Mirtazapine, a Sedating Antidepressant, and Improved Driving Safety in Patients With Major Depressive Disorder: A Prospective, Randomized Trial of 28 Patients

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Objective: The objectives of the study were to investigate the effects of mirtazapine, a sedating antidepressant, on driving safety in major depressive disorder (MDD) patients and to observe the effect of mirtazapine on daytime alertness.

Method: Twenty-eight patients who met the DSM-IV criteria for MDD completed the study in a university teaching hospital. Half of these patients took mirtazapine 30 mg at bedtime for 30 days. A computerized driving simulator test (DST) and the Maintenance of Wakefulness Test (MWT) were conducted at baseline and on days 2, 9, 16, and 30 after commencement of antidepressant use. Fourteen untreated depressed patients performed a DST and MWT at baseline and on days 2 and 9 to evaluate the possibility of a learning effect. Data collection was from June 2005 through January 2006.

Results: There were significant linear effects of the treatment on road position at All Trials ($p = .018$) and on the morning sessions at 10:00 a.m. ($p < .001$) and 12:00 p.m. ($p = .022$) and on the number of crashes at All Trials ($p = .034$) and the 4:00 p.m. session ($p = .050$) for the group on active treatment. Compared with the values at baseline, those of road position at 10:00 a.m. significantly improved on days 2 ($p < .05$), 9 ($p < .01$), 16 ($p < .01$) and 30 ($p < .01$) and road position at 12:00 p.m. significantly improved on days 16 ($p < .05$) and 30 ($p < .05$). The number of crashes significantly decreased on day 30 ($p < .05$). The untreated patients showed no improvement in performance in any of the measures, suggesting that the results are not due to a learning effect.

Conclusion: A sedating antidepressant can increase driving safety in MDD patients.

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Depression, a disorder affecting 1 in 5 people,[1] influences cognitive functioning,[2] daytime alertness,[3] and sleep.[4–6] The effects of decreased cognition, poor daytime alertness, and impaired sleep not only affect quality of life, but also may alter driving ability and work performance,[7] endangering patients and others.

There is limited and somewhat dated information indicating that antidepressant treatment may improve driving ability in depressed patients,[8] but certain antidepressants have been shown to cause impairment of psychomotor functioning that is relevant to driving performance.[9,10] Mirtazapine is a sedating antidepressant[11] that increases the release of norepinephrine and serotonin neurotransmitters through an increase in cell firing. Significant efficacy has been demonstrated after only 2 weeks of mirtazapine treatment,[11,12] as opposed to the typical 4- to 6-week latency of other antidepressants. Mirtazapine has also been shown to improve sleep efficiency and preserve sleep architecture,[11,13] an uncommon feature for most antidepressants. An improvement in daytime alertness on this medication has been reported.[14] This supports the expectation that driving performance in depressed

patients might be improved after treatment with this antidepressant.

There are a total of 3 reports that are related to mirtazapine's effects on driving performance. Ramaekers et al.[15] studied 18 healthy subjects who received mirtazapine, mianserin, or placebo during separate periods of 15 days. Psychomotor function including position tracking, choice reaction time, and actual driving performance of the subjects were assessed at baseline and on days 2, 8, 9, and 16. Ridout et al.[16] studied 12 healthy volunteers and compared the effects of paroxetine with those of mirtazapine on psychomotor performance and behavior. Wingen et al.[17] investigated 18 healthy subjects who took mirtazapine for 15 days. The results of these studies showed that mirtazapine slightly impaired psychomotor and driving performance on day 2, but not on day 8 or thereafter. Although these studies included subjective and objective driving skill measurements, the subjects in all of these studies were healthy volunteers, not depressed patients. To the best of our knowledge, no prospective controlled studies concerning driving performance effects of a sedating antidepressant in major depressive disorder (MDD) patients are available. Studies of other sedating compounds including hypnotics and alcohol are well recognized to impair driving, but half-life and time of consumption of these agents are of course critical components of this generalization.[18]

The primary objective of this study was to investigate the effect of a sedating antidepressant (mirtazapine) on driving safety in MDD patients. The secondary objective was to observe the effect of mirtazapine on daytime alertness. We hypothesized that the patients receiving treatment with mirtazapine would show an improvement in driving.

