviation below mean of normative data derived from a representative sample of car drivers. Patients who failed to pass the criteria were individually counseled, taking into account compensational factors, and were informed about legal consequences and regulations.

Data were collected with the computerized Act & React Testsystem ART-90<sup>17</sup> and the Wiener Testsystem,<sup>18</sup> which had been developed in cooperation with the Austrian Road Safety Board. These test systems offer a number of tests that were found to be predictive for driving performance. The validity of these methods has been confirmed in large samples of both healthy controls and clinical samples (for validation and a detailed description see references 19–22). These authors demonstrated that in 83.3% of subjects a correct classification for adjusted and unadjusted driving behavior could be obtained with results from these test systems.

The test battery comprised the following domains: Visual perception was assessed with the Tachistoscope Test (TT15).<sup>17</sup> Typical traffic situations are presented on 15 color slides, each for 0.75 seconds. After each slide the patient has to answer 3 multiple-choice questions by pointing with an electronic pen on the screen. The number of correct and incorrect answers is registered. Selective attention was measured with the Signal Detection Test (SIGNAL).<sup>18</sup> This test requires a high level of concentration on visual stimuli over a time period of 20 minutes. Subjects have to react to critical stimuli-a square built out of 4 dots-and inhibit responses to irrelevant stimuli. *Vigilance* was assessed with the Vigilance Test (VIGIL),<sup>18</sup> in which patients have to monitor a dot on the screen moving slowly along a circle in fixed steps over a time period of 25 minutes. Subjects are asked to press a key when irregularities can be seen. Reactivity and stress tolerance were examined with the Reactive Stress Tolerance Test (RST3).<sup>17</sup> Color, tone, and light stimuli are presented in 3 test phases with 180 signals each. In the first phase, stimuli are presented with an interstimulus interval (ISI) of 1.58 seconds. The second phase (fast phase) has an ISI of 0.95 seconds, and in the third phase (moderate phase) stimuli appear every 1.07 seconds. Patients have to press corresponding keys and pedals with hands and feet.

# **Statistical Analysis**

Statistical analysis was performed using SPSS software (Statistical Package for the Social Sciences, Ver. 11.5; SPSS Inc., Chicago, Ill., 2002). Multivariate analysis of covariance (MANCOVA) was carried out for psychomotor measures, controlling for severity of illness and age. Significant results at the p < .05 level were followed by univariate F tests, identifying variables contributing significantly to differences between treatment groups. Demographic and clinical characteristics were analyzed with nonparametric tests ( $\chi^2$  and Mann-Whitney U test). All scores from psychomotor assessment were z-transformed.

# RESULTS

# **Demographic Variables**

Demographic details of depressive patients are shown in Table 2. Age significantly differed between treatment groups. Thus, subsequent analyses of test performance were conducted controlling for age.

# **Global Driving Ability Score**

First we examined the overall psychomotor performance according to the regulations of the German guidelines for road and traffic safety. Only 24% of the sample reached the threshold criterion of not more than 1 standard deviation below the mean of normative data. Ten percent of patients treated with TCAs passed the tests without impairments, as did 20% treated with venlafax-



ine, 28% treated with SSRIs, and 50% treated with mirtazapine. There were statistically significant differences in this global measure between patients treated with TCAs versus mirtazapine (p < .05, z = -2.49), mirtazapine versus SSRIs (p < .01, z = -2.62), and mirtazapine versus venlafaxine (p < .05, z = -2.04), indicating a better test performance for patients treated with mirtazapine.

Additionally, we classified, according to previous studies,<sup>12,23</sup> test results of patients as "moderate impairment" (i.e., patients failed in less than 40% of test parameters) and "severe impairment" (i.e., patients failed in more than 40% of test parameters). As the global driving ability score does not integrate information about performance above a percentage of 16, it seems justified to evaluate driving ability in the group labeled as moderately impaired (60%), individually taking into account compensational factors. In about 16% of the cases, psychomotor performance was considered to be severely impaired (Figure 1).

#### **Psychomotor and Visual Perception Tests**

In a second step, we compared treatment groups on individual functional domains. Multivariate analysis of covariance was first performed to assess group differences in psychomotor test variables. Depressive patients treated with TCAs showed a more impaired performance when compared with those treated with either SSRIs or mirtazapine. Statistically significant differences between patients treated with TCAs versus venlafaxine could not be found. Among subjects treated with the newer antidepressants, the mirtazapine-treated group showed a significantly better test performance. Table 3 summarizes results and main effects of intergroup comparisons on the psychomotor test battery.

