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Considering the P450 cytochrome system as determining combined effects of antidepressants and benzodiazepines on actual driving performance of depressed outpatients

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KEYWORDS: benzodiazepines, CYP3A3/4, CYP2C19, depression, driving, drug interactions, fluoxetine, moclobemide

ABSTRACT

Parallel groups of depressed (DSM III-R) outpatients received moclobemide ($n = 22$) and fluoxetine ($n = 19$), double blind, for 6 weeks. Respective starting doses were 150 mg twice a day and 20 mg q.a.m. These could be doubled after 3 weeks for greater efficacy. Chronic users of benzodiazepine anxiolytics continued taking them as comedication. Therapeutic and side effects were assessed using conventional rating scales. Actual driving performance was assessed during the week before therapy and at 1, 3 and 6 weeks thereafter using a standardized test that measures standard deviation of lateral position (SDLP). Similar remissions in depressive symptoms and side effects occurred in both groups. Patients drove with normal and reliable ($r = 0.87$) SDLPs before treatments. Most continued to do so but a few drove with progressively rising SDLPs and the overall trends were significant in both groups ($p < 0.03$). A post-hoc multiple regression analysis was applied for identifying factors that correlated with SDLP in separate tests after the beginning of therapy. At 3 and 6 weeks there were significant ($p < 0.03$) relationships involving the same factor; patients who drove with progressively higher SDLPs appeared to be those using benzodiazepines that are metabolized by a P450 isozyme subject to inhibition by their particular antidepressant.

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Introduction

Information pertaining to driving performance of depressed outpatients before or during antidepressant drug therapy is relatively sparse. Pharmacoepidemiological survey indicate that unmedicated depressed patients drive with a higher than normal risk of becoming involved in injurious traffic accidents (Nelson, 1986), and that elderly patients treated with higher doses of sedative tricyclic antidepressants become involved in accidents more frequently than do age- and sex-matched normal control individuals (Ray *et al.*, 1992; Leveille *et al.*, 1994). However, there are as yet no epidemiological data concerning the effects on accident risk of modern antidepressants, such as the selective serotonin reuptake inhibitors or selective and reversible inhibitors of monoamine oxidase-A.

The present attempt to measure the effects of moclobemide and fluoxetine on actual driving performance proceeded from similar research in healthy volunteers (Ramaekers *et al.*, 1992, 1995). In separate studies, individuals were treated with either moclobemide 200mg twice a day or fluoxetine 20 mg h.s. and with another antidepressant and placebo, for periods of 8 and 21 days, respectively. Driving performance was assessed on treatment day 21 in the longer series. Neither moclobemide nor fluoxetine significantly affected the respective groups' driving performance. From these results one would not expect either drug to impair the present patients' driving performance, at least not over comparable treatment periods. However the patients' treatments were scheduled to last longer than the volunteers', so the possibility of belated driving impairment could not be excluded. The contrary could also be expected if the therapeutic effect of antidepressant treatment were to determine the patient's driving performance. The remission of the patient's symptoms during moclobemide or fluoxetine therapy might lead to driving improvement if their driving performance were generally deficient to begin with. There were still other reasons to suppose that the results of the previous studies might differ from those of the present study. It is far more difficult to control the influence of factors that can interact with antidepressants to affect performance in trials involving patients. One factor, prominent in the area where this study was conducted (Liège, Belgium), is the high prevalence of benzodiazepine (BZD) use (Ansseau, 1988; Petit *et al.*, 1994). In Belgium, most patients suffering from depression are treated with an antidepressant and a BZD concurrently, particularly when the former has insomnia, anxiety or agitation as possible side effects. The protocol of the present study allowed patients entering the study to continue their longstanding use of BZD as comedication.

This offered the opportunity of applying a post-hoc analysis to determine whether certain pharmacokinetic antidepressant-BZD interactions affect patients' driving performance. Moclobemide and fluoxetine are known primarily to inhibit different cytochrome P450 isozymes that are responsible for the oxidative metabolism of many BZDs. The greatest inhibitory activity of moclobemide is at CYP2C19 and to a lesser extent also at CYP1A2 and CYP2D6 (Gram *et al.*, 1995). Inhibition of the latter produces no meaningful change in the pharmacokinetics of moclobemide (Guentert *et al.*, 1995). Fluoxetine is a potent inhibitor of CYP2D6 as well as CYP3A3/4 (Lane *et al.*, 1995). Some BZDs are substrates of CYP2C19, some are substrates of 3A3/4, and others are substrates of none of the isozymes inhibited by the antidepressants. The BZD comedication used by patients in the present study could be either metabolically

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competitive or noncompetitive with their particular antidepressant. The former might accumulate over time and cause the patient to drive progressively worse. That certain combinations of antidepressants and BZDs result in the latter's accumulation in plasma accompanied by progressive performance impairment has already been demonstrated in healthy volunteers treated with either fluoxetine or nefazodone together with alprazolam (Lasher *et al.*, 1991; Kroboth *et al.*, 1995).