METHOD

The University Health Network Research Ethics Board approved the research protocol. All potential subjects signed an informed consent form before they entered the study. The study was carried out in the Sleep Research Laboratory, Toronto Western Hospital, in accordance with the Declaration of Helsinki. The subjects enrolled in the study fulfilled *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (DSM-IV) criteria[19] for MDD based on psychiatric history and the Mini-International Neuropsychiatric Interview.[20] The subjects were 18 years of age or older and held a valid driving license. The study excluded those patients who had taken fluoxetine within 4 weeks or other psychotropic medications and herbal preparations with putative antidepressant or sleep properties within 2 weeks, those who were night shift workers, those who consumed 5 cups of coffee or more a day, those who had bipolar mood disorder or psychotic features in the current episode of depression or any psychotic disorder, as well as those who had a history of alcoholism or drug abuse within the past year. Data collection started in June 2005 and ended in January 2006.

Immediately after the baseline measurement, the treatment period started for those randomly assigned to active treatment. The treatment lasted 30 days. In the evenings during the treatment period, patients took mirtazapine 30 mg, 30 minutes prior to bedtime.

To rule out the possibility of a "learning effect," 14 patients with MDD were randomly assigned to be an untreated group. The inclusion and exclusion criteria of the patients in this group were the same as those in the treatment group. The only difference between the groups was that, after completing measurements at baseline, those patients in the treatment group started taking mirtazapine while those in the untreated group did not take this medication. The subjects in the treatment or untreated groups were assigned randomly.

For ethical reasons, it was deemed unnecessary and inappropriate to have the control group, who were studied primarily to evaluate if there was an early learning effect, to remain in an untreated state for a full month. Furthermore, we reasoned that the most likely time for a learning effect would be within the first week.[21] The untreated group was therefore studied only at baseline, day 2, and day 9. Following day 9, patients in the untreated group ended their tests and were placed on an active treatment.

In this study, we used a "virtual driving environment" consisting of a simulated highway driving scenario. The York Driving Simulator (York Computer Technologies, Kingston, Ontario, Canada) was used to assess driving performance. The simulator has been validated[22,23] as an effective and naturalistic research tool to measure psychomotor performance.

Before starting the baseline measurement, all patients underwent a 10-minute practice session to familiarize them with the driving simulator and to control for possible "learning effects." Eligible subjects were tested within 48 hours of their initial practice session on the simulator. The measurements included the following:

1. Road position: A road is potentially divided into 100 points with a middle line (point 50) separating the road into left and right lanes. During driving, the "ideal" road position is at the center of the right lane, which is the point 25. The closer to point 25, the more safe the position is.
2. Standard deviation of road position: A measurement testing the degree of weaving on the road.
3. Driving speed: The posted speed ranged from 70 to 100 km/h.
4. Reaction time: The time taken to respond to recurrent "virtual wind gust."

5. Number of crashes: Calculated as the number of times that the simulated vehicle crashed into the side of the road or an oncoming vehicle.
6. Deviation from posted speed: This measurement is the only one with a potential of negative values. To avoid a "canceling effect," the absolute values were used.

The driving simulator test (DST) was conducted at baseline and days 2, 9, 16, and 30 for the patients who received mirtazapine treatment and at baseline and days 2 and 9 for the untreated patients. On a given testing day, the DST was repeated on 4 occasions. These sessions started at 10:00 a.m., 12:00 p.m., 2:00 p.m., and 4:00 p.m. Each session lasted 30 minutes. The average of the 4 sessions is the value of All Trials. Therefore, each measurement developed 5 variables: All Trials and sessions 10:00 a.m., 12:00 p.m., 2:00 p.m., and 4:00 p.m.

