Effects of antidepressants on skilled performance

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1 Effects of amitriptyline 50 mg, desipramine 100 mg, and zimelidine 200 mg alone and in combination with ethanol 0.8 g/kg were investigated in healthy, male volunteers.

2 Amitriptyline increased body sway and impaired tracking as well as information processing. It had an additive deleterious pharmacodynamic interaction with ethanol.

3 Desipramine and zimelidine were free of adverse effects on performance and did not have significant interactions with ethanol.

4 The dose of ethanol used in the present study did not inhibit biotransformation of the antidepressants.

Keywords antidepressants performance amitriptyline desipramine zimelidine

Introduction

Two recent reviews have examined effects of antidepressants on skilled performance (Linnoila & Seppala, 1984; Seppala & Linnoila, 1984). There are four main messages in the published reports: (1) sedative antidepressants impair performance of healthy volunteers and depressed patients during the first week of treatment at a steady dose; (2) depressed patients have impaired performance compared with healthy volunteers. Their information processing is slowed down, and they have difficulties in concentrating; (3) during prolonged treatment the adverse effects of even sedative antidepressants on performance are diminished and become nonsignificant; (4) successful treatment of depression corrects the information processing and performance deficits observed in untreated depressed patients.

Because the adverse effects of antidepressants are worse at the very beginning of treatment, there is a rationale to investigate such effects after a single dose. Furthermore, the sedative antidepressant-induced impairment is qualitatively similar in depressed patients and healthy volunteers. Thus, it is reasonable to use healthy volunteers rather than depressed patients as subjects in an experiment designed to rank order antidepressants according to their impairment producing potencies. Another important characteristic of

an antidepressant for traffic safety is the quality of its interaction with ethanol. This is because a significant proportion of psychiatric out-patients are at a risk of drinking and driving during their treatment (Milner, 1969).

With these considerations in mind, we investigated effects of amitriptyline, desipramine and zimelidine both alone and in combination with ethanol on skilled performance.

Methods

Preparations

Identical appearing capsules containing amitriptyline (50 mg), desipramine (100 mg), zimelidine (200 mg) or placebo were given in combination with ethanol (0.8 g/kg of body weight) or placebo drinks.

Subjects

Twelve Caucasian male volunteers between the ages of 21 and 27 years (mean $\pm$ s.d. = 24 ± 1.7) were recruited for the study and paid for their time. The subjects qualified as social drinkers (they drank, on the average, about twice a week 1 to 6, 355 ml cans of beer at a time) and were healthy as determined by blood

pressure, pulse, respiratory and cardiovascular assessment and a psychiatric interview. They were within $\pm 15\%$ of their ideal weight. None was taking medications, had had any operations within the previous year, nor had family histories of alcoholism or mental illness, including schizophrenia, or a major affective disorder. All were right-handed and had only right-handed first degree relatives except for two subjects who had left-handed sisters.

Tests

Four tasks were used to assess psychomotor functions.

(a) *Body sway* The amount of body sway was measured with a platform, which transformed subject's sway along the fore to aft and side to side axes into voltage readings. Amount of sway was determined for three conditions lasting 30 s each: (1) eyes open looking at a fixation point at eye level about 1.5 m away, (2) eyes closed, and (3) eyes closed with the platform vibrating. Total amount of sway and a power spectrum across frequencies from 0 to 14 Hz were recorded separately for each condition.

(b) *Tracking test* Tracking ability was measured with a continuous subcritical tracking task (Linnoila *et al.*, 1978). The target (a 25 cm high and 2 cm wide, illuminated bar) was located in the middle of a 36 cm diagonal cathode ray tube (CRT). The movement of the bar across the screen horizontally was controlled by both the computer and the subject with a car steering wheel. Two levels of task difficulty were administered, the first being established by previous work to be relatively easy ($\lambda = 2$) and the second relatively difficult ($\lambda = 3$). The task was to maintain the position of the bar as close to the target as possible. The root mean square (RMS) error score and a power spectrum of the frequency of the steering wheel movements were analyzed.

(c) *Words* and (d) *Angles* Verbal and spatial information processing were measured by providing the subject with a midscreen fixation point and after a pseudo random 2 to 6 s interval flashing a three letter word or an angle 5° to either side of this fixation point. A computer monitoring the electro aculogram delivered the stimuli only when the subjects were actually staring at the fixation point without blinking their eyes. The stimulus lasted 100 ms. Thus, the information was assumed to be transmitted preferentially into only one of the cerebral hemispheres because this stimulus duration is too brief to initiate a saccade.

