# Actual Driving Performance and Psychomotor Function in Healthy Subjects After Acute and Subchronic Treatment With Escitalopram, Mirtazapine, and Placebo: A Crossover Trial

Marleen Wingen, M.Sc.; John Bothmer, Ph.D.;
Stefan Langer, M.Sc.; and Johannes G. Ramaekers, Ph.D.

***Objective:*** The effects of escitalopram 10 to 20 mg/day and mirtazapine 30 to 45 mg/day on actual driving and psychomotor performance of 18 healthy subjects were determined in a randomized, double-blind, placebo-controlled, multiple-dose, 3-way crossover trial.

***Method:*** Each treatment period lasted for 15 days and was separated from the next period by a washout period of at least 13 days. Subjects received an evening dose of escitalopram 10 mg, mirtazapine 30 mg, or placebo from days 1 to 7 and an evening dose of escitalopram 20 mg, mirtazapine 45 mg, or placebo from days 8 to 15. On days 2, 9, and 16, reflecting acute period, dose increase, and steady state, respectively, the Road Tracking Test was performed. The main parameter was standard deviation of lateral position. Psychomotor performance was also assessed on days 2, 9, and 16 by laboratory computer tasks. Subjective sleep quality was measured with the Groninger Sleep Quality Scale, and mood was measured by visual analogue scales.

***Results:*** Treatment differences were apparent during the acute treatment period, in which subjects treated with mirtazapine 30 mg performed less well on the driving test as compared to placebo. The Divided Attention Task results also revealed a significant increase in tracking error after a single dose of mirtazapine 30 mg as compared to placebo. Mirtazapine decreased feelings of alertness and contentedness. Mirtazapine did not affect performance on days 9 and 16 of treatment. Escitalopram did not affect driving, psychomotor performance, or subjective mood throughout treatment.

***Conclusion:*** Driving performance, as well as psychomotor functioning, was not affected by escitalopram treatment in healthy subjects. Driving performance was significantly impaired after ingestion of mirtazapine 30 mg during the acute treatment period.

*(J Clin Psychiatry 2005;66:436–443)*

*Received Dec. 2, 2004; accepted Jan. 27, 2005. From the Experimental Psychopharmacology Unit, Brain & Behaviour Institute, University of Maastricht, Maastricht, the Netherlands (Ms. Wingen and Dr. Ramaekers); and Lundbeck GmbH, Hamburg, Germany (Dr. Bothmer and Mr. Langer).*

*This study was sponsored by H. Lundbeck A/S, Copenhagen, Denmark.*

*The results have previously been presented (as a poster) at the 25th Congress of the College of International Neuropsychopharmacology, Paris, France, June 20–24, 2004, and at the 17th congress of the European College of Neuropsychopharmacology, Stockholm, Sweden, October 9–13, 2004.*

*We are thankful to A. van Oers; P. van Ruitenbeek, M.Sc.; M. Klomp; J. van Hoogh, M.Sc.; and C. J. van Leeuwen, M.D., for their assistance in the data collection.*

*Corresponding author and reprints: Marleen Wingen, M.Sc., Maastricht University, Faculty of Psychology, Department of Neurocognition (Experimental Psychopharmacology Unit), P.O. Box 616, 6200 MD Maastricht, the Netherlands (e-mail: m.wingen@psychology.unimaas.nl).*

Escitalopram is the S-enantiomer of citalopram, and it is the most selective serotonin (5-HT) reuptake inhibitor (SSRI). Escitalopram treats major depressive disorder effectively[1] and has been shown to be superior to citalopram.[2] The standard dose is 10 or 20 mg daily and the most common side effect is nausea.[3] Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA), and its therapeutic effect is derived by blockade of the $\alpha_2$-adrenoceptors and by indirect stimulation of the 5-$HT_1$ receptors, via blockade of 5-$HT_2$ and 5-$HT_3$ receptors.[4] Mirtazapine has shown antidepressant efficacy in placebo-controlled trials.[5] The most prominent side effects of mirtazapine are drowsiness or sedation, dry mouth, increased appetite, and weight gain.[6,7] Sedation is attributed to mirtazapine's high affinity for blocking the histaminergic $H_1$ receptor.[5] The sedative effects of mirtazapine may potentially last for a prolonged period, as the drug possesses an elimination half-life of 20 to 40 hours.

Antidepressants can have an impairing effect on psychomotor function and car driving due to side effects, such as sedation, blurred vision, or dizziness. These side effects may reduce the driving ability of depressed patients. However, not all antidepressants influence driving ability to the same extent. In cases of severe major depression, an effective antidepressant with few side effects may even improve driving performance when alleviating the

depression.[8–10] Selective antidepressants, such as SSRIs, are known to have fewer impairing effects on car driving than tricyclic antidepressants (TCAs) in depressed patients.[11] In addition, driving should be contraindicated during the starting phase of treatment with TCAs, because of the sedating effects that appear immediately after acute doses.[12]

A few studies have determined the effects of citalopram or escitalopram on psychomotor performance and tasks related to driving performance in healthy volunteers.[13–16] An acute dose of citalopram 10 mg showed comparable effects to placebo on a number of psychomotor tests and on a driving simulator test.[13] Herberg[14] found that citalopram 20 and 40 mg daily did not impair psychomotor performance in healthy subjects. In another placebo-controlled study,[15] an improvement in choice reaction time and critical flicker fusion threshold was shown 1 to 4 hours after citalopram 20 mg administration. Other psychomotor tests showed no improvement, i.e., the Digit Symbol Substitution Test and the Trailmaking B Test.[15] After 1 and 8 days' administration of 10, 20, and 40 mg of citalopram in another study,[16] there were no detrimental effects on psychomotor functioning, including the choice reaction time test and compensatory tracking, compared to placebo.