Methods

SUBJECTS

Intake interviews were conducted by five psychiatrists under the supervision of the Professor of Psychiatry, University of Liège. Outpatients were included if they satisfied the following criteria: age 18-65 years, diagnosis of major depression according to DSM IIIR criteria, symptom severity associated with a score ≥ 17 on the 17-item Hamilton Depression Rating Scale (HDRS), possession of a valid driver's license, and written informed consent after reading 'Information for Volunteers'. Patients were excluded on the basis of the following: alcohol or drug abuse, or both; acute confusional state, delusions or hallucinations; hypersensitivity to the investigational drugs; serious concomitant illness or intercurrent disease; presumption of a need for hospitalization because of suicide or other factors; engagement in structured analytical or behavioural psychotherapy that might influence the course of the depressive illness during the trial, excluding psychotherapeutic support; renal or liver failure or previous viral or drug hepatitis; treatment with cimetidine; personality disorders presenting an important risk of noncompliance; occurrence of cerebrovascular accidents in the year before study entrance; duration of the present depressive episode of less than 2 weeks; use of fluoxetine within 5 weeks before study entrance; use of other marketed antidepressants or investigational drugs within 7 days or electroconvulsive therapy within 4 weeks before study entrance; and, for women, pregnancy, lactation or the failure to use reliable contraceptives for less than 3 months.

A total of 41 patients (25 men and 16 women) were included. Their demographics and diagnostic categorization are summarized in Table I. The study was carried out in accordance with the Declaration of Helsinki (Hong Kong Modification, 1989). The study protocol and information for volunteers were reviewed and approved by the standing Medical Ethics Committees of the Universities of Liège and Maastricht.

DESIGN

The study was conducted according to a two-leg, double-blind, parallel-group design. A period of 3-7 days elapsed between patient enrollment and the beginning of trial medication. Then patients were randomly assigned to receive moclobemide 150mg twice a day or fluoxetine 20mg q.a.m. for 6 weeks (43 days). At the discretion of the attending psychiatrist this dosage could be doubled from day 22 on in case of insufficient efficacy. Moclobemide and fluoxetine were administered in identical appearing capsules containing 150mg and 20mg, respectively. One or two moclobemide capsules were taken in the morning and evening of every treatment day. One

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or two fluoxetine capsules were taken in the morning, and matching placebo capsules were taken in the evening. Patients were instructed to take their medication after a meal. In order to ensure patient compliance with the medication regime, the returned medication was checked and counted at each visit.

Concomitant BZD medication was allowed for patients who had already been prescribed a single drug for more than 3 months before study entrance. In these cases, prescription of the same BZD continued throughout the study. If needed, patients who had not used a BZD before study entrance were allowed to receive one or two doses of oxazepam, 10mg over the day or 30mg h.s. Type and dose of BZD comedication were filed in prescription records. Compliance with BZD prescription was not checked. Other psychoactive drug or electroconvulsive therapy were prohibited during trial.

CLINICAL ASSESSMENTS

Clinical assessments were conducted by the attending psychiatrists at day 1, 8, 15, 22 and 43. Beside the HDRS, the Montgomery-Asberg Depression Rating Scale (MADRS), Beck's Depression Inventory (BDI), and a Clinical Global Impression (CGI) scale were used. In addition, the occurrence of side effects was checked using a standardized adverse events questionnaire.

DRIVING ASSESSMENTS

Patient undertook a driving test on six occasions. A training session and two baseline tests occurred during the week preceding the onset of treatment. Thereafter, driving performance was tested in the morning of day 8, 22 and 43 of treatment. Patients were met at home by an investigator and transported to the driving site. He/she then entered a primary highway (four lane, divided) at the beginning of a 100 km circuit between the Belgian cities Tongeren and Haelen. He/She proceeded to drive while attempting to maintain the vehicle at a constant speed (95 km/h) and steady lateral position between the delineated boundaries of the slower traffic lane. The patient was allowed to deviate from this procedure in order to pass slower vehicles travelling in the same lane. At an intersection halfway through the circuit, the patient drove off the highway and then reentered, travelling in the opposite direction. At the end of the driving test, the patient was driven home by the investigator.

The patient was accompanied by a technician, whose task was to operate the equipment, and a licensed driving instructor seated in the front passenger's seat with access to dual controls. His sole function was to ensure test safety. Patients were instructed to drive safely at all times and that the treatments might affect their ability to do so. They were informed of their legal responsibility to stop a test in progress if they felt for any reason that to continue would be unsafe. They were further informed that they would asked to stop by the instructor if, in his opinion, their physical appearance or driving performance indicated the possibility of a control loss. An electro-optical device mounted at the rear of the instrumented vehicle continuously measured the 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 and analysis. The off-line editing routine involved removal of all data segments that revealed signal loss, disturbance or occurrence of passing manoeuvres. The remaining clean data were then

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used to calculate means and variance for lateral position. The square root of the variance or standard deviation of lateral position (SDLP) was then taken as the primary measure of driving performance.