Depending on the stimulus, subjects responded by switching two levers either up (HAY and WAX, or largest and second smallest angle) or down (HAM and TAX, or smallest and second largest angle). The total number of words and angles presented in a session was 48 each. The faster reaction time from either the left or right lever was recorded, as well as the number of correct and incorrect responses. Because in a majority of responses the right-hand reaction time was shorter than the left-hand reaction time only the former were used.

Study design

Subjects participated in training sessions prior to actual drug administration and experimental testing. At the beginning of these sessions they were fully informed about the protocol, received the physical and psychiatric interview and spent 1–2 h practising each of the three psychomotor tests (Tracking, Words, and Angles). The purpose of the training sessions was to ensure proficiency at less than a 10% error rate in each of the information processing tasks, and to improve tracking skills to a level where major learning effects were excluded.

The four drug treatments were administered in random order, crossover, in combination with ethanol or ethanol placebo on eight separate days approximately 1 week apart. Subjects were blind to the medication; however, the experimenter was not.

On each testing day, subjects were first administered a breath test for ethanol and acet-aldehyde levels. They ate a light breakfast between 07.00 h and 08.00 h, received their medication at 08.00 h and ingested the drinks (a total volume of 400 ml) 2 h after the medications. They were allowed 30 min to consume the drinks. Psychomotor testing started 30 min after drinking and was repeated three times during a test day.

Pharmacokinetics

Venous 5 ml blood samples were drawn into heparinized clean glass tubes 2, 3, 4, 6, 8 and 24 h after drug administration. Plasma amitripty-line, nortriptyline, desipramine and their hydroxy metabolite concentrations were quantified with a modified liquid chromatographic method according to Sutfin & Jusko (1979). Zimelidine and norzimelidine concentrations were measured according to the method of Westerlund *et al.* (1979). Breath ethanol concentrations were measured with a gas chromatographic analyzer (Intoximeter Mark IV) immediately prior to and after each test session.

Statistical analysis

Each of the 12 subjects was tested on the psychomotor tasks during three separate sessions (1 h, 2 h, and 4 h after starting to drink) with four drugs (amitriptyline, desipramine, zimelidine, and placebo) in combination with ethanol (ethanol and ethanol-placebo). The statistical analysis thus consisted of a $2 \times 3 \times 4$ (ethanol by session by drug treatment) repeated measures analysis of variance. For the Words and Angles testing, an additional factor for left and right visual field presentation was included to result in a $2 \times 2 \times 3 \times 4$ repeated measures analysis of variance. Greenhouse-Geisser adjusted degrees of freedom were used to adjust for the liberal application of the univariate repeated measures ANOVA. Duncan's multiple range test was used to assess differences between individual means. Nonparametric analysis of variance using ranked scores was computed as well. Because the parametric and nonparametric tests were found to yield similar levels of statistical significance, only the results of the parametric analyses are reported.

Results

(a) Body sway

Effects of ethanol Body sway with eyes open was significantly increased by ethanol administration ($F = 12.05$; d.f. = 1, 8; $P < 0.008$), but not while the eyes were closed ($F = 3.71$; d.f. = 1, 8; $P = 0.09$) or while the platform was vibrating ($F = 2.45$; d.f. = 1, 8; $P = 0.15$). For eyes open, when placebo with ethanol was compared to each drug in combination with ethanol, amitriptyline administration during sessions 1 and 2 resulted in more body sway while desipramine administration during session 3 resulted in less body sway. Zimelidine administration did not significantly alter body sway (Table 1) either alone or in combination with ethanol.

Effect of drugs Body sway was significantly affected by drug treatment with the eyes open ($F = 6.78$; d.f. = 1, 6; 12, 79; $P < 0.008$), with the eyes closed ($F = 19.68$; d.f. = 1, 29; 10, 34; $P < 0.007$), and while the platform was vibrating ($F = 157.11$; d.f. = 1, 64; 13, 10; $P = 0.002$). More body sway was observed with amitriptyline administration than with any of the other experimental drugs. Zimelidine and placebo produced very similar body sway (Table 1).

Effects of testing over time Significant differences were not found between the three daily testing sessions while the eyes were open ($F = 0.18$; d.f. = 1, 3; 10, 43; $P = 0.67$) or closed ($F = 2.05$; d.f. = 1, 37; 10, 97; $P = 0.18$) or while the platform was vibrating ($F = 1.69$; d.f. = 1, 7; 13, 57; $P < 0.22$).