In general, it can be said that citalopram is free of impairing psychomotor effects. There are some indications that citalopram as well as escitalopram in some degree decreases vigilance.[17–19] The relevance of this finding for actual driving performance is, however, presently unclear. No previous studies have been carried out to assess the effects of citalopram or escitalopram on actual driving performance. The aim of the present study was to compare the influence of acute and subchronic treatment with escitalopram and mirtazapine on actual driving performance and psychomotor functioning in healthy subjects.

## METHOD

### Subjects

Eighteen healthy subjects, 9 men and 9 women, mean (SD) age = 31.4 (5.8), were recruited by advertisement in local newspapers. Subjects were screened by a telephone interview and a health questionnaire, and all underwent a medical examination (including a standard 12-lead electrocardiogram, blood hematology and chemistry, urinalysis, and drug and pregnancy screening). Selection was based on the following inclusion criteria: possession of a valid driving license for more than 3 years, driving experience of > 5000 km per year on average, normal binocular visual acuity corrected or uncorrected, and body mass index of 19 to 29 kg/m$^2$. Subjects who met 1 or more of the following criteria were excluded from the study: history or present evidence of a serious illness such as renal, hepatic, cardiovascular, pulmonary, endocrine, neurologic or psychiatric, hematologic, or gastrointestinal diseases; medical history of glaucoma; pregnancy (as determined at screening) or breastfeeding; known hypersensitivity to medicinal drugs; treatment with an investigational drug within 3 months prior to screening; use of medicines (except oral contraceptives and paracetamol); excessive smoking (more than 10 cigarettes a day); overconsumption of alcohol (more than 35 g of ethanol a day, comparable to 3.5 standard drinks) or caffeine (more than 6 cups of regular coffee a day); positive result of urine drug screening at the screening visit for alcohol and/or drug of abuse; positive result of hepatitis C virus antibody or hepatitis B surface antigen testing or blood donation.

The study was approved by the standing medical ethics committee of Maastricht University and was carried out in accordance with the World Medical Association's Declaration of Helsinki (Edinburgh, 2000). Written informed consent was obtained from each subject prior to participation.

### Design and Treatments

The study was a randomized, double-blind, placebo-controlled, 3-way crossover design. Treatments were administered in separate 15-day series, and treatment orders were balanced and assigned by a predetermined randomization schedule. Subjects received 10 mg/day of escitalopram on days 1 to 7 followed by 20 mg/day of escitalopram on days 8 to 15, 30 mg/day of mirtazapine on days 1 to 7 followed by 45 mg/day of mirtazapine on days 8 to 15, or placebo. Drugs and placebo were always ingested at fixed times in the evening. Dosing started the evening before (day 1) the first test day (day 2). The treatment sessions were separated by washout periods of at least 13 days.

### Testing Procedure

Subjects were trained in 2 sessions 1 week prior to their first treatment condition in driving and psychometric tests to minimize learning effects. Training in the Critical Tracking Task and the Divided Attention Task (see detailed descriptions below) continued until the subject had performed each test with less than 5% variance from the average over the final 3 trials. The assessments were done on day 2 (referred to as *acute*), day 9 (dose increase), and day 16 (steady state) of each treatment series, 12 to 16 hours after drug administration. Subjects were not allowed to consume alcohol 48 hours prior to testing and caffeine-containing beverages 4 hours prior to testing. On each test day, subjects were screened for alcohol use in breath and for recent drug use in urine for opiates, methadone, cocaine, amphetamines, Ecstasy, and cannabinoids. During testing, subjects were not allowed to smoke. Subjects arrived at 9:00 a.m., and psychometric tests started at 9:30 a.m. The driving test started at 10:30 a.m.

***Actual Driving Performance (Road Tracking Test).*** In the Road Tracking Test,[20] subjects operated a specially

instrumented vehicle over a 100-km primary highway circuit while maintaining a constant speed (95 km or 58 miles per hour) and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. The vehicle was dual controlled, and the subject was accompanied by a driving instructor. An electro-optical device mounted at the rear of the car continuously measured lateral distance separating the vehicle and the left lane line. This signal was digitized at a rate of 4 Hz and stored on an onboard computer disk file for later editing analysis. The offline editing routine involved removal of all data segments that revealed signal loss, disturbance, or occurrence of passing maneuvers. The remaining data were then used to calculate means and variances for lateral position and speed. Standard deviation of lateral position (SDLP in centimeters) was taken as a variable. SDLP is a measure of road tracking error; in practical terms, it is a composite index of allowed weaving, swerving, and overcorrecting. The standard deviation of the speed was also taken as a performance measure. The test duration was to be about 1 hour; the actual test duration varied between 45 and 120 minutes.

***Critical Tracking Task.*** Critical Tracking Task[21] measures the subject's ability to control a displayed error signal in a first-order compensatory tracking task. Error was displayed as an increasing horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements nulled the error by returning the cursor to the midpoint. The frequency at which the subject lost control was the critical frequency or $\lambda_c$ in rad/s. The test included 5 trials, of which the lowest and the highest scores were discarded; the average of the remaining scores was taken as the final score.

***Divided Attention Task.*** Divided Attention Task[22] measures the ability to divide attention between 2 tasks performed simultaneously. First, the subject performed the Critical Tracking Task as described above but at a constant level of difficulty set at 50% of his or her maximum capacity for 12 minutes. Tracking error is measured as the difference in millimeters between the position of the cursor and the midpoint of the scale. Second, the subject monitored 24 peripheral displays upon which single digits change asynchronously at 5-second intervals. The occurrence of the digit "2" was a signal for the subject to remove the foot from a pedal as rapidly as possible. Signals occurred twice at every location, in random order, at intervals of 5 to 25 seconds. Mean absolute tracking error (in millimeters) and average reaction time (in milliseconds) were taken as variables.

