A Randomized Trial on the Acute and Steady-State Effects of a New Antidepressant, Vortioxetine (Lu AA21004), on Actual Driving and Cognition

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The aim of this study was to assess the effects of a novel antidepressant, vortioxetine 10 mg, on driving, cognitive, and psychomotor performance in 24 healthy subjects in a double-blind, placebo-controlled, three-way crossover design. Mirtazapine 30 mg was included as an active comparator. Drugs were administered in the evening of 15 consecutive days. Performance was measured in the morning of days 2 and 16, using standardized tests measuring on-the-road driving, memory, tracking, divided attention, and vigilance. The statistical analysis on the primary measure of driving, i.e., SD of lateral position showed noninferiority of vortioxetine on days 2 and 16, and inferiority for mirtazapine on day 2. Vortioxetine did not cause cognitive or psychomotor impairment. Mirtazapine, however, impaired cognitive and psychomotor performance on day 2. Most of these effects disappeared after multiple doses of mirtazapine. To conclude, vortioxetine did not impair driving, cognitive, or psychomotor performance after single or multiple doses.

Several different classes of antidepressants are currently being used for the treatment of depression. Most antidepressants act by enhancing the postsynaptic monoamine concentrations through inhibiting the reuptake of serotonin (5-hydroxytryptamine (5-HT)) and/or noradrenaline. Side effects often reported with antidepressants include sedation, drowsiness, blurred vision, dry mouth, increased appetite, and weight gain. These occur because many antidepressants also have affinity for α_1 adrenergic, cholinergic, and histaminergic receptors. As a result of these side effects, antidepressants can impair psychomotor function and driving performance in patients and healthy volunteers.[1–5] Because of differences in affinity for these receptors, the effects of antidepressants on psychomotor function and driving performance are very diverse. Tricyclic antidepressants and the noradrenergic and specific serotonergic antidepressants have serious sedative effects and were previously found to cause significant psychomotor and driving impairment.[2,6,7] Less sedation is reported for selective serotonin reuptake inhibitors, serotonin receptor antagonist and reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors.[2,6,8]

Sedation and impaired performance can diminish the clinical usefulness of an antidepressant and affect patients' quality of life. Patients are more likely to be involved in traffic accidents, and their performance at work or school may deteriorate.[4,5,9,10] Therefore, it is important to assess and compare the effects of antidepressants on driving and cognitive skills,[2,11] so that physicians can prescribe the drug with the fewest adverse effects on a patient's daily functioning.

To assess the effects of antidepressants and other psychoactive drugs on driving performance, the standard highway driving test has been used in more than 80 studies. Since its first use in 1982,[12] the driving test has not undergone any substantial changes. The primary measure of this test is the SD of lateral position (SDLP), which measures continuous road tracking error (TE). SDLP is a very reliable characteristic of individual driving performance and has also proven sensitive to many sedating agents, including blood alcohol concentrations (BACs) as low as 0.35 mg/ml.[13,14] It is a validated and sensitive tool for comparing the driving impairment potential of different drugs such as antidepressants.[15] Likewise, cognitive and psychomotor

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tasks have previously been shown to be sensitive for the impairing effects of antidepressants.[7,11,16,17]

Vortioxetine (1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine-hydrobromide) is a novel, multimodal, investigational compound for the treatment of major depressive disorder. Vortioxetine belongs to a new chemical class of psychotropics, the bis-aryl-sulfanyl amines, which possess unique properties and are structurally different from all currently known psychotropics. *In vitro* studies indicate that vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and inhibitor of the 5-HT transporter.[18,19] All of these activities are considered to be of potential clinical relevance and may be involved in the therapeutic mechanism of action of vortioxetine.

Because antidepressants that mainly act via 5-HT receptors and reuptake inhibition have previously been found not to impair driving, psychomotor, or cognitive performance,[1] we expected this to be true for vortioxetine as well. Previous studies with vortioxetine at doses of 5 and 10 mg q.d. have already demonstrated that vortioxetine did not increase subjectively reported fatigue or somnolence in patients with major depressive disorder.[20,21]

This study was designed to compare the effects of vortioxetine with those of mirtazapine and placebo on driving, psychomotor, and cognitive performance in healthy volunteers after a first dose and at steady state.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant, and its therapeutic effect is derived by blockade of the α_2-adrenoceptors and by indirect stimulation of the 5-HT1 receptors, via blockade of 5-HT2 and 5-HT3 receptors. As a result of its strong affinity for the histamine H1 receptor, mirtazapine also has sedating effects.[22,23] Mirtazapine has been found to impair psychomotor function, cognition, and driving performance after acute dosing.[16,17,24]

RESULTS

Missing data

Because of bad weather conditions, the driving test could not be performed by two subjects on one test day.