(b) Tracking

Easy The easy tracking task revealed an interesting pattern of significant effects. Both the drug by ethanol interaction ($F = 4.98$; d.f. = 1, 23; 13, 54; $P = 0.04$) and the drug by session interaction ($F = 5.2$; d.f. = 1, 68; 18, 52; $P < 0.02$) suggested two patterns of response confirmed by Duncan's test of multiple comparisons. Administration of placebo, amitriptyline, and zimelidine in combination with ethanol showed an increase of the RMS score from session 1 to session 2, while in session 3 the score decreased (Table 2).

The RMS score remained relatively stable across time after desipramine in combination with ethanol. Amitriptyline in combination with ethanol produced significantly larger values than placebo in combination with ethanol.

Difficult The difficult tracking task was differentially affected by ethanol administration during placebo, desipramine, and zimelidine ($F = 21.8$; d.f. = 1, 11; $P = 0.007$) but not during amitriptyline administration (Table 2). Repeated daily testing showed a pattern similar to the easy tracking task, as confirmed by the drug by session interaction ($F = 4.17$; d.f. 2, 9; 31, 92; $P \leq 0.01$). Overall ethanol administration also produced higher values, as confirmed by its main effect ($F = 21.8$; d.f. = 1, 11; $P \leq 0.0007$).

(c) Words

Correct responses Ethanol significantly impaired responses in either the left or right visual field of presentation ($F = 6.21$; d.f. = 1, 11; $P = 0.03$; Table 3). Amitriptyline reduced the number of correct responses more than any other drug treatment (main effects = $F = 11.95$; d.f. = 1, 49; 16, 37; $P = 0.001$) either alone or in combination with ethanol (drug by ethanol interaction: $F = 4.84$; d.f. = 1, 23; $P = 0.04$). Overall significant differences between left or right side presentation were also revealed (main effect: $F = 4.71$; d.f. = 1, 11; $P \leq 0.05$) with the right side being more adversely affected.

Reaction time While ethanol did not significantly impair performance ($F = 2.39$; d.f. = 1,

Table 1 Body sway (mean $\pm$ s.d.)

	Session	Drug treatment					
		Placebo No	ALC	DMI No	ALC	AMI No	ALC
Eyes	1	99.3 (120.8)	80.8 (30.66)	88.4 (94.1)	111.6 (262)	193.9 (178)	388.6** (422.4)
	2	61.6 (59.6)	113.5 (98.9)	65.5 (43.5)	118.6 (67.5)	179.0 (149.9)	458.0** (301.8)
	3	55.6 (19.72)	191.0† (194.7)	78.5 (93.3)	70.9** (49.9)	91.5 (48.3)	213.7 (175.9)
Eyes closed	1	116.3 (85.6)	158.4 (102.5)	112.3 (88.6)	147.2 (144.9)	499.5 (414.3)	531.8** (587.6)
	2	91.3 (63.2)	171.2† (114.4)	144.2 (178.6)	151.2 (113.3)	354.4 (323.1)	622.3** (290.2)
	3	120.4 (134.4)	154.9 (147.7)	108.6 (112.2)	125.3 (162.6)	264.8 (314.9)	349.4** (187.0)
Eyes closed platform vibrating	1	186.8 (96.6)	300.3 (99.9)	226.0 (127.1)	299.8 (187.6)	429.6 (657.6)	611.4†** (590.9)
	2	184.8 (58.2)	317.5 (201.4)	181.5 (120.7)	283.8† (151.6)	330.6 (266.3)	601.5 (469.2)
	3	182.1 (119.8)	377.0 (105.1)	191.8 (146.9)	189.8 (167.1)	390.3 (254.1)	463.7 (335.9)

** Pairwise comparisons between placebo + ethanol vs drug and ethanol treatment significant at the 0.01 level

* Pairwise comparisons between placebo + ethanol vs drug and ethanol treatment significant at the 0.05 level

† Pairwise comparisons between drug treatment alone vs drug treatment + ethanol significant at the 0.05 level

ALC ethanol, DMI desipramine, AMI amitriptyline, ZMI zimeidine

Table 2 Tracking (RMS error) (mean $\pm$ s.d.)

