The Impact of Reboxetine and Mirtazapine on Driving Simulator Performance and Psychomotor Function in Depressed Patients

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Objective: The aim of the present study was to examine the influence of reboxetine and mirtazapine on psychomotor functions related to driving skills and on driving simulator performance in depressed inpatients.

Method: Forty depressed inpatients diagnosed according to DSM-IV-TR criteria were randomly assigned to treatment with either reboxetine (N = 20) or mirtazapine (N = 20). To control for retest effects in psychomotor measures, a group of 10 healthy controls was examined on the same time schedule. Participants were tested once before pharmacologic treatment and twice after initiation of treatment (days 7 and 14) with computerized tests related to car-driving skills. Data were collected with the Act and React Testsystem ART-90 and the Wiener Testsystem, measuring visual perception, reactivity, stress tolerance, concentration, and vigilance. In addition, patients went through various risk simulations on a static driving simulator. Data were analyzed with nonparametric statistics and repeated-measures analysis of variance. The study was conducted from June 2004 through June 2006.

Results: Before onset of treatment with antidepressants, about 65% of patients did not reach the threshold criterion according to the German guidelines for road and traffic safety. After 14 days of treatment with reboxetine or mirtazapine, patients improved in driving ability skills. Controlling for retest effects in psychomotor measures, data indicate that both patient groups significantly improved in tests measuring selective attention and reactivity (all $p < .01$). Furthermore, the frequency of accidents in the risk simulations markedly decreased in patients receiving mirtazapine and reboxetine (all $p < .05$). Statistically significant differences between treatment groups could not be shown.

Conclusion: Our results indicate that partially remitted depressed inpatients treated with reboxetine or mirtazapine show a better performance on tasks related to driving skills than do untreated depressives.

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Driving is a daily activity for most people in developed countries and is important in maintaining independence. A meta-analysis[1] of 62 studies concerning disease and road safety points to an almost doubled risk for psychiatric patients to be involved in road accidents. Depressed patients may have an impaired driving behavior because of the pathology itself, with psychomotor and cognitive disturbances.[2–4] Additionally, adverse effects of antidepressant treatment, such as sedation, agitation, sleep disturbances, and central anticholinergic effects, may be detrimental. According to a study by Ray and coworkers,[5] treatment with tricyclic antidepressants is associated with a 2.2-times greater relative risk of accidents in elderly drivers. The intake of amitriptyline at doses ≥ 125 mg/day increases the risk of road accidents by 6 times.

Most antidepressants in use are comparable in their therapeutic efficacy but differ concerning their side effects.[6] Nonsedating antidepressants generally seem not to affect driving performance but have a serious impact on driving ability when combined with benzodiazepines with incompatible pharmacokinetic profiles.[7] The effects of

pharmacologic treatment on actual driving performance were predominantly investigated in healthy volunteers (for a review, see reference 8). So far, there is little research available about patients' fitness to drive while receiving clinically relevant dosages of antidepressive treatment. Laboratory studies,[9–11] as well as results of on-the-road driving tests,[12] suggest impaired road safety in almost-remitted depressed patients under steady-state pharmacologic conditions. Especially monotherapy with newer antidepressants had less side effects compared to treatment with tricyclic antidepressants.[9,10] However, causal relationships cannot be drawn from these studies, as confounding factors of illness and medication could not be separated within these study designs.

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 (1) whether there are salutary effects of the newer antidepressants reboxetine and mirtazapine on psychomotor functions and in driving simulator performance in depressive inpatients and (2) whether the 2 antidepressants differ concerning their effects on driving ability skills. In accordance with the German guidelines for road and traffic safety,[13] we focused on psychomotor functions that are considered to be critical for driving ability.

METHOD

Subjects

We conducted a randomized, comparative clinical study from June 2004 through June 2006 at the Inn-Salzach-Klinikum, Academic Hospital of Psychiatry, Psychotherapy, and Neurology, with 40 depressed inpatients. Subjects completing the study included 18 women and 22 men diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Additionally, 10 healthy controls (5 women, 5 men) matched in age and years of education were recruited from our staff. Patients were rated on the Hamilton Rating Scale for Depression (HAM-D)[14] at each assessment. In addition, depressive symptoms were rated by the patients using the Beck Depression Inventory (BDI).[15] The mean ± SD age in the patient group was 47.4 ± 8.5 years (range, 25–67 years), and in the control group, 44.0 ± 4.4 years (range, 27–56 years). Twenty patients received mirtazapine, and 20 received reboxetine. Mean dosages of antidepressant treatment in the patient groups are given in Table 1.