Table I. *Patient demographic data and characteristics of their depressive episode*

	Moclobemide (n = 22)	Fluoxetine (n = 19)	All patients (n = 41)
Sex			
Male	13 (59%)	12 (63%)	25 (61%)
Female	9 (41%)	7 (37%)	16 (39%)
Age (years)			
Mean	42.3	42.4	42.3
Minimum	27.0	28.2	27
Maximum	55.4	54.2	55.4
HDRS (inclusion)			
Mean	21.7	22.4	22.0
Minimum	17	18	17
Maximum	27	32	32
Precipitating factor			
None	1 (5%)	2 (11%)	3 (7%)
Somatic illness	1 (5%)	0 (0%)	1 (2%)
Psycho-social stressors	16 (73%)	15 (79%)	31 (76%)
Somatic illness and psycho-social stressors	3 (14%)	2 (11%)	5 (12%)
Uncertain	1 (5%)	0 (0%)	1 (2%)
Time between last and current episode (months)			
Mean	20.3	12.6	16.8
Minimum	1.4	0.5	0.5
Maximum	157.7	73.8	157.5
Characterization			
Depression with anxiety	9 (41%)	10 (53%)	19 (46%)
Depression with mainly somatic symptoms	2 (9%)	3 (16%)	5 (12%)
Agitated depression	5 (23%)	3 (16%)	8 (20%)
Retarded depression	3 (14%)	1 (5%)	4 (10%)
Neurotic depression	3 (14%)	1 (5%)	4 (10%)
Neurotic depression with anxiety	0 (0%)	1 (5%)	1 (2%)

HDRS, Hamilton Depression Rating Scale.

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STATISTICS

A PRIORI COMPARISONS

Efficacy and driving variables were evaluated in two ways: between patients' baseline and the last visit for the intent-to-treat population and over all visits for those completing the study. A repeated measures analysis of variance was used to test for the effects of the factors drug, time and their interaction on HDRS, MADRS and BDI scores. Original CGI scores were compared between drugs for every visit separately by means of a nonparametric Mann-Whitney test. Side effects were evaluated using the chi-square test or in the case of too small expected frequencies, the Fisher exact test.

The coefficient of correlation between all patients' two baseline SDLP scores was calculated before averaging them, per patient, to a single pretreatment score. SDLP scores at baseline and during treatment then entered a repeated measures, multivariate analysis of variance to evaluate the effects of drugs, time and their interaction. Orthogonal polynomial contrasts were used to measure linear, quadratic and cubic trends over time.

A POSTERIORI COMPARISONS

A post-hoc multiple linear regression analysis was applied to determine whether other factors independently correlated with driving performance. Selected factors were either continuous variables or dichotomous indicator (0 or 1) variables. Factors belonging to the former category were: pretreatment SDLP (average of two baseline scores) and depression severity (MADRS). Those belonging to the latter were the following: antidepressant (moclobemide or fluoxetine); double dose (1X or 2X the starting antidepressant dose after treatment week 3); sleep disturbance, nervousness, nausea (presence or absence); BZD Comedication (presence or absence); high dose BZD Comedication [presence or absence of doses exceeding the local definition of 'defined daily doses' of Petit *et al.*, (1994)]; competitive BZD comedication (presence or absence).

The rationale for identifying certain BZDs taken by these patients as competitive with moclobemide and others with fluoxetine, is lengthy and is for that reason reserved for Discussion. For now, the former are simply listed as clorazepate, prazepam, diazepam, cloxazolam and clotiazepam, and the latter as bromazepam and alprazolam.

Stepwise construction of multiple linear regression equation began with the calculation of product moment or biserial coefficients of correlations between each of the independent variables and the dependent variable, SDLP. The first independent variable considered for entry into a regression equation was the one with the largest positive or negative correlation with the dependent variable. The proportion of variance 'explained' by the equation (i.e. R^2 or goodness of fit) was then evaluated relative to the residual variance by F-test. The variance entered the regression equation if R^2 was significant. Once a variable was selected, the partial correlations between SDLP and each of the other independent variables not in the equation, adjusted for the independent variable in the equation, were used to select the next one. The independent variable with the largest partial correlation was the next candidate for inclusion in the equation.

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It was entered if it was associated with a significant change in R^2 as indicated by the T-test. Subsequently, a new set of partial correlations was calculated, again adjusted for independent variable(s) in the equation. Variable selection terminated when no more variables significantly increased R^2. This analysis was separately applied on data collected after 1, 3 and 6 weeks of treatment.