	Session	Drug treatment					
		Placebo	DMI		AMI		ZMI
		No ALC	ALC	No ALC	ALC	No ALC	ALC
Easy ($\lambda = 2$)	1	446.8 (206.0)	468.3 (252.2)	461.8 (186.3)	616.0 (417.2)	1601.7 (1531)	2435.8** (2171)
	2	399.5 (161.0)	794.3† (867.7)	490.3 (321.7)	584.5 (308.2)	1916.8 (1938)	3303.0* (3262)
	3	434.9 (180.5)	432.6 (134.3)	621.0 (766.6)	621.6 (449.2)	720.6 (402.3)	1701.3** (1783)
Difficult ($\lambda = 3$)	1	957.3 (608.4)	1921.4† (1399)	1009.0 (670.1)	2551.5† (1798)	3212.6 (2195)	4721.3** (2681)
	2	970.8 (519.6)	2328.9† (1539)	1274.7 (1007)	2286.7† (1374)	4082.7 (2452)	5261.4** (2731)
	3	933.1 (567.7)	1830.9† (1210)	1335.2 (1334)	1945.3† (1425)	2323.3 (1783)	3698.9* (2659)

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ALC, ethanol, DMI desipramine, AMI amitriptyline, ZMI zimelidine

Table 3 Correct response to words (mean $\pm$ s.d.)

		Drug treatment									
Session		Placebo		DMI		AMI		ZMI		ALC	
		No	ALC	No	ALC	No	ALC	No	ALC	No	ALC
Right side presentation	1	23.7 (0.42)	23.5 (0.45)	22.8 (2.4)	22.3 (4.2)	20.0 (5.1)	16.3** (7.5)	23.3 (1.7)	23.2 (1.5)		
	2	23.8 (0.39)	23.3 (1.5)	22.9 (2.8)	22.8 (1.6)	17.1 (7.6)	15.1** (8.1)	22.8 (2.8)	23.3 (0.9)		
	3	23.8 (0.21)	23.7 (0.42)	23.8 (6.1)	23.8 (0.6)	21.1 (5.2)	19.2**† (5.1)	23.7 (1.2)	23.2 (2.3)		
Left side presentation	1	23.9 (0.29)	23.4 (0.66)	22.6 (2.4)	22.4 (4.2)	19.8 (5.32)	16.5* (7.7)	23.3 (1.4)	23.3 (1.8)		
	2	23.3 (0.78)	23.3 (1.2)	23.0 (3.1)	22.9 (1.7)	17.7 (8.02)	14.9** (7.5)	23.5 (1.7)	23.1 (1.8)		
	3	23.7 (0.65)	23.8 (0.87)	23.7 (0.5)	23.6 (0.9)	21.7 (4.6)	20.3** (4.3)	23.6 (1.2)	23.6 (0.9)		

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ALC, ethanol, DMI desipramine, AMI amitriptyline, ZMI zimeidine

Table 4 Right hand reaction time (ms) for correct responses to words (mean $\pm$ s.d.)

	Session	Drug treatment					
		Placebo		DMI		AMI	
		No ALC	ALC	No ALC	ALC	No ALC	ALC
Right side presentation	1	789.2 (144.7)	842.1 (165.5)	796.6 (181.0)	843.9 (178.0)	891.5 (163.5)	924.0 (195.2)
	2	806.1 (184.9)	849.8 (201.6)	777.1 (163.7)	833.8 (187.7)	999.9 (232.1)	1023.3** (277.3)
	3	766.4 (159.6)	803.9 (172.9)	798.5 (138.2)	761.9 (119.6)	825.3 (174.3)	864.4 (178.6)
Left side presentation	1	795.3 (157.8)	819.4 (158.2)	769.3 (159.8)	830.6 (212.9)	887.6 (153.1)	936.0* (187.0)
	2	815.7 (210.7)	870.7 (213.0)	789.6 (157.7)	805.8 (174.2)	947.6 (206.9)	960.4 (193.1)
	3	777.0 (176.8)	815.8 (177.0)	807.8 (132.2)	767.0 (114.0)	826.6 (171.4)	888.2 (212.0)
						ZMI No ALC	ALC
						807.1 (187.3)	823.1 (186.6)
						877.4 (210.4)	830.6 (189.8)
						838.4 (193.8)	812.8 (185.8)
						812.0 (179.0)	832.8 (214.7)
						875.1 (229.9)	830.4 (173.4)
						822.1 (175.5)	816.3 (184.0)

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 † Pairwise comparisons between drug treatment alone vs drug treatment + ethanol significant at the 0.05 level
 ALC, ethanol, DMI desipramine, AMI amitriptyline, ZMI zimeldine

Table 5 Correct responses to angles (mean $\pm$ s.d.)

