Br. J. clin. Pharmac. (1992), **33**, 589–601

Pharmacodynamics of venlafaxine evaluated by EEG brain mapping, psychometry and psychophysiology

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1 In a double-blind, placebo-controlled study the effects of venlafaxine—a novel non-tricyclic compound inhibiting neuronal uptake of serotonin, noradrenaline and to a lesser extent dopamine—were investigated utilizing EEG brain mapping, psychometric and psychophysiological measures.

2 Sixteen healthy volunteers (eight males, eight females) aged 21–36 years received randomized and at weekly intervals single oral doses of placebo, 12.5 mg, 25 mg and 50 mg venlafaxine. EEG recordings, psychometric and psychophysiological tests, and evaluation of pulse, blood pressure and side-effects were carried out at 0, 2, 4, 6, and 8 h.

3 EEG brain mapping demonstrated that venlafaxine exerted a significant action on human brain function as compared with placebo at all three doses, characterized mostly by attenuation of absolute power, increase of relative delta/theta and beta, and decrease of alpha power, as well as by an acceleration of the total centroid fronto-temporally and by its slowing centrally and parietally. These findings are similar to antidepressants such as imipramine. Topographically, drug-induced alterations were most pronounced over both fronto-temporal and the right temporal to temporo-occipital regions.

4 Psychometric and psychophysiological investigations demonstrated significant dose-dependent psychotropic properties of the drug. Multivariate statistics exhibited an improvement of both the noopsyche (e.g. attention, concentration, attention variability, memory, fine motor activity, reaction time performance) and thymopsyche (e.g. drive, wakefulness)) but also significant psychophysiological activation (e.g. in c.f.f., pupillary and skin conductance measures).

5 Time-efficiency calculations showed significant central effects from the 2nd hour onwards, with increasing differences between placebo and treatment up to the 8th hour. Nausea was the most frequent complaint and appeared dose dependent.

Keywords human psychopharmacology venlafaxine antidepressant EEG brain mapping psychometry psychophysiology time-course tolerability

Introduction

Venlafaxine (Wy-45,030) is a novel non-tricyclic compound (1-2-(dimethylamino)-1-(4-methoxyphenyl)ethyl cyclohexanol, hydrochloride) (Husbands *et al.*, 1985) which has *in vitro* and *in vivo* pharmacological activity similar to the tricyclic antidepressants (Langer *et al.*, 1980; Raisman *et al.*, 1980). It inhibits neuronal uptake of serotonin, noradrenaline and dopamine in order of decreasing potency (Muth *et al.*, 1986). It does not inhibit monoamine oxidase. Unlike the tricyclic antidepressants, it has no antimuscarinic action in the guinea pig ileum, nor does it have appreciable affinity for brain α_1-adrenoceptor or histamine-1 binding sites. Venlafaxine is also without affinity for α_2- or β-adrenoceptor, benzodiazepine, serotonin-1, serotonin-2, dopamine-2 and opiate receptors. Unlike tricyclic antidepressants, it rapidly causes β-adrenoceptor down regulation as determined by its effect on isoprenaline stimulated increase in cyclic adenosine monophoshate (cAMP) levels in the rat pineal gland.

Venlafaxine is rapidly absorbed with peak plasma

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levels at approximately 1.8 h after oral administration (Fabre & Putman, 1987). The mean half-life of venlafaxine is about 4 h and that of its active metabolite 10 h. Open dose finding studies of Schweizer *et al.* (1988) and Goldberg & Finnerty (1988) in depressed outpatients showed that venlafaxine was generally well-tolerated. The occasional nausea they observed was reminiscent of side-effects after serotonin reuptake blockers.

The aim of the present double-blind, placebo-controlled trial was to investigate encephalotropic and psychotropic properties of venlafaxine utilizing EEG mapping, psychometric and psychophysiological techniques (Grünberger & Saletu, 1980; Saletu, 1976, 1982, 1987; Saletu *et al.*, 1987a). The latter have been shown to provide important information at an early stage of drug develpment about: 1) whether a drug has CNS effects in comparison with placebo; 2) at which dosage it acts; and 3) at what time it acts on the target organ—the human brain.

Methods

Design, subjects, drugs

Sixteen healthy volunteers (eight males, eight females) aged 21–36 years (mean 29 years), weighing from 53–100 kg (mean 70.5 kg) and ranging in height from 164–186 cm (mean 173 cm) participated in the double-blind, placebo-controlled, cross-over study. A 17th volunteer withdrew after placebo for non-drug related reasons. They took no psychoactive drugs for 3 weeks before or during the study. Subjects received, at weekly intervals, in random order as single oral doses: placebo, 12.5 mg, 25 mg and 50 mg venlafaxine. The study was performed in accordance with the rules and regulations for the conduct of clinical trials stated in the Declaration of Helsinki as revised by the World Medical Assembly at Tokyo and Venice. Informed written consent was obtained. The volunteers were free to withdraw from the study at any time. EEG recordings, psychometric and psychophysiological evaluations and monitoring of blood pressure, pulse and side-effects were carried out at 0, 2, 4, 6, and 8 h post-drug.

Measures

Neurophysiological investigations included a 3 min vigilance-controlled EEG recorded by a 21 channel Nihon Kohden 4321 G polygraph (time constant: 0.3 s; high frequency response: 35 Hz; filter characteristic: −12 dB/octave; frequency range: 0.5–35 Hz; amplification: approximately 1:20,000; maximal noise level: 2 μV peak-to-peak) with the subjects lying relaxed with eyes closed in an electrically-shielded room. Electrodes were attached to the scalp, according to the international 10/20 system. During the V-EEG recordings the technician tried to keep the subjects alert; as soon as drowsiness patterns appeared in the record, the subjects were aroused. 21 leads (E1, E2, F_p1, F_p2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, 01 and 02 to averaged mastoids) were digitized on-line by a Hewlett-Packard Vectra system with a sampling frequency of 102.4 Hz; the frequency resolution was 0.2 Hz (Anderer *et al.*, 1987; Saletu *et al.*, 1987a). Spectral analysis was performed using the fast Fourier transform technique in floating-point arithmetic to maintain precision.