Each subject performed the Maintenance of Wakefulness Test (MWT)[24] on the same day as the DST days. An MWT is a standardized test[24] in which the subject is placed in a dark room in a sleep laboratory for 30 minutes and asked to attempt to stay awake. This procedure was conducted at 9:00 a.m., 11:00 a.m., 1:00 p.m., and 3:00 p.m. The purpose of the MWT is to determine the subject's ability to stay awake. The mean of the 4 sessions is reported as the value of the MWT. The MWT has been demonstrated to be capable of discriminating normal individuals from patients with a variety of sleep disorders[25] and to be sensitive to treatment effects related to sleep disturbance.[26]

The mood of all study subjects was evaluated with the Beck Depression Inventory-II (BDI-II).[27] The BDI-II is a 21-item self-report questionnaire with a score range between 0 and 63. A high score on the BDI-II is indicative of a severe depressive condition. BDI-II data were collected at baseline and on days 9, 16, and 30 in the treatment group and at baseline and on day 9 in the untreated group.

The data were stored and analyzed using SPSS version 15.0 (SPSS Inc., Chicago, Ill.). The repeated-measures analysis of variance (rMANOVA), including pairwise comparisons, was used to analyze the progressive effects of the DST and MWT data of the treatment group at 5 time points (baseline and days 2, 9, 16, and 30) and those of the untreated group at 3 time points (baseline and days 2 and 9). The rMANOVA was also used to evaluate the progressive linear effect of BDI-II at baseline and days 9, 16, and 30 in the treatment group. Mixed-model analysis of variance (ANOVA) was used to compare the values of 3 time points (baseline and days 2 and 9) between treated and untreated groups to observe group-over-time (factor × time) effect. The Student t test was used to compare the decrement values of BDI-II from baseline to day 9 between the treated and untreated groups. Decrement value is calculated with the BDI-II value at baseline minus that on day 9. Due to the high standard deviations (SDs), the BDI-II data were modified with a logarithmic management.

Table 1. Demographic and Clinical Characteristics of the Subjects in the Treated and Untreated Groups

Characteristic	Treated Group	Untreated Group
Sample size, N	14	14
Female	12	10
Male	2	4
Age, mean ± SD, y	45.9 ± 11.9	45.4 ± 11.8
Age range	29–67	26–62
BDI-II score, mean ± SD	25.8 ± 14.8	26.1 ± 10.8

Abbreviation: BDI-II = Beck Depression Inventory-II.

RESULTS

Subject Characteristics

Table 1 shows the sample size, age distribution, and the scores of BDI-II at baseline in the mirtazapine-treated and untreated groups. The number of female patients in the treated group was slightly higher than that in the untreated group. The sample sizes of the 2 groups were the same (N = 14). The age distribution and range and BDI-II values were very similar in the 2 groups.

Of the 14 subjects in the treatment group, 13 completed. One patient failed to complete the DST and the MWT on day 30. Missing data were managed with a last-observation-carried-forward procedure. All the subjects in the untreated group completed data collection.

Distributions of the Measurements

Table 2 provides the information on the distributions of DST measurements. Distributions of the variables in the categories of road position, standard deviation of road position, driving speed, and reaction time are presented with means ± SDs. Because of a lack of normal distribution, the variable distributions in the categories of number of crashes and deviation from posted speed are expressed with median.

Untreated Depressed Patients

No significant progressive time effects were found on any of the driving measurements or variables for the untreated group (p values were between .062 and .988), indicating that the values of any given variable at the 3 time points (baseline and days 2 and 9) were not significantly different. There were no progressive time effects on the mean values of MWT ($F = 2.653$, $df = 2,52$; $p = .080$), indicating that there were no significant changes in alertness measures among baseline and days 2 and 9 assessments. Paired t test results showed that the depressive scores between baseline and day 9 on the BDI-II did not change significantly ($t = 1.825$, $p = .089$).

Table 2. Distributions of the Variables of the Driving Simulator Test Measurements in the Treated and Untreated Groups