Results

INTENT-TO-TREAT POPULATION AND COMPLETERS

The intent-to-treat population comprised 41 patients of whom 22 and 19 were assigned to moclobemide and fluoxetine groups, respectively. Two patients withdrew after 2 and 3 weeks of moclobemide treatment; one for reasons unrelated to treatment and the other because of side effects (nervousness, agitation, sleep disturbances). Another patient's moclobemide treatment was stopped after 5 weeks because the psychiatrist suspected that the patient's might develop mania. This patient completed the final driving test, albeit 1 week earlier than the others. One patient withdrew during the first week of fluoxetine treatment because of nervousness, agitation and sleep disturbance. Another member of the fluoxetine group provided all clinical data but did not perform his last driving test because he immediately departed on a vacation. In summary, complete clinical data were collected for 18 and 19 patients, and complete driving data for 20 and 17 patients in the moclobemide and fluoxetine groups, respectively.

EFFICACY

Descriptive statistics and results of statistical of HDRS, MADRS and BDI scores are given in Table II. Analysis of variance and Mann-Whitney tests provided similar results for the intent-to-treat population and completers. Moclobemide and fluoxetine produced similar, significant reductions in mean depression ratings on all scales during 6 weeks of treatment. The drugs' similar effects on depressive symptoms were further demonstrated by HDRS scores at the final assessment. In the moclobemide group, 55% of the intent-to-treat population and 58% of the completers showed HDRS scores less than 10 or a decrease from baseline of more than 50%. In the fluoxetine group, 53 and 61% of patients showed these positive responses, respectively. CGI ratings at baseline and during therapy did not differ between treatment groups.

ADVERSE EVENTS

Nausea, nervousness/agitation, sleep disturbances and dizziness were reported by six, five, three and two patients in the fluoxetine group and by five, six, 11 and one patient in the moclobemide group. None of these frequencies differed significantly between groups. In addition, five patients reported dry mouth during fluoxetine treatment.

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Table II. *Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS) and Beck's Depression Inventory (BDI) scores by groups and times of assessments*

	HDRS		MADRS		BDI	
Time of Assessments	FLU	MOC	FLU	MOC	FLU	MOC
Baseline	22.7	20.8	28.1	26.5	16.1	15.6
	(4.0)	(3.1)	(7.2)	(6.2)	(7.4)	(5.5)
Week 1	17.5	18.6	21.2	22.5	12.6	13.2
	(4.8)	(3.6)	(8.1)	(6.4)	(4.7)	(5.4)
Week 2	14.6	15.9	18.5	19.6	9.7	13.7
	(4.8)	(6.7)	(7.4)	(9.6)	(5.8)	(8.7)
Week 3	13.5	14.1	16.8	18.7	11.1	13.0
	(5.2)	(5.9)	(7.7)	(9.6)	(7.2)	(7.0)
Week 6	11.1	12.2	13.7	14.3	9.2	10.8
	(6.1)	(5.8)	(8.8)	(8.5)	(8.5)	(6.7)
Last visit	11.7	12.1	14.5	14.2	9.5	10.3
	(6.6)	(5.4)	(9.2)	7.9	(8.3)	(6.4)
ANOVA	Completers ($n = 37$)	Intent-to-treat ($n = 41$)	Completers ($n = 41$)	Intent-to-treat ($n = 41$)	Completers ($n = 37$)	Intent-to-treat ($n = 41$)
Drugs	$p = 0.528$	$p = 0.381$	$p = 0.650$	$p = 0.667$	$p = 0.118$	$p = 0.603$
Time	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Drugs by time	$p = 0.727$	$p = 0.654$	$p = 0.761$	$p = 0.650$	$p = 0.394$	$p = 0.877$

ANOVA, analysis of variance; FLU, fluoxetine; MOC, moclobemide

DOSE DOUBLING AND BENZODIAZEPINE COMEDICATION

After 3 weeks of treatment, daily dose was doubled for 14 (67%) patients in the moclobemide group and for six (33%) patients in the fluoxetine group ($p = 0.08$). BZD anxiolytics were being taken by 30 patients at study entrance and their use continued during treatment. One patient started taking BZD Comedication during the study. In total, 16 (73%) and 15 (79%) patients in the moclobemide and fluoxetine group, respectively, used BZD during treatment. The types of Comedication taken by patients in both groups, the numbers using each one and the numbers taking them in higher than the respective defined daily doses are given Table III.

DRIVING PERFORMANCE: A PRIORI ANALYSES

Fig. 1 shows the relationship between the patients' two SDLP scores from consecutive baseline tests. They drove with similar SDLP (mean ± SE) values on both occasions (24.2 ± 0.95 versus 24.1 ± 0.81 cm) and the individual values were highly reliable (r = 0.87). There was no difference between SDLP scores of patients who were taking BZDs and those who were not, either for each test separately or for both tests combined (combined mean ± SE, 24.1 ± 0.91 versus 24.2 ± 1.59 cm: F1.39 = 0.004, $p = 0.95$).