***Syntactical Reasoning Task.*** A series of 32 sentences were presented to the subject. Each described the order of 2 letters, e.g., "B follows A." Each sentence is followed immediately by the same letters, printed on the computer screen, e.g., "AB." In half of the trials, the order is the same as described by the preceding sentence, and in the other half of the trials, the order is opposite. Sentence difficulty varies within the series, from simple active sentences as given above to more complicated sentences involving passives, negatives, or both, e.g., "B is not followed by A." The required response was to indicate as quickly as possible, using appropriate push buttons, whether or not the pair of letters was in the same order as given in the preceding sentence. This task measures working memory.[23] Correct number of responses and mean reaction time were the measurements.

***Digit Symbol Substitution Test.*** The Digit Symbol Substitution Test (DSST) is a computerized version of the original paper-and-pencil test taken from the Wechsler Adult Intelligence Scale[24] and is a measurement of psychomotor speed, concentration, and attention. The subject was briefly shown an encoding scheme consisting of a row of squares at the top of the screen in which 9 digits were randomly associated with particular symbols. The same symbols were presented in a fixed sequence at the bottom of the screen as a row of separate response buttons. The randomization procedures were chosen such that symbols never appeared at the same ordinal position within both rows. The encoding scheme and the response buttons remained visible while the subject was shown successive presentations of a single digit at the center of the screen. The task was to match each digit with a symbol from the encoding list and click the corresponding response button. The number of digits correctly encoded within 3 minutes was the performance measure.

***Subjective Measurements.*** Different visual analogue scales were used to assess subjective measurements of mood and drug effects on driving. In addition, each test day subjects filled out the Groninger Sleep Quality Scale[25] to assess sleep quality during the preceding night. The measurements were a total score of 14 yes/no questions to score the number of sleep complaints (ranging from good sleep [score = 0] to worst possible sleep [score = 14] and specific questions about time needed to fall asleep, number of awakenings during the night, and sleep duration in hours. Adverse events observed, spontaneously reported by the subject, or elicited by a nonleading question were recorded. After the psychometric tests, subjects were asked to assess their mood by filling in a 16-item mood scale from which the factors alertness, contentedness, and calmness were derived.[26] Subjects were asked to rate their driving performance after the Road Tracking Test, and the driving instructor was asked to rate the driving performance and the degree of sedation of the subject after the Road Tracking Test.

### Pharmacokinetics

Blood samples for serum drug level analysis were collected on days 2, 9, and 16 of each treatment period using the following procedure: peripheral venous access was established, and the required blood sample of 7 mL of whole

blood was taken. The blood samples were analyzed for serum concentration of escitalopram, the S-enantiomer and R-enantiomer of the metabolites demethylcitalopram (DCT) and didemethylcitalopram (DDCT), and for mirtazapine by means of a validated analysis method according to the principles of Good Laboratory Practice.

### Statistical Analyses

Sample size was based on a power calculation for detecting a treatment difference of 2.0 cm or more on the primary measure, i.e., SDLP. A treatment difference of 2.4 cm was found to be clinically relevant, which corresponds with a blood alcohol concentration (BAC) of 0.5 mg/mL in a study of social drinkers performing the same Road Tracking Test.[27] The power of detecting a mean difference of 2.0 cm was calculated to be greater than 90% using the noncentral T-distribution, with the within-subject standard deviation being 2.1 cm as estimated in previous studies carried out by the Maastricht University research group.[12]

Parameters of the Road Tracking Test, psychometric tests, and subjective mood scales were subject to analyses of variance with subject, treatment, and period as factors. Driving and psychomotor data were analyzed for each test day separately. In case of a main treatment effect, drug-placebo effects were determined using simple contrasts.

The results of the Groninger Sleep Quality Scale were not normally distributed. To examine the main treatment effects, the variables were analyzed by the Friedman test (nonparametric). In case of a significant treatment effect, drug-placebo comparisons were defined through the Wilcoxon signed-rank test (nonparametric). All statistical tests were conducted using SPSS (version 11.5 for Windows; SPSS Inc., Chicago, Ill.).

## RESULTS

### Missing Data

A total of 18 subjects completed the study. The Road Tracking Test was interrupted by the driving instructor in 1 subject after treatment with mirtazapine 30 mg/day (day 2) because he fell asleep while driving. In this case, the remaining data (64% complete) were used to calculate driving measurements. There were no missing data concerning the psychometric tests. One subject did not complete the Groninger Sleep Quality Scale during the second day of placebo treatment. These incomplete data were treated as missing values.

### Driving and Psychometric Tests

Summary of the results of the driving test and the psychometric tests is shown in Table 1. Standard deviation of lateral position showed a significant effect of treatment and period ($F = 5.59$, $df = 2,32$; $p < .05$) on day 2. Drug-placebo comparisons revealed an impairing effect of mirtazapine (30 mg), but not of escitalopram (10 mg). No interaction was found between treatment and period. Treatments did not affect SDLP on days 9 and 16. Results of the SDLP are presented in Figure 1.

Mean (SE) tracking error in the Divided Attention Task is presented in Figure 2 for each treatment condition. Significant effects of treatment and period ($F = 3.46$, $df = 2,32$; $p < .05$) were found on tracking error in the Divided Attention Task on day 2. Mirtazapine (30 mg) significantly increased tracking error, as demonstrated by drug-placebo contrasts. Escitalopram (10 mg) had no effect on tracking error on day 2 compared to placebo. No interaction was found between treatment and period. There were no significant treatment effects demonstrated on days 9 and 16.

For the remaining performance measurements, no statistically significant effects of treatment were established.

### Subjective Measurements

Summary of the results of subjective mood measurements is shown in Table 1. Alertness and contentedness were significantly affected by treatment on day 2. Drug-placebo comparisons revealed that mirtazapine (30 mg) reduced alertness and contentedness. No significant treatment effects were demonstrated on day 2 for the factor calmness or on days 9 and 16 for the 3 factors.