	Session	Drug treatment					
		Placebo		DMI		AMI	
		No	ALC	No	ALC	No	ALC
Right side presentation	1	21.0 (2.1)	20.2 (2.4)	20.3 (5.5)	19.2 (6.2)	14.4 (6.9)	11.6** (8.8)
	2	21.3 (2.5)	21.7 (1.6)	20.0 (5.7)	19.8 (3.7)	12.8 (8.3)	9.2** (7.5)
	3	21.3 (2.5)	21.5 (1.8)	22.0 (1.8)	20.4 (4.2)	17.1 (5.5)	13.9** (6.9)
Left side presentation	1	20.7 (3.1)	19.6 (3.3)	19.8 (5.3)	18.8 (6.5)	14.3 (7.2)	12.0 (9.3)
	2	21.5 (2.5)	21.5 (2.2)	19.8 (5.1)	20.2 (3.5)	13.4 (7.6)	10.7** (8.6)
	3	21.3 (2.6)	21.5 (2.1)	21.5 (2.8)	19.8 (5.4)	17.0 (5.6)	14.9** (7.1)
							20.6 (3.2)
							22.0 (2.2)
							21.4 (2.1)
							21.0 (1.8)
							20.9 (2.1)
							20.3 (3.7)
							21.4 (2.7)
							20.2 (3.8)

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* Pairwise comparisons between placebo + ethanol vs drug and ethanol treatment significant at the 0.05 level

† Pairwise comparisons between drug treatment alone vs drug treatment + ethanol significant at the 0.05 level
ALC, ethanol, DMI desipramine, AMI amitriptyline, ZMI zimetidine

Table 6 Right hand reaction time (ms) for correct response to angles (mean $\pm$ s.d.)

	Session	Placebo		Drug treatment					
		No	ALC	ALC	DMI No ALC	ALC	AMI No ALC	ALC	ZMI No ALC
Right side presentation	1	1171.3 (99.4)	1138.0 (119.2)	1065.3 (165)	1120.0 (348.6)	1151.8 (226.0)	1128.9 (379.2)	1160.3 (160.9)	1121.0 (129.5)
	2	1121.3 (170.4)	1091.9 (147.7)	1073.0 (145.5)	1087.9 (167.7)	1157.1 (524.3)	1144.1 (490.7)	1128.1 (145.1)	1092.3 (128.2)
	3	1063.8 (121.7)	1163.3 (267.1)	1168.0 (284.5)	1067.5 (166.7)	1287.9 (327.4)	1117.7 (252.8)	1044.0 (133.2)	1093.2 (183.7)
Right side presentation	1	1171.7 (111.8)	1153.8 (120.1)	1085.6 (195.6)	1139.2 (153.6)	1210.3 (256.1)	1187.2 (432.5)	1156.5 (184.3)	1161.9 (158.9)
	2	1129.8 (190.0)	1116.1 (168.6)	1067.3 (183.7)	1113.4 (168.7)	1161.8 (203.4)	1174.8 (434.4)	1116.3 (145.3)	1084.0 (126.3)
	3	1100.6 (169.0)	1099.8 (123.9)	1089.2 (175.8)	1081.8 (186.9)	1129.4 (204.4)	1183.3* (243.9)	1081.3 (163.8)	1090.9 (157.6)

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 ALC, ethanol, DMI desipramine, AMI amitriptyline, ZMI zimelidine

Table 7 Plasma antidepressant and metabolite concentrations (ng/ml) (mean $\pm$ s.d.)