Generally, a single spectral distribution curve from one electrode and for a particular clinical state (e.g. pretreatment, treatment) and various recording procedures (e.g. V-EEG, R-EEG) is formed as the mean of 5 s spectra from artifact-free EEG during that state. Artifact-free epochs were selected using the Automatic Artifact Rejection Method (AARM) as described by Anderer *et al.* (1987). In the present study, 27.8 ± 1.2 out of 36 epochs were taken for statistical analysis. The mean spectral curves contained data from 1.3–35 Hz quantified into 36 variables: total power (TP); the absolute and relative power in 12 different frequency bands; the dominant frequency (DF) (in Hz), the relative (RP) and absolute (AP) power of the dominant frequency; further, the centre-of-gravity frequencies (centroids) (C) and their standard deviations (S) of the combined delta and theta (DT), alpha (A) and beta (B) bands as well as of the total activity (TP). Nineteen numbers representing variables from each of the 19 electrodes are mapped onto a 64 × 64 numerical matrix. Each interpolated value is based on the cubic distance from the values at the three nearest electrodes. The resulting matrix is maintained for statistical analysis and displayed as a video image in pseudocolor scaled format. In this manner topographic images can be viewed that represent the values and spatial distribution of 36 variables and are subsequently printed by the Hewlett-Packard 'paint jet'.

To display the differences in the distribution of particular EEG variables before and after drug administration, significance probability mapping (SPM) (Bartels & Subach, 1976; Duffy *et al.*, 1981; Saletu *et al.*, 1987a) was used. Mean and variance matrices of the Q-EEG variables of 18 subjects before administration were compared with similar matrices 2, 4, 6 and 8 h postdrug. Results of this exploratory process were expressed in t-scored and displayed as SPM images. With such displays, regions of drug-induced changes are graphically delineated for each variable separately. Subsequently, the same method was utilized to demonstrate differences between drug-induced and placebo-induced alterations ('pharmaco-EEG maps').

Psychometric and psychophysiological tests

Noopsychic tests (i.e. tests of intellectual and mnestic performance) included the alphabetical cross-out test (AD-test—Alphabetischer Durchstreichtest) of Grünberger (1977); the microprocessor-assisted alphabetical reaction test (Grünberger *et al.*, 1984) for evaluation of the quantitative aspects (total score), qualitative aspects (errors in percent of the total score) of attention and the attention variability (difference between extreme scores); the Pauli test (correct calculations; errors); numerical memory (short-term memory) (Grünberger, 1977); the fine motor activity (Feinmotoriktest) of Grünberger (1977) for measurement of motor skills and drive; the reaction time (in ms) by the Viennese reaction-apparatus and errors occurring in the test; complex reaction by the Viennese Determinationsapparatus; and microprocessor-

assisted rigidity and perseveration tests reflecting flexibility (Grünberger *et al.*, 1988).

Thymopsychic assessments (assessments of the instincts-drive-emotion sphere) were by the von Zerssen Bf-S scale (von Zerssen *et al.*, 1970) for evaluation of subjective well-being and four 100 mm visual analogue scales for self-rating of mood, wakefulness, affectivity and drive.

Psychophysiological measures included the critical flicker frequency (c.f.f., descending threshold); and microprocessor-assisted measurements of the static and dynamic pupillometry and skin conductance (SCL, in μmhos) (Grünberger *et al.*, 1984).

Statistics

Exploratory statistical analyses included discriminant analysis, MANOVA, ANOVA and Newman-Keuls test, the *t*-test, and the Friedman and multiple Wilcoxon test.

Results

Pharmaco-EEG mapping

Pharmaco-EEG maps—multivariate analysis To determine whether the investigational drug had significant effects on the human brain as compared with placebo and at what times, MANOVAs were performed (for each of the 19 electrodes) considering group (drug, placebo), time (pre, post) and relative power values in all nine Q-EEG frequency bands. The latter were transformed (ln(power%/(100 − power%)) to fulfil the conditions for the MANOVA (homogeneity of the variances and co-variances as well as the symmetric unimodal distribution (Gasser *et al.*, 1982). Hotelling's T^2-values were used to avoid Type I errors with inflated degrees of freedom and were imaged in terms of brain maps (Figure 1). As can be seen venlafaxine at all three doses caused significant changes in brain function as compared with placebo in the 4th to the 8th hour—mostly in the temporal, temporo-frontal and temporo-occipital regions.

Pharmaco-EEG maps—univariate analysis Total power (absolute power, 1.3–35 Hz) decreased as compared with placebo and significantly so in the 4th hour (Figure 2) and 8th hour (Figure 3) after 12.5 and 25 mg over various brain regions. Only in the 2nd hour was there a temporal increase after the two higher doses. Absolute delta/theta power (1.3–7.5 Hz) remained unchanged with the exception of an augmentation over the left occipital region in the 4th hour after the highest doses (Figure 2). Absolute alpha power (7.5–13 Hz) decreased extensively after the lower doses and significantly so in the 4th (Figure 2) and 8th hour (Figure 3). Absolute beta power (13–35 Hz) decreased over the central and parietal areas, while it increased over the temporal and fronto-temporal regions (Figure 2 and 3). Relative delta/theta power (1.3–7.5 Hz) increased as compared with placebo over the frontal, central parietal and occipital areas with a left-sided accentuation, while in the temporal region there was a decrease (Figures 4 and 5). Relative alpha power (7.5–13 Hz) was attenuated after all three doses over many brain regions (Figures 4 and 5). Relative beta power (13–35 Hz) increased after all doses of venlafaxine as compared with placebo at all times, particularly over the temporal, temporo-frontal, temporo-occipital but also fronto-polar to frontal and occipital regions, while interestingly over the vertex there was an attenuation (Figures 4 and 5). The centroid of the total power spectrum (1.3–35 Hz) was accelerated over the temporal to temporo-frontal regions, and slowed over the central and parietal leads (Figures 4–5).

Cerebral bioavailability determined by multi-lead EEG analysis

Time-efficacy relations were calculated by ranking sign-adjusted data obtained at the hours 0, 2, 4, 6 and 8 in 28 EEG variables recorded in 19 leads utilizing the Friedman's rank analysis of variances and a subsequent multiple Wilcoxon test comparing the different time periods. The rank sum for the three doses and placebo at the hours 0, 2, 4, 6 and 8 are shown in Table 1. There was generally an increase in the pharmacodynamic effect over time with significant differences reached at the hours 4, 6 and 8 as compared with pre-treatment. In contrast, there were no significant differences between different hours after placebo.