Summary of the results of Groninger Sleep Quality Scale and subjective driving measurements is shown in Table 2. Friedman test revealed effects of treatment on sleep duration on nights 1 and 15. Drug-placebo comparisons showed that escitalopram significantly reduces sleep duration by 67 minutes, whereas mirtazapine increased sleep duration by 58 minutes during the first night of treatment. Other drug-placebo comparisons did not reveal significant differences.

Effects of treatment on day 2 were significant for the ratings of driving performance by the driving instructor and by the subjects. Drug-placebo comparisons, however, revealed no significant treatment effects on driving performance rated by the driving instructor. Subjects rated their driving performance worse after mirtazapine (30 mg) treatment, demonstrated by placebo-drug comparisons. There was also a significant treatment effect on day 9 on driving performance as rated by the subjects, but this could not be attributed to any of the drugs as compared to placebo.

### Adverse Events

The adverse event with the highest incidence in the escitalopram group was fatigue followed by insomnia, somnolence, and headache (Table 3). In the mirtazapine group, the adverse event with the highest incidence was fatigue, followed by somnolence and dizziness. In the placebo group, fatigue, insomnia, and headache occurred most frequently.

**Table 1. Summary of the Results of the Driving Test, Psychometric Tests, and Subjective Mood Measurements in Healthy Subjects Enrolled in a Crossover Trial of Escitalopram, Mirtazapine, and Placebo (N = 18)**

| | | Mean (SEM) | | | Treatment Effect Overall | | | Contrast Analyses: Escitalopram[a] vs Placebo | Contrast Analyses: Mirtazapine[a] vs Placebo |
|---|---|---|---|---|---|---|---|---|---|
| Measure | Day | Placebo | Escitalopram[a] | Mirtazapine[a] | F | df | p | p | p |
| Driving test | | | | | | | | | |
| Standard deviation of lateral position, cm | 2 | 17.9 (0.72) | 18.1 (0.87) | 21.8 (1.36) | 13.1 | 2,32 | < .001 | NS | < .001 |
| | 9 | 18.2 (0.87) | 19.2 (0.97) | 19.5 (1.03) | 2.34 | 2,32 | NS | … | … |
| | 16 | 18.6 (1.01) | 19.4 (0.94) | 19.2 (0.94) | 0.503 | 2,32 | NS | … | … |
| Standard deviation of speed, km/h | 2 | 1.68 (0.09) | 1.61 (0.08) | 1.68 (0.09) | 0.470 | 2,32 | NS | … | … |
| | 9 | 1.71 (0.11) | 1.72 (0.11) | 1.66 (0.08) | 0.108 | 2,32 | NS | … | … |
| | 16 | 1.68 (0.82) | 1.76 (0.08) | 1.68 (0.07) | 0.578 | 2,32 | NS | … | … |
| Psychometric test | | | | | | | | | |
| Critical Tracking Task, rad/s | 2 | 4.17 (0.18) | 4.20 (0.18) | 3.96 (0.17) | 2.60 | 2,32 | NS | … | … |
| | 9 | 4.08 (0.17) | 4.20 (0.16) | 4.02 (0.16) | 1.62 | 2,32 | NS | … | … |
| | 16 | 4.28 (0.16) | 4.21 (0.15) | 4.19 (0.14) | 0.516 | 2,32 | NS | … | … |
| Divided Attention Task | | | | | | | | | |
| Tracking error, mm | 2 | 17.0 (0.96) | 15.5 (0.91) | 19.1 (1.14) | 7.65 | 2,32 | .002 | NS | .032 |
| | 9 | 17.2 (1.26) | 16.0 (0.81) | 18.0 (1.13) | 1.96 | 2,32 | NS | … | … |
| | 16 | 16.2 (1.03) | 16.0 (1.07) | 17.0 (1.01) | 0.749 | 2,32 | NS | … | … |
| Reaction time, ms | 2 | 1683 (79) | 1633 (56) | 1717 (60) | 1.12 | 2,32 | NS | … | … |
| | 9 | 1727 (80) | 1659 (67) | 1671 (63) | 0.687 | 2,32 | NS | … | … |
| | 16 | 1646 (59) | 1616 (65) | 1612 (53) | 0.233 | 2,32 | NS | … | … |
| Syntactical Reasoning Task | | | | | | | | | |
| No. of correct responses | 2 | 22.7 (1.53) | 23.4 (1.48) | 23.7 (1.60) | 0.516 | 2,32 | NS | … | … |
| | 9 | 24.0 (1.63) | 24.3 (1.32) | 23.6 (1.50) | 0.348 | 2,32 | NS | … | … |
| | 16 | 23.4 (1.69) | 25.3 (1.19) | 23.3 (1.44) | 1.17 | 2,32 | NS | … | … |
| Reaction time, ms | 2 | 1489 (94) | 1530 (88) | 1613 (85) | 2.27 | 2,32 | NS | … | … |
| | 9 | 1417 (93) | 1474 (98) | 1483 (88) | 0.603 | 2,32 | NS | … | … |
| | 16 | 1430 (92) | 1463 (81) | 1406 (85) | 2.79 | 2,32 | NS | … | … |
| Digit Symbol Substitution Test, no. of correct responses | 2 | 76.1 (2.76) | 77.2 (2.35) | 75.1 (2.16) | 0.945 | 2,32 | NS | … | … |
| | 9 | 78.1 (2.88) | 78.9 (2.45) | 77.0 (1.92) | 0.629 | 2,32 | NS | … | … |
| | 16 | 79.6 (2.07) | 78.8 (2.02) | 78.4 (2.11) | 0.279 | 2,32 | NS | … | … |
| Subjective mood measurement | | | | | | | | | |
| Alertness, mm | 2 | 79.2 (3.88) | 74.6 (4.65) | 60.3 (5.10) | 11.9 | 2,32 | < .001 | NS | < .001 |
| | 9 | 71.5 (5.15) | 73.6 (3.68) | 68.9 (5.52) | 0.812 | 2,32 | NS | … | … |
| | 16 | 76.9 (5.78) | 76.0 (4.28) | 71.3 (4.53) | 1.70 | 2,32 | NS | … | … |
| Contentedness, mm | 2 | 85.3 (3.42) | 82.7 (3.55) | 80.5 (3.51) | 4.24 | 2,32 | .023 | NS | .007 |
| | 9 | 81.5 (3.72) | 83.9 (3.51) | 80.8 (4.35) | 1.35 | 2,32 | NS | … | … |
| | 16 | 84.9 (3.54) | 84.8 (3.94) | 83.6 (3.80) | 0.235 | 2,32 | NS | … | … |
| Calmness, mm | 2 | 83.7 (4.06) | 80.1 (4.68) | 83.1 (4.14) | 3.05 | 2,32 | NS | … | … |
| | 9 | 83.6 (3.38) | 81.9 (4.72) | 85.2 (3.21) | 0.502 | 2,32 | NS | … | … |
| | 16 | 87.8 (2.54) | 81.9 (4.58) | 82.3 (3.68) | 1.74 | 2,32 | NS | … | … |