Figure 2 shows each group's mean SDLP (SE) in baseline tests and in those given after 1, 3 and 6 weeks of treatment. Multivariate analysis of variance revealed no significant overall mean differences in SDLP between the fluoxetine and moclobemide groups for either the intent-to-

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treat population or the completers. Within individuals the overall linear increase in SDLP over tie was significant for the intent-to-treat population and the completers ($F_{1.38} = 5.35$, $p = 0.026$ and $F_{1.35} = 5.44$, $p = 0.026$ respectively). The interaction between drug and time was not significant.

Table III. *Number of patients receiving benzodiazepine (BZD) comedication, and doses higher than defined daily dose (DDD)*

	Fluoxetine ($n = 19$)		Moclobemide ($n = 22$)	
BZD (DDD)	No. patients	Doses > DDD	No. patients	Doses > DDD
Clorazepate (20 mg)	-	-	3	2
Prazepam (30 mg)	1	-	21	1
Diazepam (10 mg)	1	-	1	1
Cloxazolam (2 mg)	-	-	1	1
Clotiazepam (5 mg)	-	-	1	1
Bromazepam (10 mg)	4[1]	2[1]	1	1
Alprazolam (1 mg)	3	2	1	-
Oxazepam (50 mg)	3	-	5	-
Lorazepam (2.5 mg)	3	3	1	1
Total cases	15	7	16	8

[1]One patient only completed driving tests at baseline

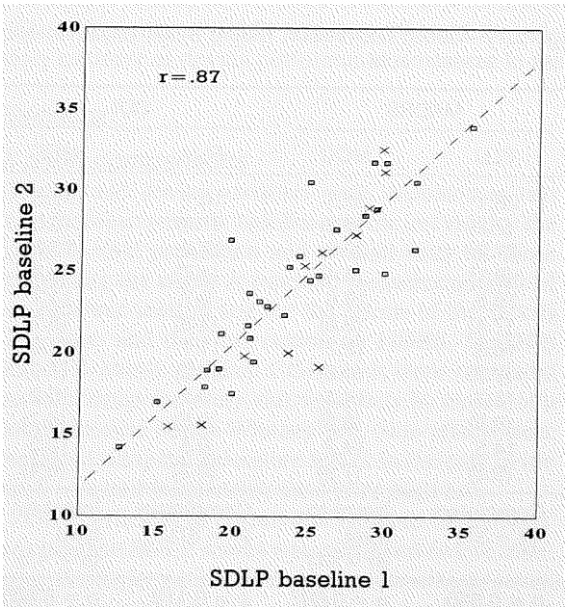

FIG. 1. Individual driving performance of 41 depressed patients at the first and second baseline tests. Thirty patients were benzodiazepine users (▯), others were nonusers (X).

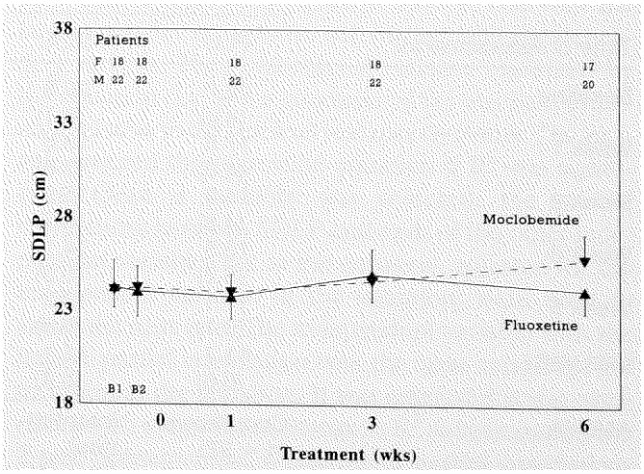

FIG. 2. Mean (± SE) standard deviation of lateral position (SDLP) during baseline tests and those given after 1, 3 and 6 weeks of therapy with fluoxetine and moclobemide. Number of patients participating are noted separately for groups receiving (▲ F) fluoxetine and (▼, M) moclobemide.

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Table IV. *Variables entering the multiple linear regression analysis and their associated p-values as indicated by F and T tests*

	Week 1			Week 3			Week 6		
Variables in the equation	B	T	*p*	B	T	*p*	B	T	*p*
(Constant)	3.88	2.45	0.018	1.67	0.83	0.394	3.52	1.31	0.198
Pretreatment SDLP	0.82	12.88	0.000	0.92	11.53	0.000	0.86	7.77	0.000
Competitive BZD				2.04	2.46	0.019	2.81	2.39	0.023
Multiple R		0.902			0.901			0.830	
R square 1st variable		0.813			0.779			0.635	
R square 2nd variable					0.811			0.689	
Analysis of variance	$F_{1.38} = 165.89$; $p < 0.001$			$F_{2.36} = 77.41$; $p < 0.001$			$F_{2.33} = 36.61$; $p < 0.001$		
Variables not in the equation		*p*			*p*			*p*	
Antidepressants		0.707			0.612			0.236	
Double dose		not applicable			not applicable			0.842	
Depression severity		0.336			0.884			0.421	
BZD Comedication		0.210			0.201			0.340	
High doses BZD		0.801			0.419			0.790	
Competitive BZD		0.832							
Sleep disturbances		0.062			0.905			0.953	
Nervousness		0.468			0.213			0.220	
Nausea		0.463			0.491			0.196	