	Treated Group (N = 14)					Untreated Group (N = 14)		
Variable	Baseline	Day 2	Day 9	Day 16	Day 30	Baseline	Day 2	Day 9
Road position, mean ± SD								
All trials	28.5 ± 2.9	27.8 ± 2.3	27.5 ± 2.4	26.8 ± 2.6	26.8 ± 2.2	28.7 ± 4.9	29.7 ± 5.8	30.4 ± 7.7
10:00 a.m.	29.7 ± 3.3	27.9 ± 2.5	27.2 ± 2.5	26.8 ± 2.6	26.8 ± 2.1	29.2 ± 5.6	29.2 ± 6.0	30.2 ± 7.4
12:00 p.m.	28.1 ± 2.7	27.4 ± 2.6	27.4 ± 2.5	26.4 ± 2.3	26.5 ± 2.1	28.8 ± 5.9	29.5 ± 7.0	31.1 ± 9.4
2:00 p.m.	27.3 ± 3.0	27.4 ± 2.6	27.6 ± 2.7	26.7 ± 3.1	26.6 ± 2.7	27.6 ± 2.9	29.3 ± 5.4	30.8 ± 8.7
4:00 p.m.	28.9 ± 4.2	28.4 ± 2.9	27.8 ± 2.8	27.4 ± 3.2	27.4 ± 2.7	29.2 ± 6.4	30.7 ± 6.1	29.4 ± 6.1
Road position, standard deviation, mean ± SD								
All trials	7.6 ± 1.7	7.5 ± 1.6	7.2 ± 1.5	7.1 ± 2.0	7.1 ± 1.7	8.8 ± 4.2	8.7 ± 4.4	9.2 ± 4.8
10:00 a.m.	8.1 ± 2.3	7.4 ± 2.2	7.3 ± 1.9	7.0 ± 2.1	7.1 ± 2.0	8.5 ± 3.8	8.1 ± 3.8	9.1 ± 4.7
12:00 p.m.	6.9 ± 1.1	6.9 ± 1.4	6.7 ± 1.4	7.0 ± 1.7	6.7 ± 1.4	8.4 ± 4.2	8.5 ± 4.9	9.2 ± 5.0
2:00 p.m.	7.4 ± 1.8	7.6 ± 1.8	7.8 ± 2.4	6.9 ± 2.1	7.1 ± 1.8	8.9 ± 4.5	8.6 ± 4.4	9.7 ± 5.1
4:00 p.m.	8.0 ± 2.6	8.2 ± 2.7	7.0 ± 1.7	7.5 ± 3.1	7.3 ± 2.0	9.3 ± 4.6	9.6 ± 5.9	8.6 ± 5.0
Driving speed, mean ± SD								
All trials	91.5 ± 7.4	95.4 ± 10.3	101.2 ± 25.8	105.6 ± 36.9	97.7 ± 28.4	88.7 ± 6.7	86.3 ± 9.4	88.4 ± 8.9
10:00 a.m.	90.0 ± 7.8	91.2 ± 3.5	98.4 ± 19.8	105.0 ± 34.9	97.1 ± 27.4	85.4 ± 6.0	85.6 ± 9.1	87.0 ± 6.5
12:00 p.m.	90.5 ± 3.8	89.9 ± 2.7	100.7 ± 24.8	106.3 ± 37.4	98.0 ± 29.0	87.9 ± 5.2	85.3 ± 11.3	89.7 ± 14.2
2:00 p.m.	90.1 ± 8.4	93.0 ± 9.4	103.0 ± 27.7	105.3 ± 37.5	97.4 ± 28.0	90.7 ± 9.6	87.1 ± 11.6	88.8 ± 9.7
4:00 p.m.	95.5 ± 15.7	107.3 ± 32.9	102.8 ± 31.9	106.0 ± 37.8	98.5 ± 29.1	90.9 ± 12.9	87.2 ± 7.2	88.2 ± 9.0
Reaction time, mean ± SD								
All trials	1.3 ± 0.3	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.4	1.7 ± 0.3	1.7 ± 0.4	1.7 ± 0.4
10:00 a.m.	1.4 ± 0.6	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.4	1.7 ± 0.3	1.7 ± 0.4	1.7 ± 0.4
12:00 p.m.	1.2 ± 0.5	1.2 ± 0.5	1.2 ± 0.3	1.2 ± 0.4	1.3 ± 0.4	1.7 ± 0.3	1.7 ± 0.4	1.7 ± 0.5
2:00 p.m.	1.3 ± 0.4	1.2 ± 0.5	1.1 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	1.8 ± 0.4	1.8 ± 0.4	1.7 ± 0.5
4:00 p.m.	1.2 ± 0.4	1.2 ± 0.3	1.0 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.7 ± 0.5	1.7 ± 0.4	1.7 ± 0.4
Number of crashes, median								
All trials	1.25	0.88	0.50	0.25	0.25	0.25	0.25	0.25
10:00 a.m.	1.50	0.00	0.50	0.00	0.00	1.00	1.00	0.00
12:00 p.m.	1.00	0.00	0.50	0.50	0.00	0.00	0.50	0.00
2:00 p.m.	1.00	0.00	0.50	0.00	0.00	0.00	0.00	0.00
4:00 p.m.	0.00	1.00	0.00	1.00	0.00	0.50	0.50	0.00
Deviation from posted speed, median								
All trials	1.65	2.80	2.10	1.49	1.56	3.43	2.15	1.29
10:00 a.m.	2.87	2.52	1.98	1.86	1.65	2.32	0.66	1.64
12:00 p.m.	1.02	1.79	3.46	3.82	1.52	2.88	0.90	1.34
2:00 p.m.	1.51	2.29	4.06	1.51	1.75	2.16	2.89	2.17
4:00 p.m.	1.76	3.40	2.09	2.04	1.87	2.55	2.21	1.71