Highway driving test

A summary of the results on SDLP after single doses (day 2) and multiple q.d. doses (day 16) of vortioxetine, mirtazapine, and placebo is presented in **Table 1**.

Intention-to-treat analyses. The primary statistical analysis of the SDLP (primary parameter) during actual driving performance concluded noninferiority of vortioxetine as compared with placebo on days 2 and 16, i.e., the upper limit of the 90% confidence interval (CI) (0.05 and 0.80, respectively) was lower than the inferiority limit of 2.0 cm (as well as the alcohol limit of 2.4 cm). Mirtazapine showed inferiority on day 2, i.e., the upper limit of the 90% CI was higher than the inferiority limit

Table 1 Summary of results of the driving test (SDLP)

Driving test SDLP (cm)	*n*	Mean (SE)	Least squares mean	Difference from placebo	Lower 90% CI	Upper 90% CI
Intention-to-treat analyses						
Day 2						
Vortioxetine	20	20.33 (0.85)	20.41	−1.03	−2.12	0.05
Mirtazapine	22	22.84 (1.05)	22.96	1.52	0.32	2.71
Placebo	23	20.99 (1.01)	21.44			
Day 16						
Vortioxetine	21	20.30 (0.97)	20.18	−0.23	−1.24	0.080
Mirtazapine	21	20.60 (1.06)	20.48	0.07	−1.01	1.15
Placebo	22	20.11 (1.06)	20.41			
Driving test SDLP (cm)	***n***	**Mean (SE)**	**Estimated marginal means**	**Difference from placebo**	**Lower 90% CI**	**Upper 90% CI**
Per-protocol analyses						
Day 2						
Vortioxetine	20	20.33 (1.16)	20.33	−0.99	−2.09	0.11
Mirtazapine	21	22.54 (0.85)	22.83	1.51	0.27	2.75
Placebo	21	21.05 (1.06)	21.32			
Day 16						
Vortioxetine	21	20.30 (1.11)	20.1	−0.32	−1.39	0.75
Mirtazapine	21	20.60 (0.97)	20.43	−0.10	−0.92	1.11
Placebo	20	20.33 (1.06)	20.33			

Shown are the intention-to-treat analyses on the full analysis set and the per-protocol analyses on the all-subject-completed set.

CI, confidence interval; SDLP, SD of lateral position.

of 2.0 (2.71) but not on day 16, as the value (1.15) was below the inferiority limit.

Per-protocol analyses. In the all-subject-completed set, vortioxetine showed noninferiority on both days 2 and 16 (0.11 and 0.75, respectively), whereas mirtazapine showed inferiority on day 2 (2.75).

Cognitive tests

Mean (SE) values of all cognitive parameters and results of the statistical analyses are presented in **Table 2** for the intention-to-treat analyses and in **Table 3** for the per-protocol analyses. Overall, the effects are comparable between the two analyses.

In the critical-tracking task, a significant overall effect of treatment was found on days 2 and 16. On day 2, the critical-tracking test score was not significantly different between the vortioxetine and placebo groups, but the mirtazapine group was significantly different from the placebo and vortioxetine groups. On day 16, the critical-tracking test score was not significantly different between the vortioxetine and placebo groups but was significantly different between the mirtazapine and placebo groups.

Table 2 Summary of the results of the cognitive tests on days 2 and 16 of the intention-to-treat analysis