Slope and intercept values are shown in the column labelled B.
BZD, benzodiazepine; SDLP, standard deviation of lateral position.

DRIVING PERFORMANCE: A POSTERIORI ANALYSES

Results from the multiple linear regression analysis are given in Table IV. The data show that pretreatment SDLP correlated strongly with scores measured on subsequent occasions. The proportions of SDLP variance 'explained' by pretreatment scores were 0.81, 0.78 and 0.64 after 1, 3 and 6 weeks of therapy, respectively. That this proportion dropped between weeks 3 and 6 implies the growing influence of other factors on the patients' driving performance. There may have been several such factors but the only one to emerge as a significant determinant of SDLP variation was competitive BZD Comedication. Inclusion of this dichotomous variable in the equation increased the proportion of 'explained' SDLP variance by 0.02 after week 3 and by 0.05 after week 6.

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Fig. 3 illustrates the effects on mean (SE) SDLP of both antidepressants, separately and together, in the presence or absence of competitive BZD Comedication. Although data from subgroups using noncompetitive and no BZD Comedication were combined in the regression analysis, their respective mean SDLP values are shown separately in the figure. It is clear that none of these subgroups' performances changed substantially from baseline levels over the course of treatment. In contrast, mean SDLP rose progressively from baseline for the subgroup taking moclobemide in combination with competitive BZD Comedication. The subgroup taking fluoxetine in combination with competitive Comedication showed a similar rise in mean SDLP after treatment week 3 but then a recovery to baseline levels after week 6.