Dose-efficacy relations were obtained also by Friedman's rank ANOVA of sign-adjusted data obtained 2–8 h post-drug in 28 V-EEG variables. Overall (mean of all leads) placebo induced the least changes between the 2nd and 8th hour, while venlafaxine induced significantly more changes. However, there were no inter-dosage differences. The respective rank sums for placebo, 12.5 25 and 50 mg venlafaxine were: 243.5, 270.7, 293.5 and 292.3 ($\chi^2 = 9.7$, $P < 0.05$). The multiple Wilcoxon test showed the 25 mg dose to differ from placebo at the 0.05 level, and both 12.5 mg and 50 mg at the 0.1 level. A topographic display of the chi square values demon-

Table 1 Time-efficacy relations after single oral doses of 12.5, 25 and 50 mg venlafaxine and placebo in 16 healthy subjects based on Friedman's rank ANOVA of sign-adjusted data obtained at various hours post-drug in 28 V-EEG variables (rank sums, means of 19 leads)

	Time (h)						
Treatment	*0*	*2*	*4*	*6*	*8*	r^2	*Multiple Wilcoxon*
A 12.5 mg venlafaxine	57.4	76.4	78.6	104.6	102.9	22.5**	0:6**, 0:8**
B 25 mg venlafaxine	64.2	76.4	98.0	85.1	96.3	11.5*	0:4*
C 50 mg venlafaxine	64.6	70.1	83.1	101.2	100.9	16.4**	0:6*, 0:8*
D Placebo	77.1	79.3	86.2	91.6	85.8	NS	NS

*$P < 0.05$, **$P < 0.01$.

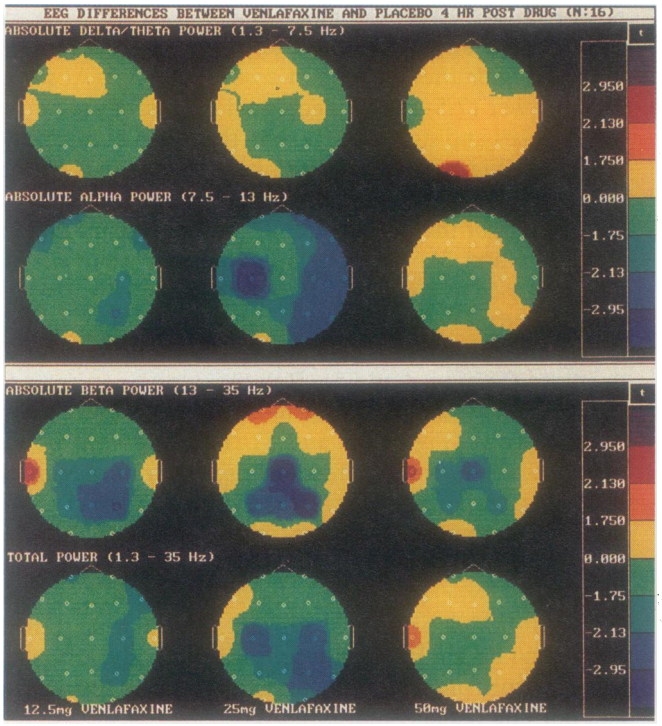


Figure 1

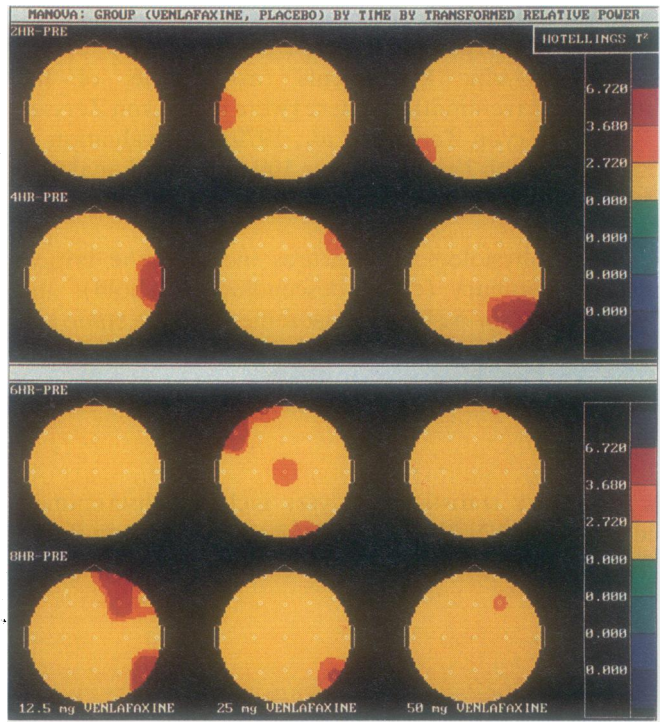
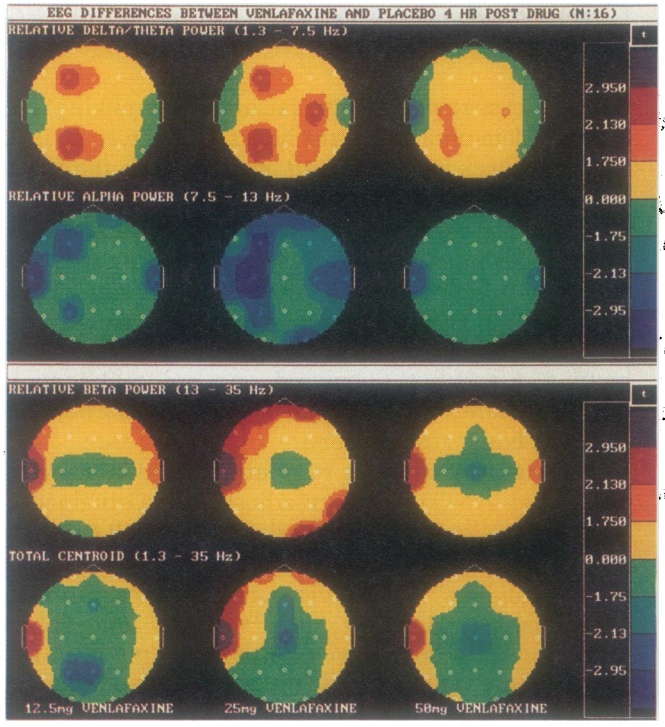