Road Position

There were significant progressive linear effects of treatment on road position at All Trials and sessions 10:00 a.m. and 12:00 p.m. (Table 3). This tendency was most significant for the 10:00 a.m. session (Figure 1). Pairwise comparisons analysis showed that compared with baseline (mean ± SD = 29.75 ± 3.30), the mean ± SD value of road position for session 10:00 a.m. significantly decreased on day 2 (27.88 ± 2.47, $p < .05$), day 9 (27.20 ± 2.46, $p < .01$), day 16 (26.79 ± 2.65, $p < .01$), and day 30 (26.77 ± 2.09, $p < .01$). During session 12:00 p.m., the road position significantly decreased from 28.07 ± 2.75 at baseline to 26.39 ± 2.29 on day 16 ($p < .05$) and 26.54 ± 2.14 on day 30 ($p < .05$). These results indicate that after taking the sedating antidepressant, the road position of the patients in the treatment group improved, with patients moving toward the safest point (25), i.e., in the center of the right lane of the road.

Results of the mixed-model ANOVA indicate significant group-over-time (factor × time) effect for 3 time points (baseline and days 2 and 9) for All Trials and session 10:00 a.m., indicating that the difference in these 2 variables between the treated group and the untreated group became significant on day 9 (Table 3 and Figure 1).

Number of Crashes

At baseline the difference in the number of crashes between the 2 groups was not statistically different ($t = –0.987$, $p = .333$). After taking mirtazapine, the patients in the treatment group showed a progressive and linear reduction in number of crashes at All Trials ($p = .034$) and session 4:00 p.m. ($p = .050$) (Table 3). Compared with baseline (1.88 ± 1.91), the number of crashes at All Trials significantly decreased on day 30 (0.37 ± 0.65, $p < .05$) in the treatment group.

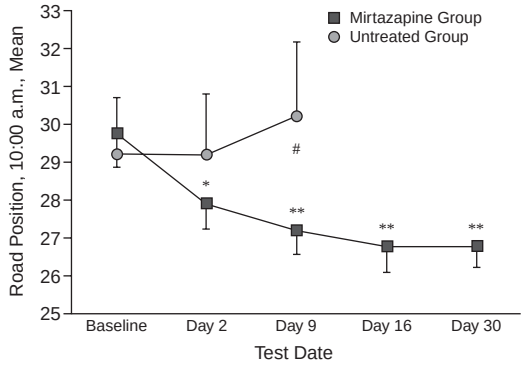
Other Measurements

The results of the rMANOVA show that there were no time effects or group-over-time effects of mirtazapine on any session for standard deviation of road position,

Table 3. Time and Factor-Over-Time Effects on the Measurements of the Driving Simulator Test