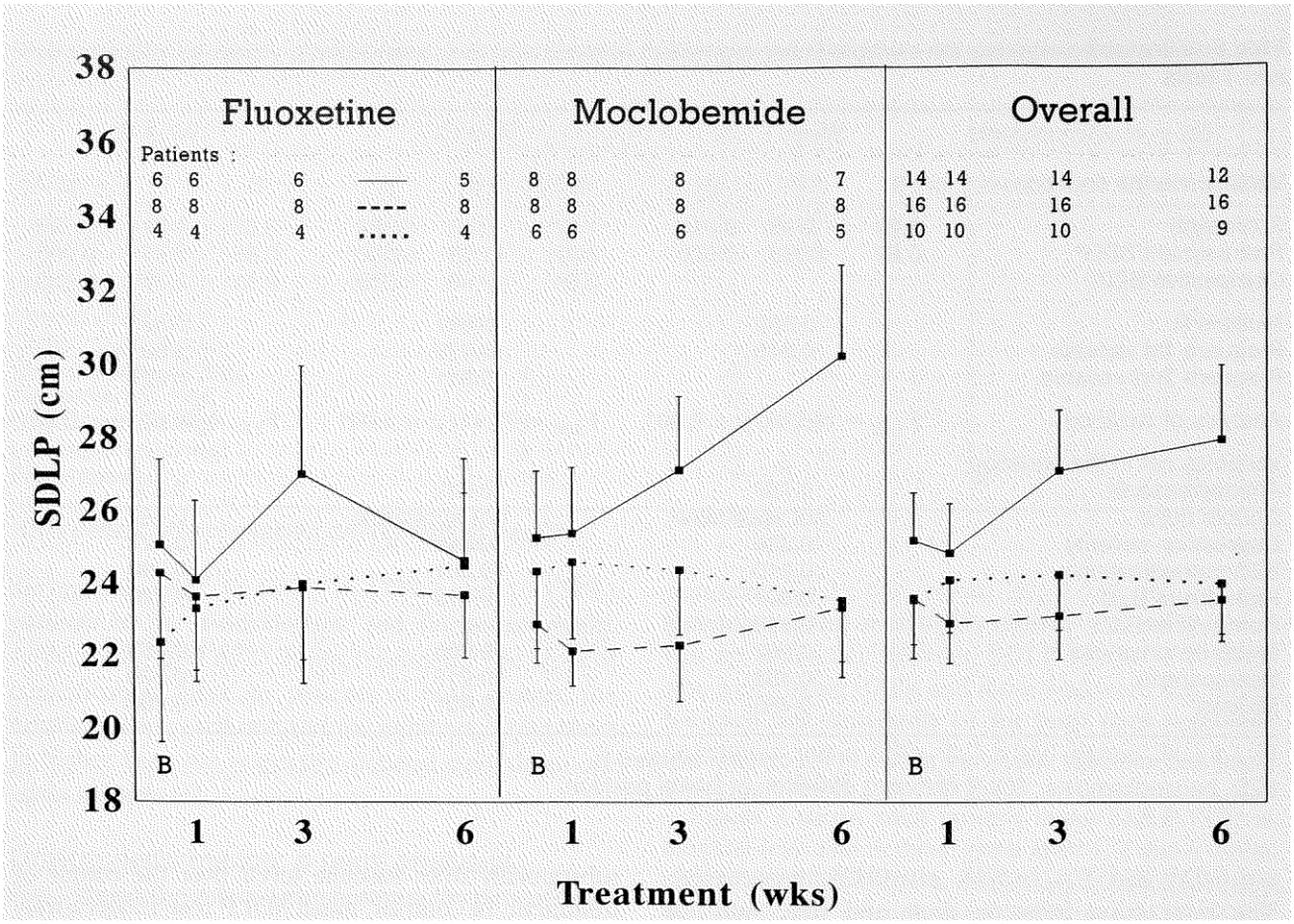

FIG. 3. Mean standard deviation of lateral position (SDLP) (SE) as a function of time for subgroups of patients receiving (—) competitive benzodiazepine comedication, (····) noncompetitive comedication or (····) none at all during treatment with fluoxetine and moclobemide.

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Discussion

This was the first study to assess objectively the driving performance of depressed outpatients before and during antidepressant drug therapy. The purpose was to determine whether the drugs' therapeutic or side effects influence patients' driving performance. Moclobemide and fluoxetine produced similar remissions in the respective group's depressive symptoms over the course of parallel 6-week treatment periods. It should be noted, however, that a higher proportion of the moclobemide group required dose-doubling to achieve this improvement (i.e. 67 versus 33%, $p = 0.08$). The drugs' side effects (nervousness, irritability and sleep disturbances) were likewise similar in frequency and severity.

The patients' baseline driving performances were reliable, as indicated by a test-retest correlation of 0.87. They drove with a mean SDLP of approximately24 cm during both tests. This is only slightly higher than mean values recorded for healthy volunteers or anxious patients in similar studies [i.e. 19-23 cm (Van Laar *et al.*, (1995)]. All but one of the present patients drove at baseline with SDLPs that were well below the established normal limit of 35 cm. Most of them were chronic BZD users. Yet the users' mean SDLP was little different from that of the minority who were not using BZDs. This finding confirms results from previous experimental and epidemiological research. Van Laar *et al.* (1992) treated anxious patients for 4 weeks with diazepam 5 mg three times a day. Their driving impairment was substantial after the first week but gradually diminished over time. After 4 weeks, their driving performance no longer significantly differed from baseline. Neutel (1995) calculated the risk of becoming involved in an injurious traffic accident for 148000 patients as a function of time after receiving a prescription for BZD anxiolytics relative to that of 98000 control individuals. Patients drove with a risk that was 13.5 times higher than that of the control individuals during the first week after their prescription were filled, but after 4 weeks the relative risk had decreased to a value of 2.6 with no measurable effect after that. Together these results indicate that depression itself, but not long-term use BZDs, was responsible for the patients' slightly deficient driving performance at the time of study entry.

The progressive remission in both groups' depressive symptoms was not accompanied by an improvement in driving performance. In fact the opposite occurred; mean SDLP for all patients combined rose throughout the 6-week treatment period. The rising trend was very gradual but statistically significant. Although there was no significant difference in trends between the groups, that for the moclobemide group was most pronounced. This was surprising because moclobemide does not accumulate with repeated dosing, whereas fluoxetine and its active metabolite do, and to marked degrees. Thus we suspected that some factor beside or in addition to the antidepressants was responsible for at least some patients' progressive deterioration in driving ability. Several were conceivable and the post-hoc analysis was applied in the hope of identifying the factor or factors responsible for the change.

One was suggested by concern regarding antidepressant—BZD interactions involving the P450 cytochrome system (Brøsen, 1993; Von Moltke *et al.*, 1994). Among all of the P450 isozymes so far identified in humans, only CYP2C19 and two almost identical isozymes of the CYP3A subfamily, -3 and -4 (CYP3A3/4), respectively, are able to catalyze oxidative reactions involving BZDs (Ketter *et al.*, 1995). Moclobemide is a substrate for and a relatively potent inhibitor of