Dosage of antidepressant medication was selected on an individual clinical basis by the treating psychiatrist. Subjects with a history of neurologic illness, substance dependence, or mental retardation were excluded. Each patient was in possession of a valid driver's license, participated voluntarily in the study, and gave his or her written informed consent. The study was approved by the medical ethics committee of our institution and was conducted in accordance with the Declaration of Helsinki.

Table 1. Mean Dosages of Antidepressants (mg/d)

	Reboxetine (N = 20)		Mirtazapine (N = 20)	
Variable	Day 7 (t_1)	Day 14 (t_2)	Day 7 (t_1)	Day 14 (t_2)
Mean (SD)	4.5 (1.4)	6.6 (1.9)	30.0 (0.0)	38.2 (9.0)
Range	2–8	2–8	0	30–60

Abbreviations: t_1 = test session 2 on day 7 of pharmacologic treatment, t_2 = test session 3 on day 14 of pharmacologic treatment.

Procedure

Patients were randomly assigned to either the mirtazapine group or the reboxetine group. On average, a period of 5 days elapsed between patient enrollment and the beginning of trial medication. Other psychoactive drugs were prohibited during the trial. After informed consent was given but before initiation of treatment, a baseline assessment (t_0) was carried out, which included HAM-D ratings. All subjects were tested by a technician in individual sessions at approximately 9 a.m. with computerized psychomotor tests and with the driving simulator. The complete testing lasted about 2 hours for each person and was administered in the same sequence. Examiners allowed subjects to take breaks as needed in order to obtain optimal performance. On day 7 (t_1) and day 14 (t_2) after initiation of pharmacologic treatment, assessments were repeated for each patient.

Psychomotor and Visual Perception Tests

In accordance with the German guidelines for road and traffic safety, various domains were assessed—visual perception, selective attention, vigilance, reactivity, and stress tolerance—all of which are thought to be critical for an assessment of driving ability. A test has to be considered as failed if a patient falls short of the threshold of 1 standard deviation below mean in test parameters (percentage < 16). The test performance of a patient is compared with normative data derived from a driving population representative norm sample. Patients who failed to pass the criteria were individually counseled and informed about legal regulations and consequences.

Data were collected with the computerized Act and React Testsystem ART-90[16] and the Wiener Testsystem,[17] which have been developed in cooperation with the Austrian Road Safety Board. The validity of this method has been confirmed in large samples of both healthy controls and clinical subjects (for validation and a detailed description, see references 10, 11, 18, and 19). It could be demonstrated that, with this method, an 83.3% correct classification for adjusted and unadjusted driving behavior could be obtained.

The test battery comprised the following domains: *Visual perception* was assessed with the Tachistoscope

Table 2. Demographic and Clinical Variables

Variable	Reboxetine (N = 20)	Mirtazapine (N = 20)	Healthy Controls (N = 10)
Age, mean (SD), y	45.3 (5.7)	49.2 (10.5)	44.0 (4.4)
Gender, N			
Male	11	11	5
Female	9	9	5
Diagnosis, N			
Moderate major depressive disorder, single episode (296.22)[a]	14	15	…
Severe major depressive disorder, single episode (296.23)[a]	6	5	…
Education, mean (SD), y	10.0 (0.0)	10.7 (1.9)	10.0 (0.0)
Days since admission, mean (SD)	6.7 (5.3)	6.3 (5.8)	…
HAM-D score, mean (SD), t_0	22.6 (6.5)	24.2 (6.7)	1.8 (0.4)
BDI score, mean (SD), t_0	27.4 (11.6)	22.7 (9.7)	0.8 (0.4)

[a]DSM-IV-TR code.
Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, t_0 = test session 1 before initiation of pharmacologic treatment (baseline).
Symbol: … = not collected.