[a]Treatment doses on days 1–7: 10 mg escitalopram or 30 mg mirtazapine; on days 8–15, 20 mg escitalopram or 45 mg mirtazapine.
Abbreviations: df = degrees of freedom, NS = not significant.
Symbol: … = analysis not conducted.

### Pharmacokinetics

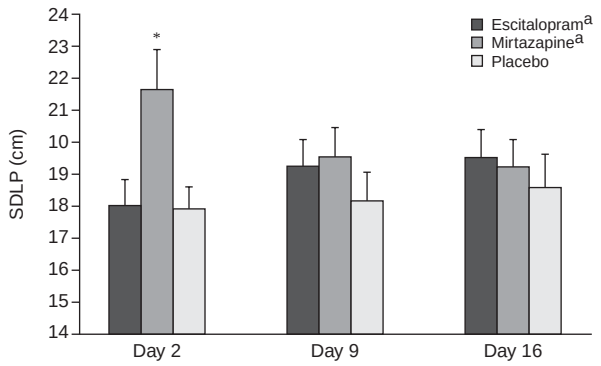
Mean (SD) plasma concentrations for escitalopram were 20.17 (4.60) nmol/L at day 2, 71.44 (27.89) nmol/L on day 9, and 97.78 (41.46) nmol/L on day 16. Mean (SD) plasma concentrations for mirtazapine were 67.67 (16.52) nmol/L on day 2, 166.07 (52.64) nmol/L on day 9, and 203.67 (98.48) nmol/L on day 16. The values were within the expected therapeutic range.

## DISCUSSION

The main goal of the present study was to compare the effect of different evening doses of escitalopram and mirtazapine on actual driving performance as measured by the subjects' mean SDLP during the Road Tracking Test. Results from the present study showed that escitalopram did not affect driving performance in the acute (10 mg), dose increase (20 mg), or steady-state treatment phase. Mirtazapine, on the other hand, produced driving impairment after the initial dose as indicated by a significant rise in mean SDLP compared to placebo. In the case of 1 subject, the driving test could not be completed due to excessive sleepiness after a single dose of mirtazapine 30 mg. Mirtazapine's detrimental effect on driving decreased over time and was no longer of clinical relevance after repeated dosing.

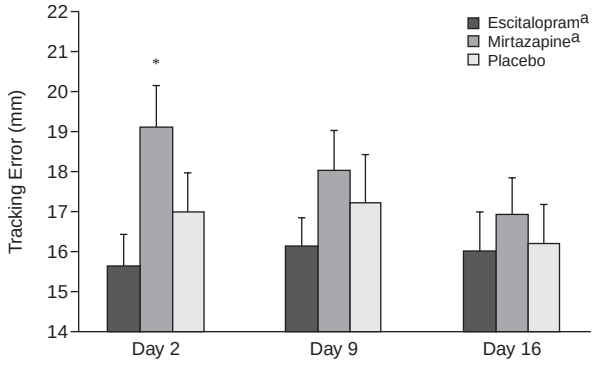
Escitalopram (10–20 mg) did also not affect psychomotor function after single and repeated doses. Mirtazapine impaired tracking in a Divided Attention Task. This effect, however, was only apparent after a single

**Figure 1. Mean (SE) Standard Deviation of Lateral Position (SDLP) After 2, 9, and 16 Days of Crossover Treatment With Escitalopram, Mirtazapine, and Placebo (N = 18)**




[a]Treatment doses on days 1–7: 10 mg escitalopram or 30 mg mirtazapine; on days 8–15, 20 mg escitalopram or 45 mg mirtazapine.
*p < .001.

**Figure 2. Mean (SE) Tracking Error of the Divided Attention Task After 2, 9, and 16 Days of Crossover Treatment With Escitalopram, Mirtazapine, and Placebo (N = 18)**




[a]Treatment doses on days 1–7: 10 mg escitalopram or 30 mg mirtazapine; on days 8–15, 20 mg escitalopram or 45 mg mirtazapine.
*p < .05.

