# Self-Reports of Anxiety Level and EEG Changes after a Single Dose of Benzodiazepines

## Double-Blind Comparison of Two Forms of Oxazepam

*Marc Ansseau*[a], *Adrienne Doumont*[a], *Jean-Luc Cerfontaine*[a], *Huguette Mantanus*[b], *Jean-Claude Rousseau*[b], *Martine Timsit-Berthier*[b]

[a] Psychopharmacology Unit and [b] Laboratory of Clinical Neurophysiology and Psychopathology, University of Liège, Belgium

**Abstract.** A new formulation of oxazepam especially designed to increase the speed of absorption and eliminate the need to use water (freeze-dried dosage formulation; FDDF) was compared in double-blind and crossover conditions with the standard tablets of the same compound. 5 inpatients with generalized anxiety disorder received at 1-week intervals a single 30 mg dose of one of the compounds. Every 8 min for 96 min after drug intake, they completed a battery of visual analogue scales and had an EEG recording with computerized spectral analysis. Results showed a significantly more rapid onset of activity of FDDF oxazepam for both the self-reports of anxiety level ($p < 0.005$) and the specific $\beta_2$ EEG changes ($p < 0.0001$), which were significantly correlated ($r = -0.73$; $p < 0.01$). Moreover, all patients rated FDDF oxazepam as having faster onset of action in clinical change than regular tablets ($p < 0.05$). This study shows the value of visual analogue scales, pharmaco-EEG, and crossover design in well-selected anxious inpatients in substantiating clinical differences between anxiolytic pharmacotherapies.

## Introduction

The latency of onset of the central effect of benzodiazepines after a single intake is a clinical parameter that has received too little attention. In fact, marked differences exist among benzodiazepine compounds concerning their pharmacokinetics of absorption, and particularly the latency of the plasma peak [review in *Kaplan and Jack,* 1983; *Detti,* 1983]. Clinically, compounds exhibiting very short latencies seem particularly suitable for the treatment of two disorders: initial insomnia (difficulties in falling asleep) [*Greenblatt* et al., 1983] and panic attacks [*Lader and Petursson,* 1983].

In this context, the synthesis of a special formulation of oxazepam, especially designed to increase the speed of absorption and to eliminate the need to use water (freeze-dried dosage formulation; FDDF) could represent an improvement in anxiolytic therapy. Pharmacokinetic data in normal volunteers showed that mean plasma peaks of oxazepam appeared earlier (2 vs. 3 h) and were higher (287 vs. 227 ng/ml) after 15 mg of FDDF oxazepam than after 15 mg of standard (regular) oxazepam; moreover, the area under the curve (between intake and 24 h later) was significantly greater with FDDF than with regular oxazepam ($2,239.5 \pm 1,303.4$ vs. $1,936.9 \pm 1,099.2$; $p < 0.02$) [*Ansseau* et al., in press].

Therefore, we performed a controlled study comparing FDDF oxazepam with the standard tablets of the same compound (regular oxazepam), using two types of strategy to detect the beginning of the acute pharmacologic effect: a clinical approach, with self-rating scales of anxiety completed at short intervals after drug intake and, concurrently, an EEG recording with computerized spectral analysis of the different frequency bands. Benzodiazepine compounds typically increase the proportion of fast rhythm waves, especially in the $\beta$ band [*Gibbs and Gibbs,* 1962; *Marjerrison,* 1974; *Itil,* 1974; *Fink,* 1975].

## Subjects and Methods

### Subjects

The study was performed in 5 male inpatients, aged 34–51 years (mean = 44.8 ± 7.3) at the Psychopharmacology Unit of the University Hospital of Liège, Belgium. They met research diagnostic criteria for 'Generalized Anxiety Disorder' [Spitzer et al., 1978] and had a score of at least 20 on the Hamilton Anxiety Scale [Hamilton, 1959] at the end of a 2-week washout period. During the last 7 days of the drug-free period, scores on the Hamilton Anxiety Scale, completed every day in the morning (at 10.00 a.m. ± 30 min), could not vary by more than 3 points, to ensure that the patient's clinical condition was stable. All clinical assessments were performed by research psychiatrists especially trained in psychopharmacology. Patients were free of medical illness, as evidenced by history, physical examination, ECG, chest X-ray, EEG, and routine laboratory tests and, prior to participation, gave informed consent.

### General Procedure

The methodology used was a double-blind crossover comparison of a single dose of oxazepam 30 mg, either FDDF or regular, in randomized order. In two different sessions, at a 1-week interval, the patients took both drugs, but whereas one was the active compound, the other was a placebo of the same appearance (double-dummy technique). At 9.00 a.m., the patient was taken to the EEG laboratory. Electrodes were placed on the scalp and a general interview was carried out allowing the completion of the baseline Hamilton Anxiety Scale. Then the patient, after comfortably lying down on a bed, had a 2-min baseline ($T_0$) EEG recording (with eyes closed) and completed a battery of visual analogue scales, composed of ten 100-mm lines, on which he had to indicate a mark, according to his current condition, between 10 pairs of opposite conditions (table I). These pairs of items were derived from the Hamilton Anxiety Scale and assess both physical and somatic symptoms of anxiety. Each score was calculated by adding the distance (in millimeters) in each line from the 'good' end, with a total maximal score of 1,000.