Test.[16] Typical traffic situations are presented on 15 color slides for 0.75 seconds each. After each slide, the patient has to answer 3 multiple-choice questions by pointing to the screen with an electronic pen. The number of correct and incorrect answers is registered. *Selective attention* was measured with the Peripheral Vision Test with tracking task.[16] This test requires subjects to perform a tracking task on a screen in front of them while monitoring a light pattern that randomly moves from the right or left visual periphery to the center of the visual field. Reaction time and tracking results are critical variables in this measure. *Vigilance* was assessed with the Vigilance Test,[17] in which patients have to monitor a dot moving on the screen 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).[16] 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 of 1.58 seconds. The second phase (fast phase) has an interstimulus interval 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.

Driving Simulator

The FT-SR 200 (Fahrsimulator für Fahreignungsuntersuchungen, SimuTech GmbH, Bremen, Germany, 1996) is a static vehicle simulator with videotaped driving scenes that allows researchers to examine responses to traffic situations that cannot be safely evaluated in the field. The driver is seated in a realistic car driver's cab with a screen in front of him or her. The steering wheel, accelerator, and break positions are read by a personal computer. It is possible to display various traffic situations that interact with the driver and to which the driver has to respond. The speedometer and indicator lights on the instrument board also provide feedback. The simulated environment is supplemented by audio effects including engine noise. At test session t_0 and test session t_2, 4 different risk simulations were presented at a time. Before starting the examination, each driver was familiarized with the simulator by driving a 5-minute simulation on a 2-lane highway. The number of accidents was the critical variable in these tests.

Data Analysis

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, Ver. 11.5; SPSS Inc., Chicago, Ill., 2002). A repeated-measures analysis of variance was carried out for psychomotor measures. Post hoc Scheffé tests were computed to specify group differences. Demographic and clinical characteristics, the driving simulator performance, and the global driving ability score were analyzed with nonparametric tests (χ^2 and Mann-Whitney U test).

RESULTS

Demographics

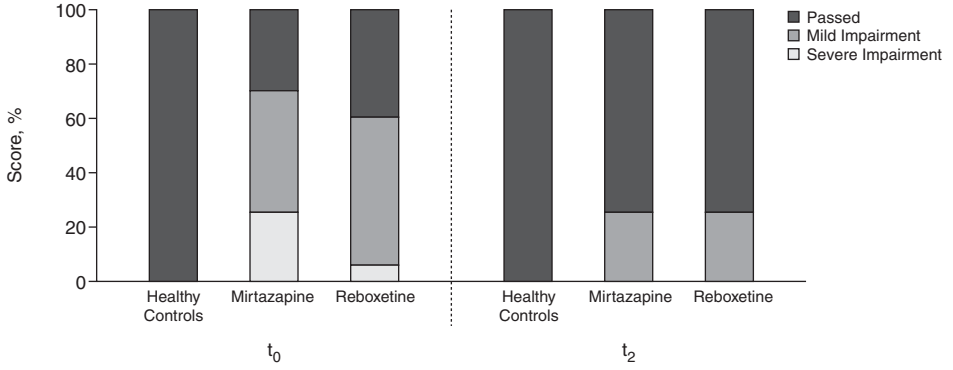
Forty patients and 10 healthy controls were enrolled in the study. A general characterization of the groups is given in Table 2. There were no significant differences between treatment groups with respect to demographic and clinical variables. As expected, treatment groups significantly differed from healthy controls in HAM-D ratings at baseline (mirtazapine vs. healthy controls [$p < .001$, $z = -4.46$], reboxetine vs. healthy controls [$p < .001$, $z = -4.45$]). There were also significant differences in BDI self-ratings (mirtazapine vs. healthy controls [$p < .001$, $z = -4.50$], reboxetine vs. healthy controls [$p < .001$, $z = -4.29$]).

Since baseline comparisons in psychomotor measures revealed significant differences between treatment groups in the peripheral vision task ($F = 4.40$, $p < .05$) and the vigilance task ($F = 9.52$, $p < .01$), subsequent analyses were performed using differential scores of trials (t_0–t_1 and t_1–t_2).