		Mean (SE)			Overall effect		Mirt–Pla	Mirt–Vort
	Day	Vort	Mirt	Pla				
n	2	21	22	23	*F*	*P*	*P*	*P*
	16	21	21	23				
Critical-tracking task								
Critical frequency (rad/s)	2	3.55 (0.92)	3.19 (0.34)[a,b]	3.47 (0.12)	9.231	0.001	0.008	0.000
	16	3.50 (0.11)	3.35 (0.21)[a]	3.61 (0.12)	4.349	0.020	0.007	NS
Divided-attention task								
Tracking error (mm)	2	17.62 (0.71)	20.77 (1.05)[a,b]	17.90 (0.86)	6.765	0.003	0.005	0.002
	16	17.47 (0.99)	19.81 (0.93)[b]	18.89 (0.86)	5.617	0.007	NS	0.002
Reaction time (ms)	2	1,865.05 (59.04)	2,047.59 (57.36)[a,b]	1,806.35 (57.31)	5.729	0.007	0.004	0.009
	16	1,777.29 (59.59)	1,950.52 (78.87)[b]	1,830.91 (57.26)	3.258	0.049	NS	0.015
Word-learning task								
Immediate recall (no.)	2	14.0 (0.28)	13.68 (0.34)	13.96 (0.25)		NS	NS	NS
	16	14.43 (0.19)	14.19 (0.21)	14.13 (0.26)		NS	NS	NS
Delayed recall (no.)	2	12.67 (0.43)	11.82 (0.53)	11.91 (0.59)		NS	NS	NS
	16	12.52 (0.48)	12.24 (0.55)	12.39 (0.46)		NS	NS	NS
Relative recall (%)	2	90.45 (2.49)	85.69 (2.67)	84.73 (3.27)		NS	NS	NS
	16	86.42 (2.57)	85.80 (3.25)	87.29 (2.43)		NS	NS	NS
Recognition score (no.)	2	14.10 (0.18)	13.86 (0.33)	13.74 (0.24)		NS	NS	NS
	16	14.38 (0.16)	13.86 (0.28)	14.26 (0.20)		NS	NS	NS
Reaction time (ms)	2	677.46 (25.23)	688.51 (22.72)	706.63 (26.36)		NS	NS	NS
	16	670.34 (29.26)	706.63 (27.62)	694.67 (19.64)		NS	NS	NS
Psychomotor vigilance task								
Reaction time (ms)	2	258.69 (6.02)	297.09 (9.14)[a,b]	259.46 (7.04)	22.198	0.000	0.000	0.000
	16	262.50 (6.39)	281.64 (8.42)[a,b]	265.89 (5.97)	5.243	0.010	0.035	0.003
Lapses (no.)	2	1.33 (0.53)	5.27 (1.25)[a,b]	1.43 (0.82)	6.985	0.003	0.003	0.002
	16	1.38 (0.53)	2.81 (0.87)	1.65 (0.40)		NS	NS	NS
Groningen Sleep								
Sleep duration (h)	2	7.53 (0.22)	7.91 (0.16)	7.54 (0.23)		NS	NS	NS
	16	7.42 (0.023)	7.87 (0.16)[a,b]	7.22 (0.15)	9.295	0.001	0.000	0.010
Sleep complaints (no.)	2	2.05 (0.55)	3.5 (0.49)[a,b]	1.65 (0.41)	5.677	0.007	0.003	0.013
	16	2.57 (0.61)	2.33 (0.43)	1.96 (0.58)		NS	NS	NS

Degrees of freedom for overall analyses were 2,38.

Groningen Sleep, Groningen Sleep Quality Scale; Mirt, mirtazapine; NS, not significant; Pla, placebo; Vort, vortioxetine.

[a]Significant placebo–mirtazapine contrast ($P < 0.05$). [b]Significant mirtazapine–vortioxetine contrast ($P < 0.05$).

Table 3 Summary of the results of the cognitive tests on days 2 and 16 of the per-protocol analysis

		Mean (SE)						
	Day	Vort	Mirt	Pla	Overall effect		Mirt–Pla	Mirt–Vort
n	2	21	21	21	*F*	*P*	*P*	*P*
	16	21	21	21				
Critical-tracking task								
Critical frequency (rad/s)	2	3.55 (0.12)	3.23 (0.09)[a,b]	3.44 (0.16)	8.494	0.001	0.016	0.002
	16	3.50 (0.12)	3.35 (0.11)[a]	3.56 (0.14)	4.316	0.032	0.018	NS
Divided-attention task								
Tracking error (mm)	2	17.62 (0.92)	20.54 (0.71)[a,b]	17.94 (1.08)	6.697	0.003	0.01	0.004
	16	17.47 (0.94)	19.81 (0.99)[b]	18.75 (0.93)	5.892	0.006	NS	0.005
Reaction time (ms)	2	1,865.05 (59.42)	2,017.81 (59.04)[a,b]	1,845.48 (51.41)	5.923	0.006	0.015	0.007
	16	1,777.29 (55.45)	1,950.52 (59.59)[b]	1,857.90 (78.87)	3.140	0.054	NS	0.012
Word-learning task								
Immediate recall (no.)	2	14.00 (0.28)	13.67 (0.28)	13.95 (0.36)		NS	NS	NS
	16	14.43 (0.26)	14.19 (0.19)	14.05 (0.21)		NS	NS	NS
Delayed recall (no.)	2	12.67 (0.50)	11.76 (0.43)[b]	12.33 (0.56)		NS	NS	NS
	16	12.52 (0.55)	12.24 (0.48)	12.52 (0.55)		NS	NS	NS
Relative recall (%)	2	90.45 (2.47)	85.35 (2.49)	87.60 (2.78)		NS	NS	NS
	16	86.42 (2.67)	85.80 (2.57)	88.62 (3.25)		NS	NS	NS
Recognition score (no.)	2	14.10 (0.18)	13.90 (0.18)	13.81 (0.34)		NS	NS	NS
	16	14.38 (0.25)	13.86 (0.16)	14.43 (0.28)		NS	NS	NS
Reaction time (ms)	2	677.46 (20.84)	675.58 (25.23)	699.02 (19.60)		NS	NS	NS
	16	670.34 (25.70)	706.63 (29.26)	691.18 (27.62)		NS	NS	NS
Psychomotor vigilance task								
Reaction time (ms)	2	258.69 (5.95)	297.26 (6.02)[a,b]	262.38 (9.58)	19.913	<0.001	<0.001	<0.001
	16	262.50 (7.20)	281.64 (6.39)[b]	268.40 (8.42)	4.427	0.018	NS	0.016
Lapses (no.)	2	1.33 (0.43)	5.05 (0.53)[a,b]	1.43 (1.29)	7.031	0.002	0.012	0.002
	16	1.38 (0.90)	2.81 (0.53)	1.71 (0.87)		NS	NS	NS
Groningen Sleep								
Sleep duration (h)	2	7.53 (0.16)	7.90 (0.22)	7.50 (0.16)		NS	NS	NS
	16	7.42 (0.25)	7.87 (0.23)[a,b]	7.16 (0.16)	8.988	0.001	<0.001	0.016
Sleep complaints (no.)	2	2.05 (0.63)	3.48 (0.55)[a,b]	1.76 (0.51)	5.399	0.008	0.007	0.006
	16	2.57 (0.44)	2.33 (0.61)	2.10 (0.43)		NS	NS	NS