Figure 2



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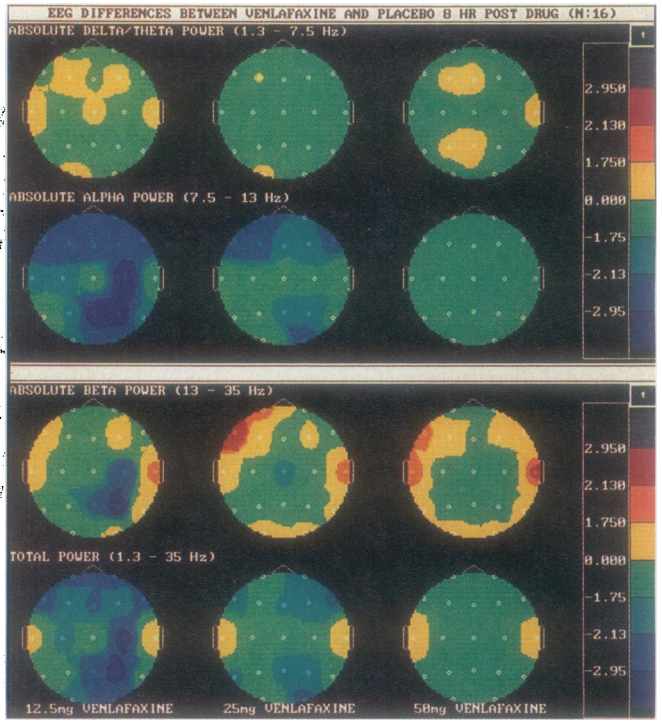

Figure 4

Figure 1 Brain maps showing differences between venlafaxine-induced and placebo-induced central effects at the hours 2, 4, 6, 8 (top to bottom row) after oral administration of single doses of 12.5 mg, 25 mg and 50 mg venlafaxine (left to right column) ($n = 16$). Maps are based on Hotelling's T^2 values obtained from multivariate tests in repeated measures ANOVA on the relative power of all nine frequency bands (ln(power%/100 – power%)) for each electrode (V-EEG, $n = 16$). Significant T^2: larger than 2.72 = $P < 0.10$, larger than 3.68 = $P < 0.05$ and larger than 6.72 = $P < 0.01$. Venlafaxine produces significant changes as compared with placebo from the 4th throughout the 8th hour, which occur mostly over the temporal, fronto-temporal to temporo-occipital regions.

Figure 2 Brain maps of pharmaco-EEG differences between venlafaxine- and placebo-induced changes in absolute power of the delta/theta, alpha, beta and the total frequency range (top to bottom row) 4 h after application of 12.5, 25 and 50 mg venlafaxine (left to right column) ($n = 16$). Each significance probability map (SPM) represents the result of statistical comparison by *t*-test of drug- to placebo-induced changes. The vertex view shows nose up, left ear left, right ear right. Electrode positions are indicated by white rings. Eight-colour scales represent drug-induced changes as compared with placebo based on *t*-values (lilac, increase at $P < 0.01$; red, increase at $P < 0.05$; ochre, increase at $P < 0.10$; pale yellow, trend towards increase; pale green, trend towards decrease; bright green, decrease at $P < 0.20$; light blue, decrease at $P < 0.05$; dark blue, decrease at $P < 0.01$). 12.5 and 25 mg venlafaxine produce a decrease of absolute power in alpha as well as total frequency range. Absolute beta power is attenuated over central and parietal regions, while augmented left temporally. Absolute delta/theta power remains unchanged with the exception of an increase left occipitally after 50 mg venlafaxine.

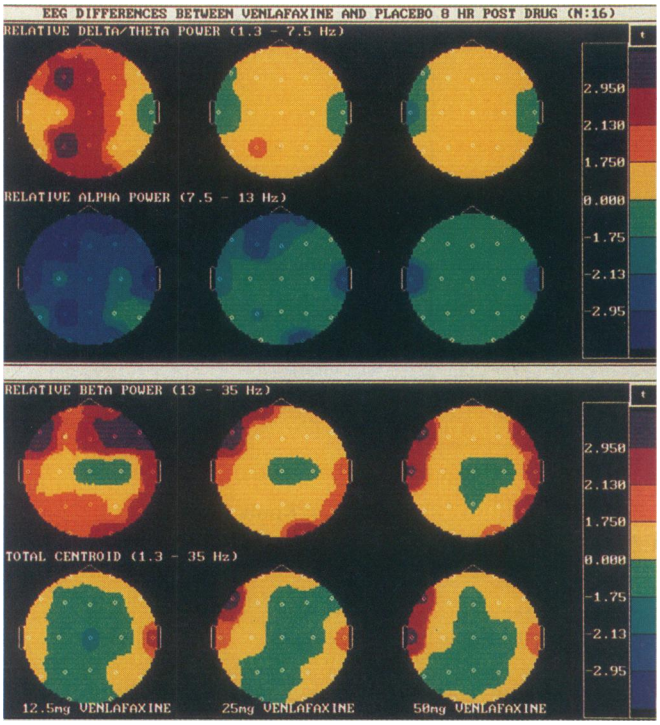

Figure 5

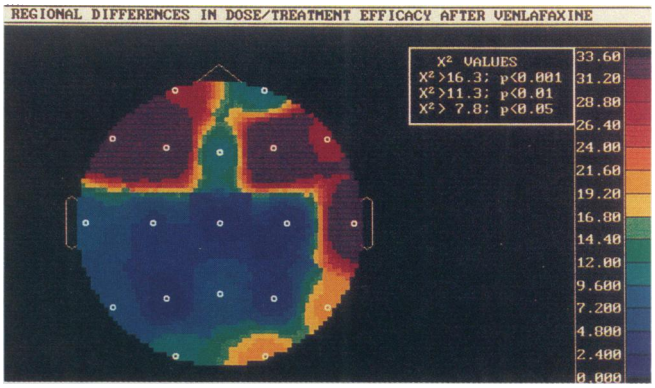

Figure 6

Figure 5 Brain maps of pharmaco-EEG differences between venlafaxine and placebo in relative delta/theta, alpha, beta power and the total centroid (top to bottom row) 8 h after oral administration of 12.5, 25 and 50 mg venlafaxine (left to right column) (n = 16). For technical description of the maps and the explanation of the colour key, see Figure 2. Venlafaxine induces dose-dependently a concomitant increase of relative delta/theta power and beta power and an attenuation of alpha power. The total centroid is accelerated over the left temporal to fronto-temporal regions. The higher the dosage, the less pronounced are venlafaxine-induced changes in vigilance of the dissociative type.

Figure 6 Regional differences in dose-treatment efficacy after venlafaxine based on chi square values of a Friedman's rank ANOVA of sign-adjusted data obtained 2–8 h post-drug in 28 V-EEG variables (n = 16). As can be seen, significant differences between three doses of venlafaxine and placebo are mostly pronounced over both fronto-temporal to frontal and right temporal, temporo-occipital and occipital regions.

strated that drug effects occurred mostly over both fronto-temporal to frontal regions, but also over the right temporal, temporo-occipital and occipital areas (Figure 6). Thus venlafaxine induced more changes over the right hemisphere than over the left.