Global Driving Ability Score

In a first step, we analyzed the overall psychomotor performance according to the German guidelines for road and traffic safety. As can be seen in Figure 1, about 65% of untreated patients did not reach the threshold criterion of not more than 1 SD below mean of normative data. After 14 days of treatment with reboxetine ($p < .01$, $z = -3.12$) or mirtazapine ($p < .001$, $z = -3.56$), patients significantly improved on the global driving ability score and about 78% of our sample could be classified as fit to drive with

Figure 1. Global Driving Ability Scores by Study Group (at t_0 and t_2)



Abbreviations: t_0 = test session 1 before initiation of pharmacologic treatment (baseline), t_2 = test session 3 on day 14 of pharmacologic treatment.

respect to psychomotor functions. Mirtazapine-treated patients ($p < .001$, $z = –3.38$) and reboxetine-treated patients ($p < .01$, $z = –2.98$) significantly differed from healthy controls at t_0. Differences at t_2 did not reach statistical significance (mirtazapine: $p = .09$, $z = –1.70$; reboxetine: $p = .09$, $z = –1.69$). Treatment groups did not significantly differ in this global score at t_0 and t_2 (Figure 1).

As already reported in previous studies,[10,11] we additionally classified patients' test results as "moderate impairment" (i.e., patients failed in less than 40% of test parameters) or "severe impairment" (i.e., patients failed in more than 40% of test parameters). From a clinical point of view, it seems justified to evaluate driving ability individually in the group labeled as moderately impaired, considering compensational factors.

Psychomotor and Visual Perception Tests

In a second step, treatment groups were compared on individual functional domains. Multivariate analyses of variance were performed to assess group differences for psychomotor test variables. Groups significantly improved over time in the selective attention task (Peripheral Vision Test), in reactivity (RST3, phase 1), and in stress tolerance (RST3, phase 2). Significant group-by-time effects, indicating differential effects, could be found for concentration and reactivity. Post hoc analyses of group differences revealed that both treatment groups significantly differed from healthy controls in the Peripheral Vision Test and the stress tolerance test (RST3, phase 1), with all $p < .01$. No significant group differences could be observed between the patient groups. Table 3 summarizes results and main effects of intergroup comparisons on the psychomotor test battery.

Reboxetine Versus Mirtazapine

Subsequent analyses to determine whether there were differential treatment effects on psychomotor performance between treatment groups yielded no significant time-by-group effects for the functional domains investigated. No significant time effects on the vigilance task could be observed for both treatment groups.

Driving Simulator Performance

Results of the performance on the driving simulator are given in Figure 2. Both treatment groups significantly differed from healthy controls in driving simulator performance at session t_0 (mirtazapine: $p < .05$, $z = –2.37$; reboxetine: $p < .05$, $z = –2.75$). As can be seen, there is a significant decline in the number of accidents from t_0 to t_2, both in the group treated with reboxetine ($p < .05$, $z = –2.23$) and in the group treated with mirtazapine ($p < .05$, $z = –1.97$). At t_2, no significant differences between treatment groups and healthy controls could be demonstrated. Differences between the reboxetine and mirtazapine groups also could not be observed in this measure.

Psychopathology

Significant improvements in depressive symptoms across trials (t_0–t_2) could be shown both for patients receiving mirtazapine (HAM-D: $p < .001$, $z = –3.74$) and for those receiving reboxetine (HAM-D: $p < .01$, $z = –3.07$). An amelioration could also be seen with the BDI, which focuses more on cognitive symptoms of depression. Mirtazapine-treated patients ($p < .01$, $z = –3.28$) and reboxetine-treated patients ($p < .001$, $z = –3.62$) reported pronounced improvements in depressive symptoms. Significant differences between treatment groups could not be shown.

Correlational analysis yielded that changes in depressive symptoms (t_0–t_2) were associated with changes in psychomotor measures (t_0–t_2). There were significant correlations between selective attention and the BDI score ($r = –0.42$, $p < .05$). Analyses also yielded significant

Table 3. Performance of Depressive Patients (by drug group) and Healthy Controls on Psychomotor Tests[a]