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CYP2C19 (Gram *et al.*, 1995). Fluoxetine's metabolite, norfluoxetine, is a potent inhibitor of CYP3A3/4 (Von Moltke *et al.*, 1994). CYP3A3/4 inhibitors retard the first steps in the metabolism of bromazepam (3-hydroxylation: Van Harten *et al.*, 1992) and alprazolam, triazolam and midazolam (n-hydroxylation: Lasher et al., 1991; Kroboth *et al.*, 1995). Andersson *et al.*, (1994) found that the inhibition both of CYP3A3/4 and of CYP2C19 retarded the N-demethylation of diazepam to form nordiazepam, but that only the former prevented the 3-hydroxylation of diazepam to form temazepam *in vitro*. Bertilsson *et al.* (1989) provided the first indication that the metabolism of nordiazepam proceeds through the polymorphic isozyme responsible for hydroxylation of *S*-mephenytoin, later identified as CYP2C19 (Wrighton *et al.* 1993; Goldstein *et al.*, 1994). They showed that clearance and elimination of diazepam and nordiazepam in extensive hydroxylation of S-mephenytoin proceeded at twice the rates found in poor metabolizers. In addition, Caraco *et al.* (1995) showed that concomitant administration of diazepam and omeprazole, a CYP2C19 inhibitor, reduced clearance of diazepam and increased the area under the curve of nordiazepam in extensive metabolizers. Fluoxetine also reduced clearance of diazepam but at the same time lowered the area under the curve of nordiazepam, presumably by inhibiting CYP3A3/4 (Lemberger *et al.*, 1988). Thus the evidence so far indicates that whereas diazepam is *N*-demethylated both at CYP3A3/4 and at CYP2C19, the 3-hydroxylation of nordiazepam occurs mainly, if not entirely, at CYP2C19.

The effects of moclobemide on the metabolism of BZDs are still unknown but for purposes of analysis they were assumed to be those of a CYP2C19 inhibitor. Thus we dichotomized between those patients taking moclobemide with any BZD that possesses nordiazepam among its metabolites, and those taking another BZD or none. We further assumed that fluoxetine primarily inhibits CYP3A3/4. Again we dichotomized between those patients taking BZD that are known substrates of that isozyme, except diazepam, and those taking another BZD or none. The former patients in both groups were defined as taking competitive comedication, and the latter as taking noncompetitive comedication or none. A question arose in the case of one patient taking the combination of moclobemide and the little known BZD clotiazepam. The combination was defined as competitive, mainly because metabolism of clotiazepam proceeds by N-demethylation and 3-hydroxylation, like that of diazepam, although more rapidly (Ochs *et al.*, 1984). We admit that this assignment was more arbitrary than the others.

The dichotomization yielded interesting results in the multiple regression analysis. Its application with the data from the driving test after 1 week of antidepressant therapy showed no significant partial correlation between patients' use of competitive BZDs and SDLP At that time, their performance was simply related to preexisting individual differences in SDLP, showing again the stability of the measure in the absence of any new factor. Subsequent applications with data from tests given both after week 3 and 6 indicated the emergence of a new factor. At these times, the dichotomous variable identifying users and nonusers of competitive BZDs correlated significantly with SDLP. In general, patients taking competitive BZDs drove progressively worse, whereas the others continued to drive in approximately the same manner as before. We assume that a rising brain concentration of the comedication or its active metabolite, because of the particular antidepressants' inhibition of the inactivating isozyme, was the root cause for the former patients' deterioration.

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There was an apparent difference between the persistence of driving impairment in patients taking competitive BZD comedication with moclobemide and fluoxetine. For the moclobemide subgroup, mean SDLP rose throughout the 6-week treatment period, but for the fluoxetine subgroup, only until week 3. Maximal elevations in mean SDLP in the fluoxetine and moclobemide subgroups were approximately 2 and 5 cm respectively, which were close to elevations previously shown in social drinkers while driving with blood alcohol concentrations of 0.50 and 0.80 mg/ml, respectively (Louwerens *et al.*, 1987). Possibly this difference is related to the respective sites of the pharmacokinetic interaction. The only known BZD substrates of CYP2C19, diazepam and nordiazepam, are slowly metabolized under normal circumstances. Except for diazepam, those of CYP3A3/4 are all more rapidly metabolized. Supposing moclobemide and fluoxetine/ norfluoxetine selectivity inhibit these respective isozymes to similar degrees, it would take longer for substrates of CYP2C19 to reach a new steady state than for substrates of CYP3A3/4. This does not imply that the interaction of moclobemide with competitive BZDs is any more consequential for patient safety than that of fluoxetine. It might have appeared that way if all of the patients had been taking nordiazepam during the study. However, exactly the opposite impression might have been given if they had been taking alprazolam.

The dual purpose of every post-hoc analysis is to explain simultaneously an unforseen result and provide hypotheses for further research. Some explanations for the unforseen deterioration in some patients' driving performance at a relatively late stage during their treatment with study medication seemed necessary in view of the likelihood that the same could occur in real life. Our explanation is for the moment tentative and mainly of heuristic value. Well-controlled studies should now be undertaken to determine which antidepressant—BZD combinations are and are not compatible with patient safety as they engage in potentially dangerous activities, like driving.

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