Degrees of freedom for overall analyses were 2,40, except for critical frequency, where Greenhouse–Geisser correction was necessary because the sphericity assumption was violated (degrees of freedom = 1.507). Degrees of freedom for drug contrasts were always 1,20.

Groningen Sleep, Groningen Sleep Quality Scale; Mirt, mirtazapine; NS, not significant; Pla, placebo; Vort, vortioxetine.

[a]Significant placebo–mirtazapine contrast ($P < 0.05$). [b]Significant mirtazapine–vortioxetine contrast ($P < 0.05$).

In the divided-attention task, both TE and reaction time (RT) showed a significant or nearly significant overall effect of treatment on days 2 and 16. Contrast analyses showed that vortioxetine was not significantly different from placebo on any of these measures on either of the test days. Mirtazapine caused a significantly larger TE than placebo and vortioxetine on day 2, and a significantly larger TE than vortioxetine on day 16. RT was significantly slower for mirtazapine as compared with placebo and vortioxetine on day 2 and as compared with vortioxetine on day 16.

In the psychomotor vigilance task, a significant overall effect of treatment was found for RT on days 2 and 16, and for number of lapses on day 2. Contrast analyses showed that these effects were not caused by vortioxetine, as it was not significantly different from placebo, but were a result of impairment caused by mirtazapine. Mirtazapine caused a significantly longer RT than placebo and vortioxetine on days 2 and 16; however, the mirtazapine–placebo contrast was not significant for day 16 in the per-protocol analyses. The number of lapses was significantly higher for mirtazapine as compared with placebo and vortioxetine on day 2. No effect of treatment was found on the word-learning task.

From the sleep scale, it appeared that treatment significantly affected the duration of sleep on day 16 and number of sleep

complaints on day 2. Contrast analyses showed that vortioxetine did not differ significantly from placebo on these measures. Mirtazapine caused an increase in sleep duration on the night before day 16 as compared with placebo and vortioxetine. The number of sleep complaints was higher for mirtazapine during the night before the first test day as compared with placebo and vortioxetine.

Safety assessment

Analysis of safety measures was performed on the full analysis set, i.e., 24 subjects. The safety and tolerability profiles were similar following multiple doses of 10-mg vortioxetine, 30-mg mirtazapine, and placebo, with all treatments being safe and well tolerated. There were no severe or serious adverse events, and no subjects withdrew due to an adverse event.

A total of 85 adverse events were reported during the study. The incidence of adverse events and subjects reporting adverse events was similar across all treatments. The most commonly reported adverse events were headache, fatigue, and somnolence. The majority of adverse events were mild and considered to have a possible or probable relationship to treatment according to the investigator. Adverse events occurring in two or more subjects are summarized in **Table 4**.

There were no clinically relevant changes in the mean clinical safety laboratory values, vital signs, electrocardiogram diagnoses, or physical examinations. Body weight assessments at the beginning of the study and at the follow-up visit determined that 16 subjects had gained weight during the study. For eight of these subjects, the weight gain was reported as an adverse event (increase of 3–5 kg was recorded).