Test	Reboxetine (N = 20)			Mirtazapine (N = 20)			Healthy Controls (N = 10)			Time		Time × Group		Group	
	t_0	t_1	t_2	t_0	t_1	t_2	t_0	t_1	t_2	F Statistic	p Value	F Statistic	p Value	F Statistic	p Value
Tachistoscope test, correct items	32.1 (3.0)	32.4 (3.4)	33.7 (3.9)	29.9 (4.1)	32.1 (4.9)	32.5 (5.7)	33.8 (3.7)	33.6 (4.4)	34.0 (3.8)	0.33	NS	1.11	NS	2.19	NS
Peripheral vision test score[b]	2.2 (0.7)	1.9 (0.4)	1.8 (0.4)	2.7 (0.9)	2.3 (0.7)	2.2 (0.8)	2.0 (0.5)	1.7 (0.4)	1.7 (0.4)	3.73	< .05	22.19	< .001	5.95	< .001
Stress tolerance (RST3 phase 1), omissions	4.5 (5.5)	1.8 (1.6)	1.5 (3.3)	3.1 (3.9)	1.9 (2.5)	1.8 (3.2)	1.5 (1.7)	0.0 (0.0)	0.0 (0.0)	25.07	< .001	46.72	< .001	33.21	.001
Stress tolerance (RST3 phase 2), omissions	32.8 (23.9)	19.1 (21.2)	17.1 (24.3)	27.2 (20.2)	17.6 (20.5)	11.7 (13.7)	20.5 (6.3)	6.6 (2.6)	1.0 (0.0)	5.32	< .05	1.67	NS	1.27	NS
Stress tolerance (RST3 phase 3), omissions	16.7 (19.9)	10.6 (12.5)	7.8 (14.1)	16.6 (16.7)	11.8 (16.5)	6.9 (8.8)	5.9 (5.9)	2.9 (2.5)	0.2 (0.4)	0.82	NS	0.33	NS	2.73	NS
Vigilance test score[c]	1.7 (0.9)	1.6 (0.7)	1.4 (0.7)	3.0 (1.6)	2.2 (1.4)	2.0 (0.9)	1.3 (0.1)	1.7 (0.4)	1.0 (0.5)	2.66	NS	1.05	NS	2.76	NS

[a]Values are shown as mean (SD).
[b]√(reaction time × tracking performance).
[c]reaction time + √[reaction time × (omissions + errors)].
Abbreviations: NS = not significant, RST3 = Reactive Stress Tolerance Test, t_0 = test session 1 before initiation of pharmacologic treatment (baseline), t_1 = test session 2 on day 7 of pharmacologic treatment, t_2 = test session 3 on day 14 of pharmacologic treatment.

correlations between the HAM-D score and reactivity ($r = 0.45$, $p < .01$) and the driving-simulator performance ($r = 0.43$, $p < .01$). There was also a trend toward significant correlations between the HAM-D score and vigilance ($r = 0.38$, $p < .06$).

DISCUSSION

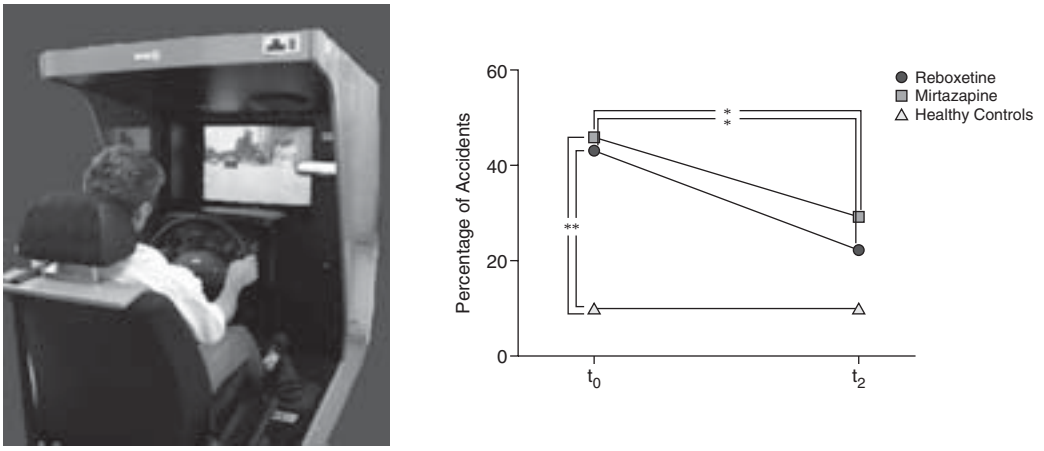
The objective of pharmacologic treatment of mental illness is to enable patients to participate in activities of daily living by inducing a persistent remission. Fitness to drive is essential for many patients in maintaining independence. Thus, road safety under pharmacologic treatment is of great relevance.