Psychometric findings

Noopsychic variables Multivariate statistical analysis by means of MANOVA and discriminant analysis considering changes in all 14 noopsychic variables at all times (0, 2nd, 4th, 6th and 8th hour) demonstrated after placebo a significant deterioration in the 6th hour which was attenuated or even reversed by venlafaxine (Figure 7). Specifically after 25 mg there was a significant noopsychic improvement in the 2nd, 6th and 8th hour post-drug. The 12.5 and 50 mg doses were also significantly superior to placebo in the 6th and 8th hours.

The results of the univariate analysis in the individual 14 noopsychic variables are shown in Table 2. While in the 3-way ANOVA changes over time were only significant in two variables (correct responses in the Pauli test and on the Viennese Determinationsapparatus), inter-treatment differences were observed in all but one variable. Errors in the Pauli test were reduced in the 2nd and 4th hour after 25 mg venlafaxine and increased after placebo, with these differences being significant. Attention variability after 25 and 50 mg venlafaxine was superior (decrease) to placebo (increase) in the 8th hour. Psychomotor activity in the 2nd hour after 50 mg

Figure 3 Brain maps of pharmaco-EEG differences between venlafaxine and placebo in absolute power of the delta/theta, alpha, beta and total frequency range (top to bottom row) 8 h after oral administration of 12.5, 25 and 50 mg venlafaxine (left to right column) (n = 16). For technical description of the maps and the explanation of the colour key, see Figure 2. 12.5 and 25 mg venlafaxine attenuate absolute power in the alpha and total frequency range, while beta power is attenuated centrally and parietally but augmented fronto-temporally. Absolute delta/theta power remains unchanged.

Figure 4 Brain maps of pharmaco-EEG differences between venlafaxine and placebo in relative delta/theta, alpha and beta power and the total centroid (top to bottom row) 4 h after oral administration of 12.5, 25 and 50 mg venlafaxine (left to right column) (n = 16). For technical description of the maps and the explanation of the colour key, see Figure 2. Venlafaxine induces an increase of relative delta/theta and beta power, decrease of relative alpha power as well as an acceleration of the total centroid left fronto-temporally and a slowing over the vertex and parietal regions.

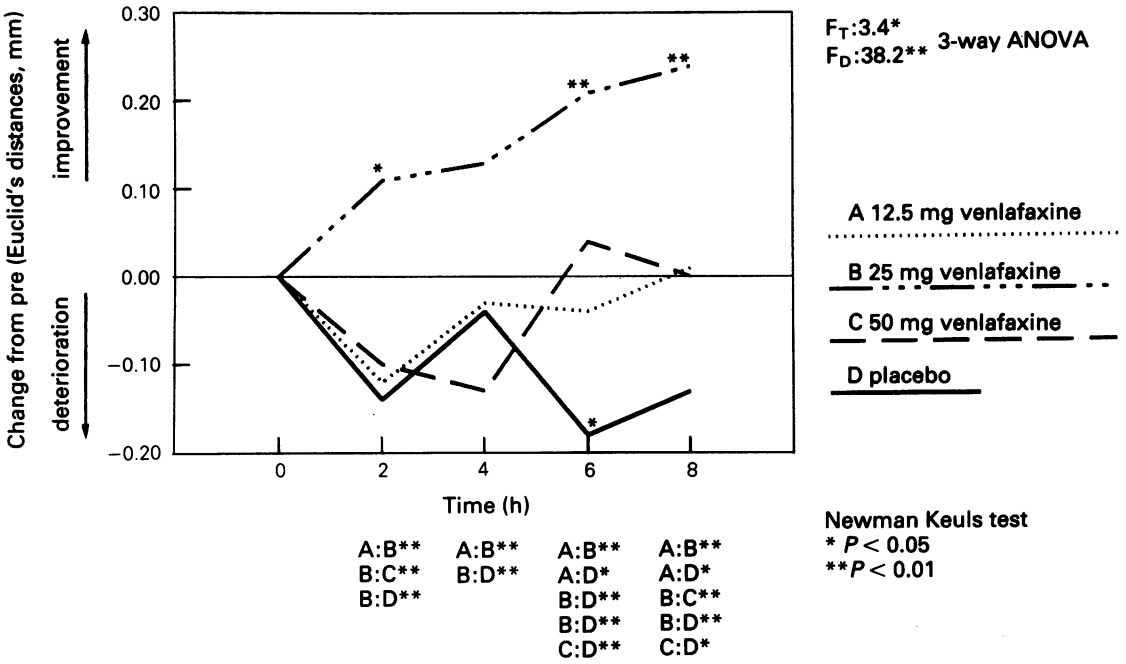

Figure 7 Effect of venlafaxine on the noopsyche (time- and dose/treatment efficacy relations based on discriminant analysis (centroids) of changes in 14 noopsychic variables obtained at 2, 4, 6, 8 h post-drug). Time is shown in the abscissa, changes from pre-treatment expressed in Euclid's distances are represented in the ordinate. While noopsychic performance deteriorates over time after placebo, this deterioration is mitigated by 12.5 and 50 mg venlafaxine, while 25 mg venlafaxine induces significant improvement of the noopsyche. Thus, the active drug is significantly superior to placebo specifically in the 6th and 8th hour.

venlafaxine (improvement) was superior to placebo (deterioration). Errors in the reaction time task also showed treatment differences as they decreased in the 2nd and 6th hour after 25 mg venlafaxine and increased after placebo. In the latter hour 50 mg venlafaxine was also superior to placebo. In the alphabetical reaction test subjects performed better after 25 mg venlafaxine than placebo in the 8th hour. The variability in the alphabetical reaction test was attenuated after 25 mg in the 4th and 8th hour and augmented after placebo, with the difference being significant. Flexibility measures improved significantly in the hours 2, 4, and 6 after 25 mg and at hours 4, 6 and 8 after 50 mg venlafaxine (Figure 8). These two doses were also significantly superior to the 12.5 mg dosage at hours 4 through 8, as there was decrease of flexibility after the lowest dose.