Pharmacokinetics

Plasma concentrations in the acute and steady-state phases of the study for vortioxetine, the metabolites Lu AA34443 and Lu AA39835, and mirtazapine are presented in **Table 5**.

DISCUSSION

In the current study, the acute and steady-state effects of vortioxetine 10 mg and mirtazapine 30 mg were assessed on driving, psychomotor, and cognitive performance. Vortioxetine showed noninferiority as compared with placebo on the primary measure of the driving task (SDLP) on both days 2 and 16. In addition, the results of the safety assessment show that vortioxetine 10 mg is safe and well tolerated. Moreover, on the measures of cognitive and psychomotor performance, vortioxetine was not significantly different from placebo.

Mirtazapine, on the other hand, showed inferiority as compared with placebo on the driving performance task on day 2 but not on day 16. The acute impairing effects of mirtazapine 30 mg were also demonstrated on tracking, divided-attention, and psychomotor performance. The current data on driving impairment after single doses of mirtazapine confirm results from previous studies. These showed that mirtazapine 15 mg produced a mean increase in SDLP that was close or comparable to an alcohol dose of 0.5 mg/ml BAC,[17] whereas 30-mg mirtazapine produced an acute SDLP increase that was larger than the effect of 0.5 mg/ml BAC.[16] In the current study, mirtazapine 30 mg increased SDLP by 1.49 cm on day 2, which is less than the 2.4-cm increase that was previously demonstrated for an alcohol dose of 0.5 mg/ml BAC.[25] However, examining the CI, mirtazapine showed inferiority, as the upper limit (2.9 cm) is larger than the lower limit of 2.4 cm. Differences in mean change in SDLP observed after mirtazapine may in part result from individual differences in drug metabolism. A previous study showed that the magnitude of driving impairment after single doses of the enantiomer of mirtazapine (i.e., esmirtazapine) depended on the cytochrome 2D6 phenotype, with poor metabolizers showing more serious impairment.[26] Cytochrome 2D6 is a major route of metabolism for many CNS drugs, including antidepressants. Therefore, it is possible that the effects of mirtazapine in poor metabolizers are more serious than the effects shown in the current study. In addition, because nocturnal doses are thought to alleviate the sedative effects of the drug on daytime performance, it can be expected that daytime dosing would show larger effects than nocturnal doses. Patients should therefore be informed of potential driving impairment when using mirtazapine.

The impairing potential of mirtazapine in the steady-state phase (day 16) was considerably less than that in the acute phase. On day 16, most effects had disappeared, except for those on psychomotor performance assessed by the critical-tracking task. It can therefore be concluded that the sedating effects of mirtazapine are subject to tolerance. Moreover, in previous studies

Table 4 Adverse events occurring in ≥2 subjects (FAS, *n* = 24)

Adverse event	Placebo, *n* (%)	Vortioxetine, *n* (%)	Mirtazapine, *n* (%)
Headache	7 (30)	1 (5)	8 (36)
Fatigue	4 (17)	5 (24)	4 (18)
Somnolence	2 (9)	3 (14)	3 (14)
Common cold	3 (13)	2 (10)	—
Increased appetite	—	1 (5)	3 (14)
Nausea	2 (9)	—	2 (9)
Stomach pain	—	3 (14)	—
Influenza-like illness	1 (4)	1 (5)	1 (5)
Dry mouth	—	1 (5)	2 (9)
Dizziness	—	—	2 (9)
Menstrual pain[a]	1 (8)	—	1 (8)
Difficulty falling asleep	—	1 (5)	1 (5)

FAS, full analysis set.

[a]Calculated as percentage of women (*n* = 12).

Table 5 Plasma concentrations (mean ± SD) (ng/ml) of vortioxetine, its metabolites, and mirtazapine

	Vortioxetine	Lu AA34443	Lu AA39835	Mirtazapine
Day 2	*n* = 20	*n* = 20	*n* = 20	*n* = 22
	3.31 (1.42)	5.07 (2.57)	0.0948 (0.0395)	15.8 (5.57)
Day 16	*n* = 21	*n* = 21	*n* = 21	*n* = 21
	12.8 (7.12)	11.1 (4.63)	0.427 (0.199)	27.5 (13.0)

Table 6 Schematic overview of the treatment periods and test days

Time	Activity
Evening days 1–15	Medication taken at home
Days 2 and 16	
12 h after drug	Transport to facilities
	Blood sampling
	Sleep questionnaire
	Bond and Lader questionnaire
	Cognitive and psychomotor tasks
	Snack
14 h after drug	Subjective expected driving quality questionnaire (subjects)
	Driving test
	Subjective driving quality questionnaire (subjects and instructor)
	Subjective sedation questionnaire (instructor)
16 h after drug	Transport back home

with mirtazapine, tolerance to the impairing effects was shown on driving performance, even when the dose was doubled in the second week of treatment.[16,17]