Variable	Time Effect, Treated Group (5 time points) F (df)	p Value	Time Effect, Untreated Group (3 time points) F (df)	p Value	Factor-Over-Time Effect (3 time points) F (df)	p Value
Road position						
All trials	4.467 (2.2,28.8)	.018	1.789 (1.4,17.6)	.200	4.442 (1,26)	.045
10:00 a.m.	6.420 (4,52)	< .001	0.733 (1.2,15.7)	.430	6.314 (1,26)	.019
12:00 p.m.	3.129 (4,52)	.022	1.605 (1.3,16.7)	.228	3.156 (1,26)	.087
2:00 p.m.	1.219 (3.6,46.6)	.315	1.933 (1.4,18.6)	.179	1.776 (1,26)	.194
4:00 p.m.	1.578 (2.7,34.7)	.216	1.299 (1.1,14.9)	.279	1.089 (1,26)	.306
Road position, standard deviation						
All trials	1.219 (4,52)	.314	0.731 (2,26)	.491	2.277 (1,26)	.143
10:00 a.m.	1.359 (3.2,41.5)	.268	1.910 (2,26)	.168	3.204 (1,26)	.085
12:00 p.m.	0.508 (4,52)	.730	1.429 (2,26)	.258	2.428 (1,26)	.131
2:00 p.m.	1.022 (4,52)	.404	2.250 (2,26)	.126	0.369 (1,26)	.549
4:00 p.m.	1.135 (4,52)	.351	0.626 (1.1,14.3)	.457	2.114 (1,26)	.158
Driving speed						
All trials	1.277 (2.2,28.9)	.297	3.101 (2,26)	.062	2.522 (1,26)	.124
10:00 a.m.	1.577 (1.9,24.6)	.227	0.832 (1.2,15.5)	.396	1.262 (1,26)	.271
12:00 p.m.	1.730 (2.1,27.8)	.194	1.097 (2,26)	.349	1.291 (1,26)	.266
2:00 p.m.	1.773 (2.1,27.8)	.187	3.128 (1.4,18.4)	.082	4.656 (1,26)	.040
4:00 p.m.	0.826 (3.1,40.7)	.491	2.997 (1.3,16.3)	.096	2.114 (1,26)	.158
Reaction time						
All trials	1.295 (2.1,27.6)	.291	0.012 (2,26)	.988	1.893 (1,26)	.181
10:00 a.m.	1.288 (2.1,26.8)	.293	0.447 (2,26)	.644	0.759 (1,26)	.392
12:00 p.m.	0.277 (2.0,26.1)	.761	0.015 (2,26)	.985	0.042 (1,26)	.840
2:00 p.m.	2.276 (3.1,40.5)	.092	0.016 (2,26)	.984	1.979 (1,26)	.171
4:00 p.m.	0.876 (2.5,32.5)	.447	0.064 (2,26)	.938	1.243 (1,26)	.275
Number of crashes						
All trials	2.821 (4,52)	.034	0.362 (2,26)	.700	0.478 (1,26)	.495
10:00 a.m.	2.004 (3.1,40.6)	.126	0.155 (2,26)	.857	0.424 (1,26)	.520
12:00 p.m.	1.455 (4,52)	.229	0.848 (1.4,18.6)	.408	1.348 (1,26)	.256
2:00 p.m.	0.855 (2.1,26.7)	.439	1.746 (2,26)	.194	0.435 (1,26)	.515
4:00 p.m.	2.964 (2.7,35.4)	.050	2.617 (2,26)	.092	0.012 (1,26)	.915
Deviation from posted speed						
All trials	1.058 (2.3,29.8)	.368	0.228 (2,26)	.798	1.647 (1,26)	.211
10:00 a.m.	1.316 (1.9,24.2)	.285	0.091 (2,26)	.914	0.785 (1,26)	.384
12:00 p.m.	1.729 (2.2,28.0)	.194	0.870 (2,26)	.431	0.763 (1,26)	.390
2:00 p.m.	0.870 (2.4,30.9)	.445	0.063 (2,26)	.939	2.036 (1,26)	.166
4:00 p.m.	0.759 (3.1,40.0)	.527	1.692 (2,26)	.204	1.717 (1,26)	.202

Figure 1. Changes of Road Position at the 10:00 a.m. Session of the Driving Simulator Test Among Patients With Major Depressive Disorder[a]



[a]There is a clear tendency toward reduction in the treated group (i.e., showing an improved road position) but not in the untreated group. Note that the value 25 on road position indicates the center point of the lane in the driving simulator.
*p < .05 vs. baseline.
**p < .01 vs. baseline.
#Significant difference between the mirtazapine group and the untreated group.

driving speed, deviation from posted speed, and reaction time, indicating that there was no difference between each of the time points for each measurement in the treatment group, and no difference when compared to those not on treatment.