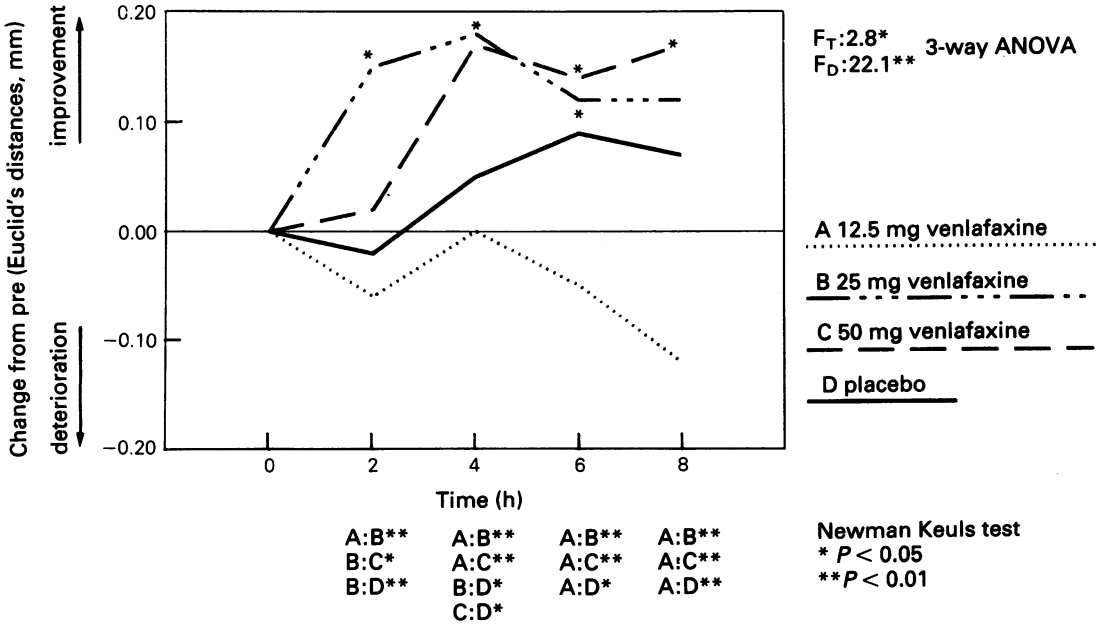

Figure 8 Effect of venlafaxine on flexibility measures (time- and dose/treatment efficacy relations based on discriminant analysis (centroids) of changes in 14 variables obtained 2, 4, 6, 8 h post-drug). Time is shown in the abscissa, changes from pre-treatment expressed in Euclid's distances are represented in the ordinate. While the low doses of venlafaxine induce a decrease in flexibility, an increase is seen after 25 and 50 mg venlafaxine.

Table 2 Changes in noopsychic variables after a single dose of 12.5, 25 and 50 mg venlafaxine and placebo in normals (n = 16; 2, 4, 6, 8 h post-drug)

		3-way ANOVA		*Pretreatment* vs *venlafaxine*				*Inter-drug differences*			
				12.5 mg	*25 mg*	*50 mg*	*Placebo*	*Time (h)*			
Variable		F_{time}	F_{drug}	*A*	*B*	*C*	*D*	*2*	*4*	*6*	*8*
Pauli-test (correct)	↑	4.8**	3.7*	+4,6,8*							
Pauli-test (% errors)	↓		13.5**		−4*			B < D*	A > B*, A < C* B < C, D**	B < A, C*	
Attention (total score)	↑		5.4**					B < C*			
Concentration (% errors)	↓		2.8*								
Attention variability	↓		5.7**								A > B*, A > C** B < D*, C < D**
Numerical memory (score)	↑		5.1**	−2** +4, 6, 8*							C > A, D*
Psychomotor activity (score)	↑		3.4**					C > D*			
Reaction time (ms)	↓										
Reaction time task (errors)	↓		7.9**					B < A, C, D*		B < A, D** C < A*, D**	
Alphabet reaction test (total score)	↑		8.2**								B > A, C, D**
Alphabet reaction test (correct %)	↑		8.0**					B > C*	B > C*		
Alphabet reaction test (errors %)	↓										
Alphabet reaction test variability	↓		12.7**						B < A** B < C, D*	B < A*	B < A* B < C, D**
Viennese determination apparatus, correct R	↑	8.6**	8.8**		+4.6 +8**		+4.8*				B > A*

*P < 0.05, **P < 0.01 Newman Keuls Test.
↑ ↓ direction of improvement.
+ increase or − decrease at certain hour.
< decrease as compared with.
> increase as compared with.

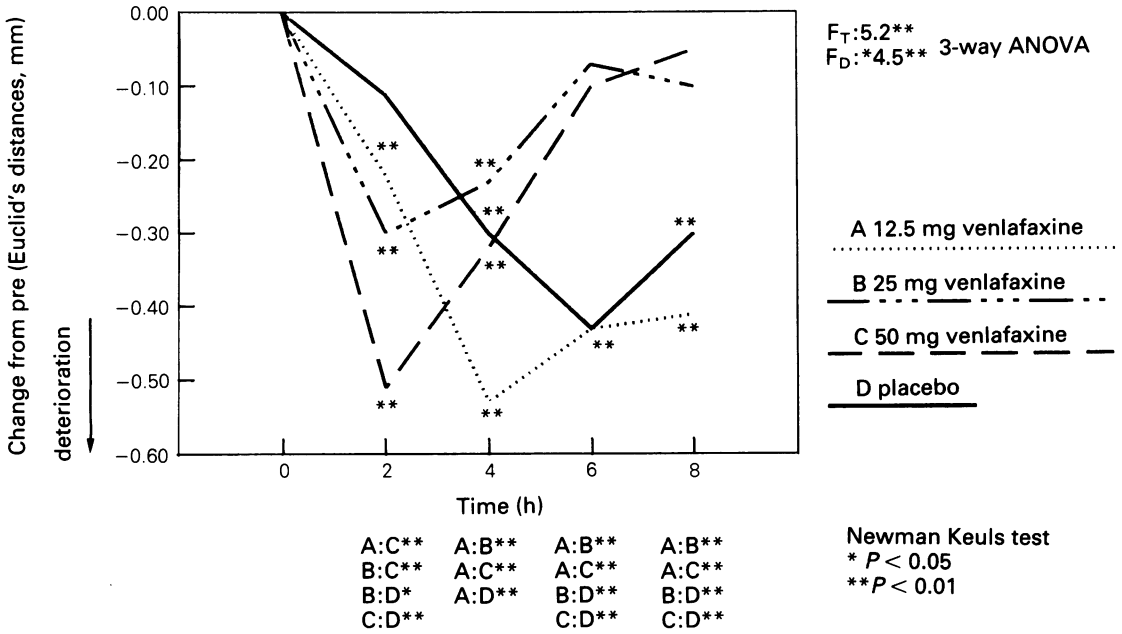

Figure 9 Effect of venlafaxine on the thymopsyche (time- and dose/treatment efficacy relations based on discriminant analysis (centroids) of changes in 5 thymopsychic variables obtained at 2, 4, 6, 8 h post-drug). Time is shown in the abscissa, changes from pre-treatment expressed in Euclid's distances are represented in the ordinate. There is a deterioration of the thymopsyche over time after placebo, which is mitigated by 25 and 50 mg venlafaxine in the 6th and in the 8th hour post-drug.