**Table 2. Summary of the Results of the Groninger Sleep Quality Scale and Subjective Driving Measurements in Healthy Subjects Enrolled in a Crossover Trial of Escitalopram, Mirtazapine, and Placebo (N = 18)**

| | | | | | | | | Contrast Analyses | |
|---|---|---|---|---|---|---|---|---|---|
| | Time Point, | Mean (SEM) | | | Treatment Effect Overall | | | Escitalopram[a] vs Placebo | Mirtazapine[a] vs Placebo |
| Measure | Night | Placebo | Escitalopram[a] | Mirtazapine[a] | $\chi^2$ | df | p | p | p |
| No. of sleep complaints | 1 | 2.29 (0.87) | 4.83 (0.96) | 3.33 (0.70) | 3.23 | 2,32 | NS | … | … |
| | 8 | 3.28 (1.00) | 4.72 (0.81) | 3.61 (0.52) | 2.49 | 2,32 | NS | … | … |
| | 15 | 3.56 (0.88) | 4.61 (0.99) | 2.72 (0.49) | 2.27 | 2,32 | NS | … | … |
| Time needed to fall asleep, min | 1 | 16.4 (4.15) | 36.1 (14.5) | 17.5 (7.00) | 4.13 | 2,32 | NS | … | … |
| | 8 | 17.6 (4.23) | 15.4 (3.09) | 25.0 (7.62) | 0.13 | 2,32 | NS | … | … |
| | 15 | 22.1 (4.85) | 21.4 (4.41) | 21.8 (4.52) | 0.98 | 2,32 | NS | … | … |
| No. of awakenings | 1 | 0.94 (0.38) | 2.11 (0.54) | 1.29 (0.34) | 4.33 | 2,32 | NS | … | … |
| | 8 | 1.44 (0.33) | 1.44 (0.35) | 1.17 (0.39) | 2.72 | 2,32 | NS | … | … |
| | 15 | 1.14 (0.33) | 1.83 (0.48) | 0.61 (0.22) | 5.77 | 2,32 | NS | … | … |
| Sleep duration, h | 1 | 7.24 (0.23) | 6.12 (0.39) | 7.82 (0.28) | 13.7 | 2,32 | .001 | .007 | .05 |
| | 8 | 7.11 (0.34) | 7.10 (0.22) | 7.56 (0.32) | 2.86 | 2,32 | NS | … | … |
| | 15 | 7.28 (0.32) | 6.76 (0.24) | 7.78 (0.22) | 12.76 | 2,32 | .002 | NS | NS |
| | Day | | | | | | | | |
| Driving rated by subject, mm | 2 | 77.4 (4.62) | 71.3 (4.79) | 12.3 (53.7) | 6.37 | 2,32 | .041 | NS | .025 |
| | 9 | 75.4 (5.15) | 65.4 (5.02) | 67.7 (5.50) | 6.68 | 2,32 | .036 | NS | NS |
| | 16 | 71.9 (5.6) | 63.0 (3.89) | 66.3 (5.09) | 3.44 | 2,32 | NS | … | … |
| Driving rated by instructor, mm | 2 | 81.1 (2.23) | 79.2 (2.69) | 74.8 (3.27) | 6.96 | 2,32 | .031 | NS | NS |
| | 9 | 76.6 (3.82) | 75.0 (3.58) | 78.3 (4.35) | 1.94 | 2,32 | NS | … | … |
| | 16 | 77.1 (3.06) | 71.3 (4.75) | 74.4 (3.47) | 1.53 | 2,32 | NS | … | … |
| Sedation rated by instructor, mm | 2 | 19.5 (6.01) | 20.9 (6.70) | 28.2 (7.16) | 1.34 | 2,32 | NS | … | … |
| | 9 | 18.3 (5.94) | 20.0 (5.15) | 18.2 (5.83) | 0.76 | 2,32 | NS | … | … |
| | 16 | 20.2 (5.78) | 26.0 (5.58) | 18.4 (4.30) | 2.66 | 2,32 | NS | … | … |

[a]Treatment doses on days 1–7: 10 mg escitalopram or 30 mg mirtazapine; on days 8–15, 20 mg escitalopram or 45 mg mirtazapine.
Abbreviations: df = degrees of freedom, NS = not significant.
Symbol: … = analysis not conducted.

dose and not after repeated drug administration. On the first night of treatment, subjective measurements of sleep showed a reduction of sleep duration after escitalopram administration and an increase of sleep duration after mirtazapine administration. In addition, subjective measurements of driving performance showed that subjects rated their driving performance much worse after mirtazapine 30 mg treatment.

Results of the present study are fully in line with current notions regarding the effects of escitalopram and mirtazapine on psychomotor and/or driving performance. Escitalopram is an SSRI, and SSRIs have generally been shown to produce no or little effect on psychomotor function and cognition. Mild psychomotor or cognitive impairment is most likely to occur for SSRIs possessing some affinity for muscarinic receptors such as paroxetine and fluvoxamine,

**Table 3. Most Common Adverse Events in Healthy Subjects Enrolled in a Crossover Trial of Escitalopram, Mirtazapine, and Placebo, N (%) (N = 18)**

| Adverse Event | Placebo | Escitalopram[a] | Mirtazapine[a] |
|---|---|---|---|
| Fatigue | 3 (16.7) | 6 (33.3) | 11 (61.1) |
| Insomnia | 3 (16.7) | 4 (22.2) | 2 (11.1) |
| Somnolence | 1 (5.6) | 4 (22.2) | 7 (38.9) |
| Headache | 3 (16.7) | 4 (22.2) | 2 (11.1) |
| Dizziness | 1 (5.6) | 3 (16.7) | 5 (27.8) |
| Dry mouth | 1 (5.6) | 3 (16.7) | 1 (5.6) |
| Nausea | 2 (11.1) | 3 (16.7) | 1 (5.6) |
| Agitation | 0 (0) | 1 (5.6) | 0 (0) |

[a]Treatment doses on days 1–7: 10 mg escitalopram or 30 mg mirtazapine; on days 8–15, 20 mg escitalopram or 45 mg mirtazapine.

or for $\alpha_1$ receptors such as nefazodone.[12] Escitalopram, however, is the most selective SSRI available and possesses no affinity for additional receptors systems.[3] The absence of any driving and psychomotor impairment in the present study provides further evidence that therapeutic doses of escitalopram do not affect driving performance.