Because vortioxetine 10 mg was free of impairing effects in the acute phase as well as at steady state, it can be considered a nonsedating antidepressant at this dose. Although this study was performed in healthy subjects, the results can be of use to predict the effects in patients. It might be argued that the beneficial therapeutic effects of antidepressants may outweigh their impairing effects on driving because depression itself is also known to impair performance. However, patients do experience the same side effects as healthy volunteers, and of note, the therapeutic effect of antidepressants is known to occur only after 2–6 weeks of treatment. Previous studies have indeed demonstrated that antidepressant drugs can impair driving performance during initiation of treatment before the therapeutic effects become apparent.[1,27] Consequently, the current results obtained in healthy volunteers can also be generalized to the depressed patient population, and whenever possible, nonsedating antidepressants should be chosen for treatment instead of sedating antidepressants, to avoid driving impairment.

Other antidepressants that are considered nonsedating include moclobemide,[28] a reversible inhibitor of monoamine oxidase A; fluoxetine and paroxetine, selective serotonin reuptake inhibitors;[29,30] nefazodone,[31] a serotonin receptor antagonist and reuptake inhibitor; and venlafaxine,[7] a serotonin/norepinephrine reuptake inhibitor. As compared with sedating antidepressants, nonsedating antidepressants have less inhibiting effect on muscarinic, histaminergic, α-adrenergic, and dopaminergic neurotransmitter release, which explains their improved safety profile. Vortioxetine mediates its pharmacological effects by acting on 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, and 5-HT_7 receptors and the 5-HT transporter.[19] *In vivo*, vortioxetine has been found to increase the extracellular levels of serotonin, noradrenaline, dopamine, acetylcholine, and histamine.[32,33] The multimodal pharmacology of vortioxetine may explain its improved safety profile as well as the cognitive enhancing effects found in elderly patients with major depressive disorder.[21]

We conclude that vortioxetine 10 mg did not produce impairing effects on driving, cognitive, or psychomotor performance. On the other hand, mirtazapine 30 mg impaired driving, psychomotor, and cognitive performance after a single dose, and most of this impairment disappeared after repeated doses as a result of tolerance.

METHODS

Subjects. Twenty-four healthy subjects, 11 men and 13 women, with a mean (SD) age of 31 (8.3) years, were recruited by advertisement in local newspapers in the Netherlands. Subjects were screened by a telephone interview and a health questionnaire, and all underwent a medical examination (including a standard 12-lead electrocardiogram, hematology and blood 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 5,000 km per year on average, normal binocular visual acuity corrected or uncorrected, normal heart rate and blood pressure, willingness to use a double-barrier method of birth control, body mass index of 18–30 kg/m^2, and willingness to sign the written informed consent. Subjects who met one or more of the following criteria were excluded from the study: history of or presence of any clinically significant immunological, cardiovascular, respiratory, metabolic, renal, hepatic, gastrointestinal, endocrinological, hematological, dermatological, venereal, neurological, or psychiatric disease or other major disorder; pregnancy (as determined at screening) or breastfeeding; known hypersensitivity to medicinal drugs; use of disallowed medication within 2 weeks before the first administration (except oral contraceptives and paracetamol); smoking or use of nicotine-containing products; abnormal sleep patterns; consumption of more than 3 and 2 units of alcohol per day for men and women, respectively; consumption of more than six cups of regular coffee a day; positive alcohol breath test or a positive urine result for drug of abuse at the screening visit.

The study was approved by the standing Medical Ethics Committee of Maastricht University and was carried out in compliance with the current revision of the Declaration of Helsinki (Seoul modification, 2008) and the International Conference on Harmonisation Guideline for Good Clinical Practice.

Design and treatments. The study was conducted according to a randomized, double-blind, placebo-controlled, three-way crossover design. Treatments were administered for 15 days in three separate 16-day periods, and subjects were randomly assigned to one of six treatment sequences. Treatments consisted of 10-mg vortioxetine, 30-mg mirtazapine, and placebo and were encapsulated such that they were identical in appearance and indistinguishable from each other. Subjects self-administered each dose in the evening of days 1–15 of each treatment period. Subjects recorded the time of administration in a diary. The washout period between treatments was at least 14 days.

Procedure. Before the first treatment period, all subjects participated in two training sessions to familiarize them with the driving procedures and the cognitive and psychomotor tests.