On the MWT, the mean ± SD sleep latency (in minutes), compared with that at baseline (23.62 ± 6.91), was reduced on day 2 (18.39 ± 8.91, $p < .05$) in the treatment group. Then, the mean ± SD sleep latency increased over time and was not significantly different from those standardized normal values of baseline; for example, on day 30, (23.32 ± 6.84) it is close to the baseline level. The results of rMANOVA show that mirtazapine does not have linear time effects in the treated group or in the untreated group, nor does it have group × time effects between these groups.

At baseline, the mean value of the BDI-II in the treatment group (25.8 ± 14.8) was close to that of the untreated group (26.1 ± 10.8). By day 9, the mean decrement in the treatment group was 3.8, but that in the untreated group was only 1.7. The difference in the decrements between groups was significant (t = 2.164,

p = .040). The rMANOVA results show that mirtazapine had linear time effects on the BDI-II in the treatment group (F = 3.169, df = 2,39; p = .035).

Because the mean BDI-II score significantly declined during the treatment, it was of interest to evaluate the relationship between the changes of driving performance and BDI-II score and observe the effect of BDI-II when examining the effect of the drug on driving test variables. To examine if any effect of mirtazapine on the improvement in the variables of the driving test is independent of its effect on mood (BDI-II), a Pearson correlation test was performed to evaluate the correlations of the differences between the BDI-II and road position, and between the BDI-II and number of crashes at each time point and the All-time during the treatment. Differences are calculated using the values of a given time point (day 2, 9, 16, or 30; N = 14) minus those at baseline. *All-time* data (N = 56) include those of 4 time points. The correlation coefficients (r values) between the BDI-II and road position are –0.043 (p = .884) on day 2, –0.198 (p = .498) on day 9, –0.225 (p = .440) on day 16, 0.428 (p = .127) on day 30, and 0.038 (p = .779) in All-time, and the r values between the BDI-II and number of crashes are 0.066 (p = .882) on day 2, 0.390 (p = .167) on day 9, 0.220 (p = .450) on day 16, 0.410 (p = .145) on day 30, and 0.283 (p = .035) in All-time. Although the r value between the BDI-II and number of crashes in All-time (0.035) reaches statistical significance, the r value per se is very low (0.283). All other correlations have no significance statistically. The results indicate that the effect of mirtazapine on the improvements of road position and number of crashes are not affected by mood promoting effect of the medication.

DISCUSSION

This study examined the effects of the sedating antidepressant mirtazapine on driving performance in MDD patients. In this study, we show that this antidepressant has significant effects on road position and number of crashes, but not on the other 4 metrics of driving. The untreated group showed no changes in driving performance.

Road position is associated with an individual's ability to adjust to lane position while driving. It is frequently used as the primary parameter to evaluate psychomotor performance and driving safety.[28–30] After taking mirtazapine, the value of road position in the treatment group was closer to the "ideal" value of 25, indicating that driving safety had increased. This driving safety benefit was more significant at sessions 10:00 a.m. and 12:00 p.m. than at sessions 2:00 p.m. and 4:00 p.m. By day 9, the safety level in the mirtazapine treatment group at session 10:00 a.m. was significantly higher than that in the untreated group. This phenomenon was also seen at All Trials. The observation of greater improvement in the early sessions may be related to the well-recognized circadian pattern in depressed mood (lower affect in the morning), although no direct measure of mood variation across the day was made in this study.

The number of crashes is another important metric estimating driving safety. The association between the number of crashes and road position is evident. Sagberg[31] investigated 9200 subjects who were involved in vehicular collisions and found that more than half (56%) of the crashes were due to crossing the right edge-line (40%) and the centerline (16%). Mirtazapine decreased the number of crashes at All Trials from a mean value of 1.88 at baseline to 0.37 on day 30, representing a drop of 80.3%. This is in contrast to a lack of significant change in the untreated group.