Mirtazapine is an $\alpha_2$ antagonist that is known to possess strong, antagonistic binding affinities for postsynaptic serotonergic and histaminergic receptors. The antagonistic effect on histaminergic $H_1$ receptors is not thought to mediate therapeutic effects. Rather, $H_1$ blockade causes somnolence and sedation that may result in performance impairment on a range of activities. The sedative effects of mirtazapine may potentially last for a prolonged period, as the drug possesses an elimination half-life of 20 to 40 hours. Consequently, mirtazapine is generally given at night to promote sleep and reduce daytime drowsiness.

Several investigations about the effects of mirtazapine on psychomotor function and driving in healthy volunteers have been reported. Ramaekers et al.[28] assessed the effect of evening doses of mirtazapine for 15 days. Actual driving and psychomotor assessments were conducted on days 2, 8, 9, and 16 of each period. Subjects received mirtazapine in doses of 15 mg and 30 mg nocte during the first and second week of dosing, respectively. Mirtazapine 15 mg nocte increased SDLP (the main driving parameter) by 2.2 cm after the first dose, which was less than shown by social drinkers performing the same Road Tracking Test with a BAC of 0.5 mg/mL.[27] The magnitude of mirtazapine-induced impairment was much less than were those reported in other studies. Mattila et al.,[29] for example, reported that single doses of mirtazapine 15 mg and amitriptyline 50 mg produced severe and comparable psychomotor impairment after administration in the morning. The main difference with the study design of Ramaekers et al.[28] lies in the time of drug administration, namely at the test day or at the evening before the test day. Consequently, Ramaekers et al.[28] have suggested that the sedative effect of mirtazapine on daytime performance might be much alleviated by nocturnal administration. This notion has recently been confirmed by Ridout et al.,[30] who assessed the psychomotor effects after evening and daytime doses of mirtazapine (15–30 mg) in a single, comparative placebo-controlled study over a 5-day period. Daytime doses of mirtazapine 15 mg significantly impaired performance in a Brake Reaction Time test on the first day of treatment. A single nocturnal dose of mirtazapine 15 mg, however, did not affect brake reaction time after single and repeated doses. In addition, both drug regimens did not affect driving performance after 5 days of dosing.[30] These studies thus seem to suggest that the impairing potential of mirtazapine in whole or in part is mitigated by nocturnal dosing or sleep. In addition, the degree of daytime performance impairment during mirtazapine treatment may also depend on the starting dose. The 3 studies above have assessed mirtazapine 15-mg doses during treatment initiation, whereas in medical practice mirtazapine treatment is often started at higher doses, i.e., 30 mg. Data from the present study thus may provide complementary information on the impairing effects of mirtazapine treatment on daytime performance, complementary during treatment initiation.

As it turned out in the present study, an evening dose of mirtazapine 30 mg significantly impaired actual driving performance and psychomotor function after the first night of treatment. The drug increased SDLP by 3.9 cm as compared to placebo in the Road Tracking Test. The effect of mirtazapine 30 mg in the evening would be the equivalent of driving with a BAC of above 0.5 mg/mL,[27] i.e., the BAC above which drivers have an elevated risk of becoming involved in a traffic accident.[31] The rise in SDLP after the 30-mg dose of mirtazapine was also bigger as compared to the effect of the nocturnal 15-mg dose, i.e., 2.2 cm in the previous driving study.[28] The latter elevation in SDLP was associated with a BAC below 0.5 mg/mL and was generally considered of insufficient magnitude to reduce driver safety. The present data, however, demonstrate that the acute, sedative effect of mirtazapine on driving will become clinically relevant when treatment is started at higher doses, such as 30 mg nocte.

The detrimental effect of mirtazapine on driving performance was primarily limited to the acute phase of treatment. There was some indication of a rise in SDLP after mirtazapine dose escalation, but this effect was relatively small in magnitude and not significantly different from mean SDLP in the escitalopram condition. Overall, driving performance did not differ during the dose escalation and steady state compared to placebo. Other measures also demonstrated that mirtazapine impairment was limited to the acute phase of treatment. Mirtazapine 30 mg in the evening decreased tracking performance in a Divided Attention Task and decreased feelings of alertness and contentedness. The Critical Tracking Task did not show impairment after mirtazapine 30 mg. Apparently, when the cognitive load performance is increased by adding a visual search task as in the Divided Attention Task, tracking performance becomes more vulnerable to the impairing ef-

fects of a drug. None of the effects were present after 1 or 2 weeks of repeated dosing. The absence of mirtazapine impairment after repeated dosing is probably related to the development of tolerance. Many studies have shown that tolerance to the acutely impairing effects of sedative antidepressants on driving performance develops within a few days of dosing.[28] The implication is that driving under the influence of a sedative antidepressant such as mirtazapine should only be contraindicated during the acute phase of treatment.

A potential limitation of the present study is the restricted age range of the subjects (21–40 years of age). It is generally believed that elderly people are more vulnerable to side effects from pharmacologic treatment. Generalization of results from experimental driving studies in younger volunteers to the elderly population has to be done with caution.[12] The magnitude of driving impairment observed in adult volunteers might only be a conservative estimate of a drug's activity in elderly individuals who appear extra sensitive to pharmacologic treatment, particularly in case of sedating antidepressants.

In conclusion, escitalopram 10 to 20 mg did not affect actual driving, psychomotor performance, and cognitive function in healthy subjects. Mirtazapine 30 mg nocte produced significant and clinically relevant impairment of driving and psychomotor performance during the acute treatment phase. The findings on psychomotor and driving performance are supported by subjective evaluations. Mirtazapine decreased feelings of alertness and contentedness; no subjective mood changes were present during escitalopram treatment. It is recommended to avoid high doses of mirtazapine during treatment initiation in order to promote safety over the day. The results from this study show that antidepressants can affect driving performance differently because of differences in their pharmacodynamic profiles. Importantly, broad class warnings about antidepressants and driving may not be informative enough and should be specified to individual substances.