The main finding of this study is that treatment with reboxetine or mirtazapine had positive effects on driving skills in depressed inpatients. Before onset of pharmacologic treatment, 65% of our sample did not pass the threshold criterion according to the German guidelines for road and traffic safety. After 14 days of pharmacologic treatment, both groups showed a significant reduction of psychopathologic symptoms as well as distinct improvements in selective attention and reactivity; furthermore, we found a significant decline in accident rates in the risk simulations. Differences between the 2 treatment groups could not be demonstrated.

Depression is known to be associated with a slowing of psychomotor and cognitive functions that partly may persist after remission. Particularly, impairment of sustained attention is likely to be a trait marker of depression[20] and may be the reason for only slight and nonsignificant improvements in the vigilance task in both treatment groups.

The findings of this study are in line with previous studies in healthy subjects[21–24] and clinical investigations in depressive patients[9,10] that show no negative effects of the newer, selective antidepressants on driving performance. Reboxetine is a highly specific noradrenergic antidepressant, whereas mirtazapine is characterized by a strong binding affinity for the postsynaptic histamine H_1 receptor that is likely to be associated with the sedating effects. The results of several investigations revealed no negative effects of reboxetine regarding cognitive and psychomotor skills in healthy volunteers.[25,26] Furthermore, improvements in information processing speed and sustained attention in depressed patients could be shown.[27] A single daytime dose of mirtazapine produced impairment in psychomotor tasks. However, this could not be seen with nocturnal doses or after 1 week of treatment.[24,28] Actually, under pharmacologic steady-state conditions in almost-remitted depressed patients, an advantage for patients treated with the noradrenergic and specific serotonergic antidepressant mirtazapine compared with patients treated with tricyclic antidepressants or selective serotonin reuptake inhibitors citalopram and paroxetine could be shown.[9,10]

Figure 2. Percentage of Accidents in Driving Simulator by Study Group (at t_0 and t_2)



*p < .05.
Abbreviations: t_0 = test session 1 before initiation of pharmacologic treatment (baseline), t_2 = test session 3 on day 14 of pharmacologic treatment.

Both reboxetine and mirtazapine had distinct salutary effects on psychomotor functions that are considered to be critical for driving ability. The salutary effects of mirtazapine could possibly be explained by the nocturnal doses applied, i.e., in the night before being tested, and the 1-week term of application at test session t_1. This confirms findings that mirtazapine has no negative effects on driving ability under long-term treatment and under consideration of intake time.[10,24,28]

Not least, it seems appropriate to consider limitations of this study. Only patients who were able to participate without pharmacologic treatment in a test procedure that lasted 120 minutes, on average, took part in the study. In previous investigations,[9–11] it could be demonstrated that 70% to 80% of patients recovering from depression, prior to discharge to outpatient treatment, still had mild to severe impairments in skills related to driving ability. In our study, at baseline (session t_0) about 30% to 40% of patients already met the criteria of psychomotor functioning according to legal restraints. Thus, a selection bias cannot be excluded. Additionally, we tried to control for retest effects in psychomotor measures by investigating a group of healthy controls. However, we cannot exclude that there may be differences with respect to practice effects between depressed patients and normal controls.

In conclusion, analysis of our data, as well as former investigations, points to an advantage for partly remitted depressive patients receiving reboxetine or mirtazapine in contrast to nontreated patients with regard to driving skills. Our results also have important implications for risk calculations concerning newer, selective antidepressants within legal requirements. It seems that factors of the illness itself should be considered to a greater extent than pharmacologic effects. Particularly, differential effects of pharmacologic treatment need to be considered. Counseling patients with respect to driving safety must be carried out individually, taking into account cognitive disturbances as well as vocational and social rehabilitation efforts. Not least, differentiated package inserts are required, especially in the case of newer, selective antidepressants.

Drug names: citalopram (Celexa and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others).

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