Time (h)	Administration	Zimelidine	Nor- zimelidine	Desipramine	2-OH- desipramine	Amiripyline	10-OH amiripyline	Nor- tripyline	10-OH Nor- tripyline
2	Placebo	585 (260)	393 (236)	18 (16)	12 (14)	24 (19)	11 (9)	6 (4)	9 (7)
	Ethanol	610 (285)	331 (116)	23 (15)	17 (14)	28 (18)	11 (8)	10 (13)	7 (2)
3	Placebo	533 (205)	427 (151)	31 (16)	23 (12)	27 (11)	10 (7)	9 (8)	10 (6)
	Ethanol	537 (264)	382 (111)	32 (17)	16 (15)	31 (14)	11 (8)	11 (14)	7 (5)
4	Placebo	428 (167)	453 (125)	31 (15)	20 (13)	22 (11)	8 (8)	9 (5)	12 (8)
	Ethanol	434 (201)	436 (144)	43 (26)	16 (11)	26 (10)	9 (9)	8 (10)	10 (5)
6	Placebo	305 (114)	420 (97)	35 (12)	20 (15)	20 (9)	5 (5)	8 (4)	10 (7)
	Ethanol	307 (155)	398 (99)	45 (25)	17 (9)	18 (9)	6 (6)	6 (6)	8 (6)
8	Placebo	196 (86)	386 (109)	36 (13)	20 (15)	14 (6)	4 (5)	10 (4)	10 (5)
	Ethanol	242 (110)	367 (83)	34 (12)	13 (13)	14 (6)	3 (6)	8 (9)	7 (6)
24	Placebo	3 (2)	20 (7)	1 (1)	1 (1)	4 (5)	3 (9)	6 (6)	11 (5)
	Ethanol	2 (1)	19 (7)	1 (1)	-	6 (8)	3 (5)	5 (10)	8 (7)

- = undetectable

11; $P = 0.15$), drug administration did ($F = 4.99$; d.f. 2,33; 25,63; $P < 0.01$), with amitriptyline producing longer reaction times both alone and in combination with ethanol. Interestingly, repeated testing interacted significantly with drug treatment as confirmed by the session by drug interaction ($F = 2.74$; d.f. = 3,54; 38,98; $P \leq 0.05$; Table 4).

(d) Angles

Correct responses While main effects and higher order interactions did not reveal significance, Duncan's multiple range test showed that in most sessions, amitriptyline in combination with ethanol resulted in impaired performance (Table 5).

Reaction time Similar to correct responses, significant main effects for each factor were not revealed with the exception of the drug of daily testing ($F = 3.75$; d.f. = 1,7; 18,66; $P = 0.05$). The right and left side presentation by daily testing session interaction was also significant ($F = 7.43$; d.f. 1,53, 16,82; $P < 0.007$; Table 6) with the right visual field being more adversely affected.

Pharmacokinetics

Plasma amitriptyline, nortriptyline and desipramine concentrations were increased transiently but nonsignificantly after ingestion of ethanol. The hydroxymetabolite concentrations were slightly decreased after ethanol. Zimelidine and norzimelidine concentrations were unaffected by ethanol (Table 7).

Breath ethanol concentrations were not affected by the antidepressants at any test time. The maximum blood ethanol concentration (extrapolated from breath) of 560 mg/l was reached between 2 and 3 h (during the first hour after drinking).

Discussion

The main findings of the present study were: (1) amitriptyline 50 mg significantly impaired per-

formance of most subjects, in all tasks, but striking individual variability in sensitivity towards amitriptyline-induced impairment was evident; (2) amitriptyline 50 mg had an additive deleterious interaction with ethanol 0.8 g/kg body weight; (3) desipramine 100 mg and zimelidine 200 mg were remarkably free of adverse effects on skilled performance and interactions with ethanol; (4) no significant pharmacokinetic interactions were detected between the antidepressants and ethanol.

The present findings concerning effects of antidepressants on performance are in full agreement with previous research (for review; Linnoila & Seppala, 1984; Seppala & Linnoila, 1984): Drugs with relatively specific pharmacological effects such as desipramine and zimelidine are free of adverse psychomotor effects. Whereas nonspecific drugs which block receptors of several neurotransmitters at similar plasma levels to those inhibiting transmitter reuptake, such as amitriptyline, have strong adverse effects on skilled performance. Furthermore, these drugs have an additive interaction with ethanol.

Recently, Dorian *et al.* (1983) demonstrated a large increment in plasma amitriptyline concentrations during administration of ethanol. Their design was to administer 25 mg of amitriptyline during continuous drinking. The dose of ethanol was computed to yield a blood concentration of 800 mg/l maintained for several hours and was much higher than used in the present study. Assuming that Dorian *et al.*'s (1983) and the present results are correct, the practical conclusion is that depressed outpatients taking tricyclic antidepressants can drink small amounts without increasing their plasma antidepressant levels but alcoholics treated with these drugs should stay sober to avoid inhibition of drug metabolism by large doses of ethanol. However, there is a significant pharmacodynamic interaction between low doses of amitriptyline and ethanol which can become a safety hazard in traffic.

In conclusion, desipramine and zimelidine are preferred over amitriptyline in the treatment of depressed outpatients because they produce less impairment of skilled performance both alone and in combination with ethanol.

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