On day 1 of each treatment period, subjects visited the study site at Maastricht University to receive the treatment medication. Some safety measures (i.e., adverse events, weight, clinical safety laboratory tests, vital signs, electrocardiogram, and physical examinations) and drug and urine screens were also performed. On test days (days 2 and 16), subjects were transported to and from the test site. Subjects were instructed to have a normal breakfast on all test days. Subjects were to refrain from consuming alcohol for 24 h before the first dose of each period and during the

whole dosing period. Subjects were also asked to refrain from consuming caffeine or xanthine on days 2 and 16. Subjects were given a standardized snack before the driving performance test. Driving performance, psychomotor, and cognitive tests were performed on days 2 and 16 between 12 and 16 h after the preceding evening dose. The driving test was always performed after the psychomotor and cognitive performance tests. The Groningen Sleep Quality Scale was also completed on days 2 and 16. **Table 6** provides a schematic overview of test days.

Performance tests

Highway driving test. During the highway driving test,[12] the subject's task is to operate a specially instrumented vehicle over a distance of 100 km on a primary highway. The driving test is always performed at the same time during normal traffic (avoiding rush hour) and on the same road, between fixed terminal points. A licensed driving instructor, who can intervene if necessary by using duplicate controls, accompanies the subject during all tests. The subject is instructed to attempt to maintain a constant speed of 95 kph and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. The vehicle's speed and lateral position relative to the left lane delineation are continuously recorded using an electro-optical device mounted at the rear of the car. These signals are digitally sampled at a rate of 4 Hz and stored on a computer disk onboard. The offline editing routine involves removal of all data segments that reveal signal loss, disturbance, or overtaking maneuvers. The remaining data are used to calculate means, SDLPs, and speed. The primary measure is the SDLP, which measures the continuous road TE.[34] The SDLP is a very reliable characteristic of individual driving performance: the test–retest reliability coefficient for nonmedicated young and middle-aged drivers is 0.85.[15] The highway driving test has been calibrated in a manner allowing expression of any sedative drug effect in terms of the BAC required to achieve the equivalent level of driving impairment.[25] The alcohol calibration curve demonstrates that drinkers' mean SDLP rises exponentially with a linear increase in BAC. Results from the alcohol calibration study can be used for describing drug effects on SDLP in terms of respective BAC equivalencies. The change in SDLP at a BAC of 0.5 mg/ml has been used as a criterion level to quantify drug effects. Drug-induced changes in SDLP that exceed this value are defined as clinically relevant drug impairment effects.

Cognitive tests. The critical-tracking test[35] measures the subjects' ability to control a displayed error signal in a first-order compensatory tracking task. The frequency at which control is lost is called the "critical frequency" or "λ_c" (rad/s). The test includes five trials; the average score is calculated after removing the highest and the lowest scores and is the primary variable in this test.[36]

The divided-attention task[37] is used to measure the subject's ability to divide attention between two tasks performed simultaneously. The primary task consists of a tracking task in the central visual field, and the secondary task is a monitoring task in the peripheral visual field. Subjects react to peripheral targets using a foot pedal. Dependent variables are the absolute mean TE over the entire test and mean RT to peripheral targets.[36]

In the word-learning task,[38] subjects are shown 15 words on a computer screen. The words appear on the screen for 2 s, one after the other. All words are in Dutch, the native language of all subjects. Subjects are instructed to try to memorize these words and to name as many as they can at the end of the list. This procedure is repeated five times. The highest score in these trials is the immediate recall score. After at least 30 min, the subjects are asked to name as many words as they can, and this score is the delayed recall score. The number of words recalled in the delayed recall as compared with the immediate recall is defined as the relative recall score. Finally, a list of 30 words is presented on the computer screen, comprising the original 15 words and 15 new words. The subjects have to press a button when they recognize a word that belonged to the original list of words. The number of correctly recognized words and the average speed (ms) of recognition are recorded as the recognition score and the recognition time, respectively. Subjects were presented with a different version of the task on each test day.[34]

The psychomotor vigilance task is based on a simple visual RT test. Subjects were required to respond to a visual stimulus presented at variable intervals (2,000–10,000 ms) by pressing either the right or the left button with their dominant hand. The visual stimulus was a four-digit light-emitting diode counter turning on and incrementing from 0–60 s at 1 ms intervals. In response to the subject's button press, the light-emitting diode counter display stopped incrementing, allowing the subject 1 s to read the test before the counter restarted. If a response had not been made in 60 s, the clock reset, and the counter restarted. The dependent variables were median RT (in milliseconds) and number of lapses (RT >500 ms).[39]

The Groningen Sleep Quality Scale. Sleep quality during the previous night was assessed by means of the Groningen Sleep Quality Scale.[40] This questionnaire scores the number of sleep complaints and the total amount of sleep.