Univariate F tests were computed in cases in which MANCOVA yielded results at the p < .05 level. In tests

measuring reactivity and stress tolerance, mirtazapinetreated depressive patients had significantly better results compared to patients treated with TCAs (RST3, phase 2: F = 4.60, df = 1,59; p < .05), subjects treated with SSRIs (RST3, phase 1: F = 4.38, df = 1,44; p < .05; RST3, phase 3: F = 8.30, df = 1,44; p < .01), and patients treated with venlafaxine (RST3, phase 3: F = 5.61, df = 1,34; p < .05).

In the selective attention task (SIGNAL), subjects treated with TCAs significantly differed from SSRItreated patients (F = 6.53, df = 1,64; p < .05) and mirtazapine-treated patients (F = 12.76, df = 1,59; p < .001), indicating a more impaired performance for patients treated with TCAs. Selective serotonin reuptake inhibitors (F = 4.22, df = 1,39; p < .05) and mirtazapine (F = 13.47, df = 1,34; p < .001) also had a clear advantage on this measure when compared with venlafaxine.

#### DISCUSSION

Depression is known to be associated with a slowing of psychomotor and cognitive functions that may have an influence on coping with, for example, social, vocational, or interpersonal demands. The objective of pharmacologic treatment of mental illness is to induce long-lasting remission, allowing the patient to take part in activities of daily life functioning, for example, automobile operation. We investigated depressive inpatients prior to their being discharged from hospital to outpatient treatment following psychopathologic stabilization. Thus, the question of fitness for driving is of great relevance to these patients. The main findings of this study show that 76% of our sample did not pass the threshold criterion according to the German guidelines<sup>16</sup> for road and traffic safety, i.e., not more than 1 standard deviation below the mean of normative data in psychomotor domains. This is in line with previous investigations indicating impairments in fitness for driving in about 70% to 80% of patients recovering from depression.<sup>12-14</sup> Using less conservative criteria allowing patients to fail in up to 40% of test parameters, about 60% of patients can be labeled as mildly to moderately impaired with respect to fitness for driving. These patients may be counseled individually, taking into account compensational factors like driving experience or insight into cognitive and psychomotor dysfunctions. In about 16% of cases, psychomotor performance must be considered as severely impaired, and patients should be regarded as unfit to drive.

Before discussing the outcome of psychomotor functions of treatment groups, it seems appropriate to consider limitations of this study that reduce, to some degree, the interpretability of the results. Only patients who were able to participate in a test procedure that lasted 150 minutes on average were included in the study. Another point is that our study followed a naturalistic design. A causal relationship cannot be claimed from our data because

Test	TCAs $(N = 40)$	$\frac{\text{SSRIs}}{(\text{N}=25)}$	Mirtazapine (N = 20)	Venlafaxine $(N = 15)$	Intergroup Comparisons <sup>c</sup>	Statistic		
						Test	df	р
Tachistoscope Test (TT15)								
Correct items	30.4 (4.3)	30.4 (3.2)	31.6 (3.8)	29.7 (4.8)	TCAs vs SSRIs	F = 2.88	1,64	< .05
Signal Detection Test								
(SIGNAL)								
Score <sup>b</sup>	7.4 (1.6)	6.4 (0.9)	6.0 (1.0)	7.1 (0.5)	TCAs vs mirtazapine	F = 2.24	1,59	< .05
Vigilance Test (VIGIL)								
Score <sup>b</sup>	1.8 (0.8)	1.8 (0.4)	1.5 (0.7)	2.1 (0.2)	TCAs vs venlafaxine	F = 1.41	1,54	NS
Reactive Stress								
Tolerance Test (RST3)								
Phase 1 Omissions	10.2 (18.5)	10.4 (19.5)	1.9 (2.4)	16.2 (22.7)	SSRIs vs mirtazapine	F = 3.56	1,44	< .01
Phase 2 Omissions	40.1 (29.8)	38.0 (33.9)	25.4 (16.1)	53.3 (35.3)	SSRIs vs venlafaxine	F = 2.51	1,39	<.05
Phase 3 Omissions	19.8 (23.3)	23.4 (25.3)	7.9 (7.4)	36.3 (37.1)	Mirtazapine vs venlafaxine	F = 4.19	1,34	< .01

values snown as mean (SD). <sup>b</sup>Score = reaction time +  $\sqrt{[reaction time \times (omissions + errors)]}$ .