Thymopsychic variables Multivariate statistics demonstrated a deterioration of the thymopsyche in the 4th, 6th and 8th hour after placebo administration. Due to the tiring effect of the investigations thymopsychic deterioration was observed after all other treatments as well (Figure 9). In the 6th and 8th hour 25 and 50 mg venlafaxine were superior to placebo and the lowest dose; in the 2nd hour the opposite was the case. Univariate analysis showed superiority of 25 mg over placebo in the 6th hour in regard to drive and sedation, while in the 2nd hour affectivity and well-being were worse after the highest dose as compared with placebo (Table 3).

Psychophysiological variables Univariate analysis showed significant differences in c.f.f. with venlafaxine inducing an increase in the threshold of c.f.f., while it decreased after placebo in the 2nd, 4th and 8th hour (Table 4). Skin conductance increased in the 4th, 6th and 8th hour after 50 mg, while it decreased after placebo. In the last hour all three doses of venlafaxine were superior to placebo. Fluctuations in skin conductance increased after all three doses of venlafaxine at hours 4, 6 and 8. Pupillary diameter increased with all three venlafaxine doses as compared with pre-treatment, while after placebo there was no change. Thus the active drug at all three doses differed from placebo. In dynamic pupillometry measures the descending time increased with 25 mg venlafaxine, whereas placebo induced opposite changes in the 4th, 6th and 8th hour.

Tolerability

No important changes occurred in physical examination, vital signs, laboratory tests, pulse or blood pressure. Nausea, tiredness and headache were reported by at least three subjects. Nausea was reported by 2, 4, 5 and 8 out of 16 subjects after placebo, 12.5 mg, 25 and 50 mg venlafaxine respectively; tiredness by 2, 7, 7 and 7 subjects respectively; and headaches by 1, 1, 1 and 3, respectively. At least one symptom was reported after placebo by 19% of subjects; after 12.5 mg by 63%; after 25 mg by 56%; and after 50 mg by 81%.

Discussion

Double-blind placebo-controlled EEG brain mapping investigations showed that single oral doses of 12.5, 25 and 50 mg venlafaxine induced significant changes in human brain function as compared with placebo. The findings were generally characterized by attenuation of absolute power, with a concomitant increase of delta/theta and beta activity, while alpha activity was attenuated. There was acceleration of the centroid over fronto-temporal regions, while there was slowing over central and parietal regions. These findings indicate changes in vigilance of the dissociative type and are very similar to those observed with antidepressants of the imipramine type (Fink, 1969; Itil, 1974; Itil *et al.*, 1985; Herrmann, 1982; Herrmann & Schärer, 1986; Saletu, 1976, 1982, 1987; Saletu *et al.*, 1987a,b, 1988). In investigating typical and atypical antidepressants we have established at least two types of pharmaco-EEG profiles. One is characterized by a concomitant increase of slow and fast activities and a decrease of alpha activity suggesting sedative qualities (thymoleptic imipramine- and amitriptyline-like pharmaco-EEG profile), which was observed after imipramine, amitriptyline, maprotiline, danitracene, binodaline, and fluvoxamine. The other is characterized by augmentation of alpha activity, an increase in amplitude, and eventually by attenuation of slow and fast activities indicating activating properties of antidepressants (thymeretic, desipramine-like pharmaco-

Table 3 Changes in thymopsychic variables after a single dose of 12.5, 25 and 50 mg venlafaxine and placebo in normals ($n = 16$)

		3-way ANOVA		*Pretreatment vs venlafaxine*				*Inter-drug differences*			
				12.5 mg	*25 mg*	*50 mg*	*Placebo*	*Time (h)*			
Variable		F_{time}	F_{drug}	*A*	*B*	*C*	*D*	*2*	*4*	*6*	*8*
Drive (VAS)	↓		8.8**	+4**, 6*, 8**			+6*		A > B**	B < A, D*	A > B*, C**
Sedation (VAS)	↓		6.5**	+4*, 6**, 8*			+6*			A > B, C** D > B, C**	A > C*
Mood (VAS)	↑					−2*		C < A*, B**			
Affectivity (VAS)	↑					−2*		C < A, D*			A < B, C*
Well-being (BF-S)	↓			+4, 6**		+2*	+4, 6*	C > D*			

*$P < 0.05$, **$P < 0.01$ Newman Keuls Test.
↑ ↓ direction of improvement.
+ increase or − decrease at certain hour.
< decrease as compared with.
> increase as compared with.

EEG profile), and was seen with desipramine, nomifensine, tranylcypromine, sercloremine, fluoxetine, and low doses of sertraline, zimelidine and moclobemide (Grünberger & Saletu, 1985; Saletu, 1982; Saletu *et al.*, 1980a,b,c, 1982, 1985, 1986; Saletu & Grünberger, 1985a,b). In the present study of venlafaxine the increase in delta/theta and superimposed beta activity and decrease of alpha activity became smaller with increasing doses, which may indicate that the drug in higher doses may be more activating. This was also reflected by the thymopsychic data.

Our neurophysiological classification of venlafaxine as an antidepressant is in agreement with its biochemical classification (Muth *et al.*, 1986), and with clinical impressions of antidepressant properties reported by Schweizer *et al.* (1988) and Goldberg & Finnerty (1988), and in a recent fixed-dose placebo-controlled study in depressed patients by Derivan & Rudolph (1988). As far as the time-course of the encephalotropic effect was concerned, multivariate analysis revealed significant changes between the 4th and the 8th hour, although in the univariate analysis significant drug-induced changes were observed as early as the 2nd hour. This is in agreement with the published pharmacokinetic findings of Fabre & Putman (1987) who noted peak plasma concentration on average 2 h after oral drug administration and a mean half-life of 4 h for venlafaxine, and a half-life of 10 h for the active metabolite WY 45,233.

Dose-efficacy calculations in our study showed that all three doses were significantly different from placebo, although there were no significant differences between the doses themselves. This may be because the dose range investigated was rather narrow (12.5–50 mg venlafaxine). In clinical investigations the dose was as high as 150 mg three times daily (Schweizer *et al.*, 1988). Derivan & Rudolph (1988) compared 25 mg, 75 mg and 125 mg three times daily in a placebo-controlled study in depressed patients and found dose-dependent increases in responders based on the CGI score of 64%, 71% and 83%, respectively. However there were no dose-related differences in the Hamilton and MADRS scores. The authors noted that the highest dose had an earlier onset of action than the lower ones.