*Drug names:* citalopram (Celexa), escitalopram (Lexapro), methadone (Methadose, Dolophine, and others), mirtazapine (Remeron), paroxetine (Paxil and others).

## REFERENCES


1. Lepola UM, Loft H, Reines EH. Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2003;18:211–217
2. Auquier P, Robitail S, Llorca PM, et al. Comparison of escitalopram and citalopram efficacy: a meta-analysis. Int J Psychiatry Clin Pract 2003;7:259–268
3. Aronson S, Delgado P. Escitalopram. Drugs Today (Barc) 2004;40: 121–131
4. De Boer T, Ruigt GSF. The selective α2-adrenoceptor antagonist mirtazapine (ORG 3770) enhances noradrenergic and 5-HT-1A-mediated serotonergic neurotransmission. CNS Drugs 1995;4(suppl 1):29–38
5. Anttila SA, Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. CNS Drug Rev 2001;7:249–264
6. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol 1995;10(suppl 4):37–45
7. Kasper S, Praschak-Rieder N, Tauscher J, et al. A risk-benefit assessment of mirtazapine in the treatment of depression. Drug Saf 1997;17:251–264
8. Hindmarch I. The behavioural toxicity of the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 1995;9(suppl 4):13–17
9. Hindmarch I. The effects of antidepressants on psychomotor function with particular reference to reboxetine. Eur Neuropsychopharmacol 1997;7(suppl 1):S17–S21
10. Grappe HJ, Wolf T, Gratz S, et al. The influence of polypharmacological antidepressive treatment on central nervous information processing of depressed patients: implications for fitness to drive. Neuropsychobiology 1998;37:200–204
11. Brunnauer A, Laux G. Fahrtuchtigkeit und Antidepressiva. Psychiatr Prax 2003;30(suppl 2):S102–S105
12. Ramaekers JG. Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. J Clin Psychiatry 2003;64:20–29
13. Wilkinson CJ, Lee GS, Chang C, et al. The effects of escitalopram administered alone and with alcohol on cognition and psychomotor performance [poster]. Presented at the 43rd annual meeting of the New Clinical Drug Evaluation Unit; May 26–28, 2003; Boca Raton, Fla
14. Herberg K. Verkehrs-und alltagssicherheit bei medikation mit citalopram. Psychopharmakotherapie 2001;18:81–88
15. Nathan PJ, Sitaram G, Stough C, et al. Serotonin, noradrenaline and cognitive function: a preliminary investigation of the acute pharmacodynamic effects of a serotonin versus a serotonin and noradrenaline reuptake inhibitor. Behav Pharmacol 2000;11:639–642
16. Fairweather DB, Dal Pozzo C, Kerr JS, et al. Citalopram compared to dothiepin and placebo: effects on cognitive function and psychomotor performance. Hum Psychopharmacol 1997;12:119–126
17. Schmitt JA, Riedel WJ, Vuurman EF, et al. Modulation of the critical flicker fusion effects of serotonin reuptake inhibitors by concomitant pupillary changes. Psychopharmacology (Berl) 2002;160:381–386
18. Riedel WJ, Eikmans K, Heldens A, et al. Specific serotonergic reuptake inhibition impairs vigilance performance acutely and after subchronic treatment. J Psychopharmacol 2005;19:12–20
19. Edgar CJ, Preskorn S, Erickson M, et al. A randomised, double-blind, parallel group comparison of the effects of escitalopram vs sertraline on cognition [abstract]. J Neuropsychopharmacol 2004;7(suppl 168):A13
20. O'Hanlon JF. Driving performance under the influence of drugs: rationale for, and application of, a new test. Br J Pharmacol 1984;18(suppl 1):121S–129S
21. Jex HR, McDonnell JD, Phatak AV. A "critical" tracking task for man-machine research related to the operator's effective delay time, pt 1: theory and experiments with a first-order divergent controlled element. NASA CR-616. NASA Contract Rep NASA CR 1966:1–105
22. Moskowitz H. Laboratory studies of the effects of alcohol on some variables related to driving. J Saf Res 1973;5:185–192
23. Baddeley AD. A 3-minute reasoning test based on grammatical transformation. Psychonom Sci 1968;10:341–342
24. Wechsler D. The Measurement and Appraisal of Adult Intelligence. Baltimore, Md: Williams and Wilkins; 1981
25. Mulder-Hajonides van der Meulen WREH. Measurement of subjective sleep quality. In: Proceedings of the International European Sleep Congress. Amsterdam, the Netherlands: Elsevier; 1981
26. Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br J Med Psychol 1974;47:211–218
27. Louwerens JW, Gloerich ABM, Vries GD, et al. The relationship between drivers' blood alcohol concentration (BAC) and actual driving performance during high speed travel. In: Noordzij PC, Roszbach R, eds. Alcohol, Drugs and Traffic Safety-T86. Amsterdam, the Netherlands: Elsevier; 1987:183–186
28. Ramaekers JG, Muntjewerff ND, Van Veggel LMA, et al. Effects of nocturnal doses of mirtazapine and mianserin on sleep and on daytime psychomotor and driving performance in young, healthy volunteers. Hum Psychopharmacol 1998;13(suppl 2):S87–S97
29. Mattila M, Mattila MJ, Vrijmoed-de Vries M, et al. Actions and interactions of psychotropic drugs on human performance and mood: single doses of ORG 3770, amitriptyline, and diazepam. Pharmacol Toxicol 1989;65:81–88
30. Ridout F, Meadows R, Johnsen S, et al. A placebo controlled investigation into the effects of paroxetine and mirtazapine on measures related to car driving performance. Hum Psychopharmacol 2003;18:261–269
31. Borkenstein RF, Crowther RF, Shumate RP, et al. The role of the drinking driver in traffic accidents (The Grand Rapids study). Blutalkohol 1974;11(suppl 1):1–131