Safety assessment. During test periods, adverse events either observed by the investigator or spontaneously reported by the subject were recorded. Vital signs (systolic and diastolic blood pressure and pulse rate) were measured in supine and upright positions with a standard digital meter on days 1, 2, and 16 of each treatment period.

At screening and at follow-up, safety measures consisted of adverse events recording; blood sampling for hematology and clinical chemistry; urinalysis; recording of vital signs, body weight, and body temperature; physical examination; and electrocardiography.

Pharmacokinetics. Vortioxetine has a long time to peak concentration (8 h) and a long half-life (57 h).[41] Venous blood samples (9 ml) were taken in the morning on days 2 and 16, approximately 13 h after dosing to determine acute-phase and steady-state plasma concentrations of vortioxetine, the metabolites Lu AA34443 and Lu AA39835, and mirtazapine. Samples were centrifuged within 15 min of collection, after which they were stored at approximately −20 °C. Samples were shipped on dry ice to Aptuit, Edinburgh, UK, for analysis. Determination of vortioxetine, Lu AA34443, and Lu AA39835 in plasma was performed using solid-phase extraction followed by high-performance liquid chromatography with tandem mass spectrometric detection, with lower limits of quantification of 0.08, 0.2, and 0.04 ng/ml, respectively. Determination of mirtazapine in plasma was performed using protein precipitation followed by high-performance liquid chromatography with tandem mass spectrometric detection, with a lower limit of quantification of 2 ng/ml.

Sample size. A total of 24 subjects were included in the study. Three subjects withdrew prematurely, resulting in 21 subjects completing the study. A power calculation for noninferiority between vortioxetine and placebo on SDLP, with a within-subject SD of 2.1 cm and an inferiority limit of 2.0 cm, showed a total of 18 subjects to be sufficient to demonstrate noninferiority with a power of 90% and a two-sided significance level of 5%.

Statistics. Intention-to-treat analyses and the analysis of safety measures were performed on the full analysis set, i.e., 24 subjects. Per-protocol analyses were performed on the all-subjects-completed set, i.e., 21 subjects. All measures were analyzed separately on days 2 and 16.

Intention-to-treat analysis. The study was designed as a noninferiority trial with evaluation of SDLP treatment effects in relation to a conservative inferiority limit of 2.0 cm. This noninferiority limit is more conservative than the limit of 2.4 cm that is associated with a BAC of 0.5 mg/ml, which is considered clinically relevant. For SDLP, noninferiority between treatments was concluded if the upper limit of the one-sided 95% (upper limit of the 90% CI) CI of the mean difference in SDLP between drug and placebo was <2.0 cm.

Cognitive variables were analyzed using univariate analysis of variance using a model with fixed factors for treatment, period, and sequence and a random factor for subjects. Separate drug–placebo contrasts were conducted only in case of a significant main effect of treatment.

Per-protocol analysis. For SDLP, a noninferiority analysis was performed between treatments, with a two-sided 90% CI of the mean difference in SDLP between drug and placebo. Cognitive measures were analyzed using a repeated-measures analysis of variance with treatment (three levels) as factor. Type I errors associated with inhomogeneity of variance were controlled by decreasing the degrees of freedom using Greenhouse–Geisser corrections. Separate drug–placebo contrasts were conducted only in case of a significant main effect of treatment.

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AUTHOR CONTRIBUTIONS

E.L.T. and J.G.R. wrote the manuscript; J.G.R., A.V., D.S., and A.-M.H. designed the research; A.v.O., J.G.R., and A.V. performed the study; and E.L.T. analyzed the data.

CONFLICT OF INTEREST

D.S. was employed at H. Lundbeck A/S, Denmark, at the time of the study. A.-M.H. is employed at H. Lundbeck A/S, Denmark. The other authors declared no conflict of interest.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Vortioxetine is a novel compound for the treatment of major depressive disorder, with unique properties and a different structure as compared with currently known psychotropics.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ The effects of vortioxetine 10 mg (single and multiple doses) on driving, psychomotor, and cognitive performance were studied.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The standard highway driving test was used to assess the effects on driving performance. The primary measure, i.e., SDLP, is a reliable characteristic of driving performance and sensitive to many sedating agents. Vortioxetine showed noninferiority on SDLP and no cognitive or psychomotor impairment on day 2 or 16. Mirtazapine, however, showed inferiority on SDLP on day 2 and impaired cognitive and psychomotor performance on day 2.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ Vortioxetine 10 mg was free of impairing effects in the acute phase and steady state; therefore, it is considered a nonsedating antidepressant. To avoid driving impairment, nonsedating antidepressants should be chosen for treatment instead of sedating antidepressants.

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