Depressed patients may have psychomotor disturbances.[32] It is reported that a depressed novice driver has decreased driving skills,[33] and the risk of collisions in older depressed adults is 2.5 times higher than nondepressive older individuals.[34] Two studies have suggested that depression is the most important reason for driving cessation in older drivers.[35,36] Recently, we have found that, compared with normal controls, MDD patients show an increased number of crashes and lengthened steering reaction time.[37]

The reasons for increased driving risk and accidents in depressed patients may be numerous. First, depressed mood per se may be a risk factor. Depressed patients may pay less attention to the consequences of accidents. Second, depressed individuals often have impaired attention, concentration, and cognitive function.[2] Many depressed patients have anxiety and irritability, which may further decrease the driver's attention and concentration. Further, the prevalence of sleep disturbances, fatigue, and sleepiness is higher in depressed patients,[10] and it may be a critical determinant of driving performance in depressed individuals.[38]

Finally, we have alluded to the circadian aspect of depression that may interact with driving performance across the day. To the best of our knowledge this is the first study to evaluate driving performance in depressed patients with measures at different times across the day and showing some diurnal effects. It is noteworthy that these diurnal effects are not simply predicted by the usual circadian nadir in performance.

Mirtazapine increases the release of both norepinephrine and serotonin. This allows mirtazapine to be a potent antidepressant with a more rapid onset than many other antidepressants, including selective serotonin reuptake inhibitors.[11,39–41] Simultaneously, mirtazapine effectively reduces anxiety symptoms.[42] Furthermore, mirtazapine is an effective sleep promoter. In a recently completed study,[11] we found that mirtazapine significantly promoted sleep quality in patients with MDD. This included a significant and continuous increment of slow-wave sleep over a 2-month period.[11] Slow-wave sleep is widely

regarded as the restorative component of sleep,[43] and it may be this slow-wave sleep enhancement that is critical in the driving difference we have observed although, based on the information we have, one could as easily argue that the improvement of mood is also a critical factor in driving improvement.

A recently published study has further supported the above arguments. In accordance with a road and traffic safety guideline, Brunnauer et al.[32] measured global driving ability and psychomotor functions on visual perception, reaction time, selective attention, vigilance, and stress tolerance in 100 MDD patients who received treatment with various antidepressants including mirtazapine. Results showed that the global driving ability of the patients who were treated with mirtazapine ($N = 20$) was significantly better than those treated with SSRIs ($N = 25$, $p < .05$), venlafaxine ($N = 15$, $p < .05$), or tricyclic antidepressants ($N = 40$, $p < .01$). Mirtazapine-treated patients had advantages in tasks with highly complicated perception demands.[32] Clearly, the findings of the Brunnauer et al. study[32] have a facilitating effect on the clinical impact of our observations.

One concern with a sedating antidepressant is that the sedation induced may have a carry-over effect into daytime function and worsen driving performance. The results of the MWT indicate that, compared with baseline, the mean sleep latency decreases on day 2 in the mirtazapine treatment group; however, by day 9, the difference is not significant and progressively normalizes. These results are analogous to those reported by Radhakishun et al.[14] In that study, the investigators studied 140 patients and found that mirtazapine decreased alertness after the first dose. However, after the second dose (on day 2) the alertness ratings recovered and by the end of the study (day 14), the alertness ratings increased to a level 18% higher than those at baseline. The authors partially attributed the increased alertness of the patients to mirtazapine's sleep-enhancing effects.[14]

Some limitations of this study need to be discussed. As mentioned, due to ethical consideration, the untreated MDD patients could be observed for only 9 days. This renders a complete comparison of treatment and untreated study groups impossible. A small sample size may further limit the interpretation of the results. In this study, we use the MWT as an objective neurophysiologic index of alertness and recognize that alertness and sleepiness are not simply opposite ends of the same spectrum.[44] Future research in this field might benefit from having both MWT and multiple sleep latency test (an index of sleepiness)[45] performed. These symptoms (lack of alertness and/or increased sleepiness) have a negative effect on daytime function and performance.[46]

In summary, this study has demonstrated that mirtazapine has a significant time-dependent linear tendency of promoting road position centralization and decreasing the number of crashes in MDD patients taking mirtazapine in the evening. The aggregate effect of mirtazapine on driving is to increase driving safety.

To further clarify the possible sleep-related driving-promoting mechanism of mirtazapine, future study needs to compare this medication with other antidepressants.

Drug names: fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor and others).

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