<sup>c</sup>Multivariate analysis of covariance with age and HAM-D score as covariates.

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, NS = not significant, SSRI = selective serotonin reuptake inhibitor,

TCA = tricyclic antidepressant.

patients were not randomly assigned to treatments and they were not assessed before and after being placed on the medication regimen selected by the treating physicians. A selection bias cannot be excluded. Nevertheless, our patients represent a population derived from clinical psychiatric practice. Concerns regarding the generalizability of well-controlled antidepressant efficacy studies have been raised. Clinical trials to prove efficacy of pharmacologic treatments are increasingly performed in selected patient samples not taking into account peculiarities of clinical practice. Thus, results of controlled studies probably represent a subset of depressed individuals with a specific clinical profile.24

We showed an advantage for patients treated with SSRIs in global driving ability score and in tasks measuring reactivity, stress tolerance, and selective attention when compared with patients treated with TCAs. These results are in line with other investigations showing that TCAs with sedating properties cause impairments in tasks related to driving skills<sup>9,25,26</sup> and in actual driving tests,<sup>10</sup> whereas driving ability is not affected by SSRIs in healthy subjects,<sup>27-30</sup> and SSRIs may have more salutary effects on psychomotor function than do TCAs in depressive patients.<sup>13,14</sup> However, with the newer antidepressants, there seem to be dose-related side effects with respect to psychomotor and highway driving performance.31,32

Analysis of our data also revealed that venlafaxinetreated patients did not significantly differ in psychomotor performance from patients treated with TCAs. Especially in tasks with high demands on sustained attention, they did worse than patients treated with SSRIs or mirtazapine. One has to keep in mind that our venlafaxinetreated patients were significantly older than patients in the other treatment groups and thus may have been more vulnerable to side effects from pharmacologic treatment. However, in statistical analysis we controlled for confounding effects of age. Thus, data confirm previous results from our study group<sup>14</sup> and are in line with notions that venlafaxine may impair vigilance performance.<sup>33</sup>

Mirtazapine has a strong binding affinity for the postsynaptic histamine H<sub>1</sub> receptor that is thought to play a major role in the development of sedation. The impact of mirtazapine on driving performance has been investigated in studies with healthy volunteers, showing that mirtazapine produces impairments in tasks related to driving skills after the acute treatment period, especially when given as a daytime dose.<sup>27,28</sup> This could not, however, be seen with nocturnal doses of mirtazapine or after subchronic treatment.<sup>27,34</sup> All patients treated with mirtazapine were under steady-state pharmacologic conditions and received their doses as an evening or nocturnal dose, i.e., the night before assessing psychomotor function. Our data revealed that patients treated with mirtazapine performed significantly better than patients in the other treatment groups, especially on tests with high demands on psychomotor speed and integration of acoustic and visual stimuli. Treatments were given on an individual clinical basis by the treating psychiatrist, taking into account specific psychopathologic symptoms of depression and side effects of pharmacologic treatment. One explanation for our results may be that under optimized pharmacologic treatment, no impairing effects on psychomotor functions can be seen, and in tasks with a high cognitive load, there even seems to be an advantage for patients treated with mirtazapine. However, these results need further confirmation in a randomized, double-blind, on-off drug study.

In conclusion, the results of our study indicate that most depressive patients considered for discharge to outpatient treatment did not reach the level of psychomotor performance of healthy controls on tasks related to driving ability. In addition, an advantage for patients treated with selective antidepressants over tricyclics was also demonstrated. However, causal relationships cannot be claimed from our data, as confounding factors of illness and medication could not be separated within this study design. To verify our findings, future investigations should address these questions as well as dosing issues, cognitive dysfunctions, the influence of duration of illness, and personality features.

Antidepressants seem to affect fitness to drive differently in depressed patients and thus physicians should be concerned about traffic safety when prescribing antidepressants. A global evaluation of antidepressant treatment that might influence fitness for driving is not possible. The great variability within treatment groups indicates that counseling patients with respect to driving safety must be carried out individually, taking into account primary pathologies, differential effects of pharmacologic treatment, and vocational and social rehabilitation efforts. Additionally, compensational factors like driving experience, personality features, and insight into psychomotor or cognitive impairments have to be taken into consideration.

*Drug names:* citalopram (Celexa and others), doxepin (Sinequan and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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