Topographically the encephalotropic effects were located more on the right than the left hemisphere. Although our study was carried out in normal subjects, and animal studies have shown that acute administration may have quite different neurochemical consequences from chronic treatment, it is of interest that thymopsychic changes have been attributed more to the right than the left hemisphere (Davidson, 1987; Flor-Henry, 1976). The literature suggests right hemispheric dysfunction in depression (Davidson, 1987; Flor-Henry, 1976; Matousek *et al.*, 1981; Prichep *et al.*, 1986). Flor-Henry (1974, 1976) has indicated that in contrast to left hemispheric dysfunction in schizophrenia, patients with affective disorders show impaired right hemisphere contribution to neuropsychological task performance. In patients with affective disorder Yozawitz *et al.* (1979) and Bruder & Yozawitz (1979) showed a pattern of dichotic listening performance similar to that shown in patients with known right hemisphere lesions. According to Kronfol *et al.* (1978), when ECT corrects depression, right hemisphere performance improves. Similar cognitive improvement

Table 4 Changes in psychophysiological variables after a single dose of 12.5, 25 and 50 mg venlafaxine and placebo in normals ($n = 16$)

		3-way ANOVA		*Pretreatment* vs *venlafaxine*				*Inter-drug differences*			
				12.5 mg	*25 mg*	*50 mg*	*Placebo*	*Time (h)*			
Group	*Variable*	F_{time}	F_{drug}	*A*	*B*	*C*	*D*	*2*	*4*	*6*	*8*
C.f.f.	Descending threshold (Hz)		13.7**			+4, 6*		C > D*	C > D**		C > D**
Skin	SCL (μmhos)		11.4**						C > D*	C > D*	D < A, B, C**
	SCL-fluctuations (numbers width 3)		17.0*			+4, 8*			C > D**	A < B*, C** D < B*, C**	C > A, B*, D**
	SCL-fluctuations (numbers width 0)		17.1**						A, C > D** B > D*	B, C > D** A > D*	A, B, C > D**
	Pupillary diameter (mm)	17.4**	196.1**	+2, 4, 6, 8**	+2, 4, 6, 8**	+2, 4, 6, 8**		A > D** A < B, C** D < B, C**	A > D** A < B, C** D < B, C**	A < D** A < B, C** D < B, C**	A < D** A < B, C** D < B, C**
	Change (%) PR-RC		4.4**							A > B*, C**	
Dynamic pupil: 1st stimulus	Latency (s) PR-L		2.6*								
	Descending time (s)PR-DT		16.5**		+2, 4*, 6**, 8*			A < B*	D < B**, C*	A < B** D < B**, C*	B > A, C*, D**
	Half-recovery time (s) PR-RT										
	Area (PR-RT * PR-RC)										

$^*P < 0.05$, $^{**}P < 0.01$ Newman Keuls Test.
+ increase or − decrease at certain hour.
< decrease as compared with.
> increase as compared with.

specific to the right hemisphere was found following tricyclic treatment in depressed children (Brumback *et al.*, 1980). Investigating asymmetrical frontal lobe activation during transient depressed mood in normal subjects, Tucker (1981) found relatively less alpha over the right frontal region during depression. Perris & Monakhov (1979) and Perris *et al.* (1978) described beta activity of the right pre-central area related to depressive mood, while symptoms of ruminative ideations and anxiety appeared to covary more closely with activity of the pre-central regions of the left hemisphere.

Our psychometric and psychophysiological data demonstrated that venlafaxine caused improvement in the noopsyche, as regards attention, concentration, attention variability, memory, psychomotor activity and reaction time performance, and also in the thymopsyche as regards subjective drive and wakefulness, particularly in the 6th and the 8th hour post-drug. However in the 2nd hour affectivity and well-being declined after the highest dose, perhaps due to serotoninergic side-effects. Psychophysiological investigations showed clear activation as measured by critical flicker frequency, pupillary and skin conductance measurements. This activation of both the central and autonomic nervous systems was statistically significant in the 8th hour after all three doses of venlafaxine as compared with placebo.

Improvement at the noopsychic, thymopsychic and psychophysiological levels after venlafaxine is of interest because in many investigations we have observed deterioration in the noo- and thymopsyche after administration of antidepressants to healthy volunteers (Grünberger & Saletu, 1980). In accumulated data with typical and atypical antidepressants it seems that antidepressants of the amitriptyline-type tend to decrease performance, while those of the desipramine-type induce changes in the opposite direction (Grünberger & Saletu, 1985; Saletu, 1982; Saletu *et al.*, 1980a,b,c, 1982, 1985, 1986; Saletu & Grünberger, 1985a,b). However, apart from the type of the antidepressant, the dosage and length of treatment also play a great role in antidepressant-induced changes in the noo- and thymopsyche of normal subjects (Grünberger & Saletu, 1985; Saletu & Grünberger, 1985a,b; Saletu *et al.*, 1982, 1986).

The psychic improvement seen after venlafaxine may be because all three neurotransmitter systems are activated, while there is no affinity at muscarinic cholinergic, histamine-1 and α_1-adrenoceptors which may cause most side effects. Possibly an important difference between venlafaxine and the standard tricyclic antidepressants in this regard is the ability of the new compound to inhibit synaptosomal dopamine uptake (Muth *et al.*, 1986). The improved noopsychic performance, as regards attention, memory, psychomotor performance, performance in the Pauli test and errors in the reaction time task, is of interest. According to Derivan & Rudolph (1988) venlafaxine was particularly effective in treating cognitive disturbances associated with depression, and this effect comes early in treatment.

The most frequent side-effects were nausea, tiredness and headache, reported respectively by 50%, 44% and 19% of subjects after the 50 mg dose. These may be due to the serotoninergic action of the compound. Similar tolerability has been reported in healthy volunteers (Fabre & Putman, 1987) and depressed patients (Derivan & Rudolph, 1988; Goldberg & Finnerty, 1988; Schweizer *et al.*, 1988).

The authors would like to express their thanks to Drs Katzinski, and Sitterle of Wyeth Ayerst, Münster/Paris; to Miss Dawn Noble B.A., Secretary; to Mr Helmut Bernhardt, Photographer; and to the entire staff of the Section of Pharmacopsychiatry of the Psychiatric University of Vienna for their valuable assistance in this project.

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(Received 26 September 1991, accepted 20 January 1992)