First, the patient took two tablets of regular oxazepam 15 mg (or placebo) with 100 cm³ of water, and second, placed two tablets of FDDF oxazepam (or placebo) directly on his tongue. The patient completed batteries of visual analogue scales and had 2-min EEG recordings every 8 min for 96 min (13 postdrug visual analogue scales and 12 EEG recordings), except for the 1st patient for whom each session was limited to 64 min (9 postdrug visual analogue scales and 8 EEG recordings). At the end of each session, the general interview of the patient was repeated and a final Hamilton Anxiety Scale was completed.

### Electrophysiological Procedure

The EEG was recorded on a conventional EEG machine from two leads (Fz-Cz; Cz-Pz). During the selected 2-min periods, the EEG trials did not contain muscle or EOG artifacts. The EEG signals were amplified with a time constant of 1.5 and filtered with an efficient low-pass filter, eliminating frequency components greater than 30 Hz (attenuation 30 dB/octave).

The EEG signals were digitalized off-line, with a sampling rate of 64 c/s (PDP 11/40). Each period of 2 min was obtained by averaging 15 epochs of 8 s (120 s). The power spectrum of each epoch was obtained by using the FFT program [Cooley and Tukey, 1965] and distinguished 5 frequency bands: $\delta$: 1–4 Hz; $\theta$: 4.125–8 Hz; $\alpha$: 8.125–12.5 Hz; $\beta_1$: 12.625–17.5 Hz; $\beta_2$: 17.625–30 Hz.

**Table I.** Visual analogue scales for the assessment of anxiety

*Currently, I feel*

| | |
|---|---|
| Extremely quiet | Extremely nervous |
| Perfectly in shape | Extremely tired |
| Perfectly relaxed | Extremely tense |
| My heart beats perfectly normally | My heart beats very fast or very strongly |
| My breath perfectly normal | My breath extremely difficult, with a pound on my chest |
| No headache at all | Very severe headache |
| No shaking at all | Extremely shaking |
| Not anxious at all | Extremely anxious |
| My stomach perfectly normal | Very painful stomach aches or very strong nausea |
| No feeling of dizziness | Very strong feeling of dizziness, feeling of imminent fainting |

For the EEG analysis, 3 descriptors were used: (a) the relative amplitude obtained by integrating the spectrum of each band [Itil, 1974]; (b) the relative percentage of frequency, obtained by adding EEG activity (regardless of its frequency) and by calculating the relative amounts of each frequency band [Itil, 1974]; (c) the centroid values, which reflect the shape of the power spectra, and are independent of the total power in the analyzed band [Lehmann and Koukkou, 1974].

### Choice of Preference

After completion of both sessions, the fastest clinical change was selected independently: (1) globally by the patient; (2) globally by the clinician who conducted the interview; (3) by a 'blind' clinician, according to the evolution of visual analogue scales; (4) by a 'blind' electrophysiologist, according to the changes in EEG $\beta_2$ band.

### Data Analysis

The clinical changes over time after drug intake were assessed by analysis of variance with repeated measures. This method allows one to study the global evolution after all sessions (time-effect) and to test if the evolution after one of the drug formulations is significantly faster than after the other (time-drug interaction).

EEG data analysis was performed for integrative, frequency, and centroid parameters. For each single session, the EEG predrug values were taken as zero-baseline points. The successive changes during the 12 following periods (sampled every 8 min) were assessed in percentage of the baseline values, and a t test was automatically applied to evaluate the level of statistical significance of these changes. The global changes over time in $\beta_2$ activity after drug intake for all sessions and possible differences between both formulations were assessed by analysis of variance with repeated measures.

The relationships between clinical evolution on the visual analogue scales and $\beta_2$ EEG changes were assessed by analysis of covariance, and the relationships between visual analogue or Hamilton Anxiety Scale scores and $\beta_2$ EEG percentage before and at the end of the sessions were assessed using the Pearson product-moment correlation coefficient.

The distribution of preferences was analyzed according to the binomial law [Spiegel, 1972].
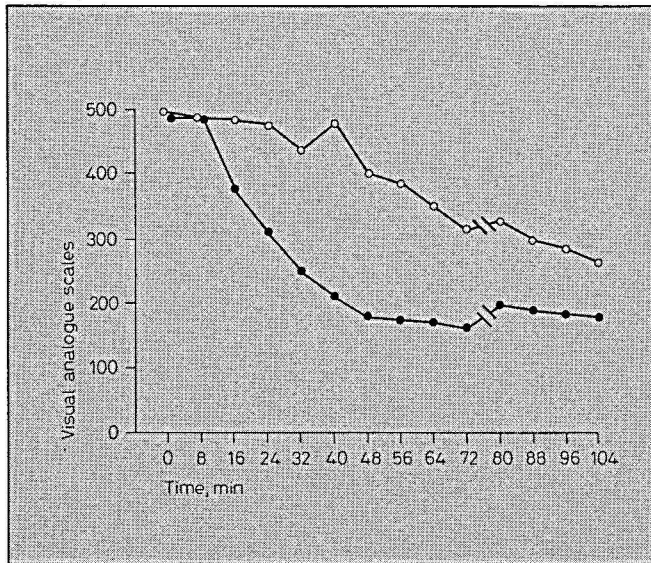
Fig. 1. Mean changes over time on visual analogue scales after a single intake of oxazepam 30 mg in either the regular (o) or the FDD (•) formulation.
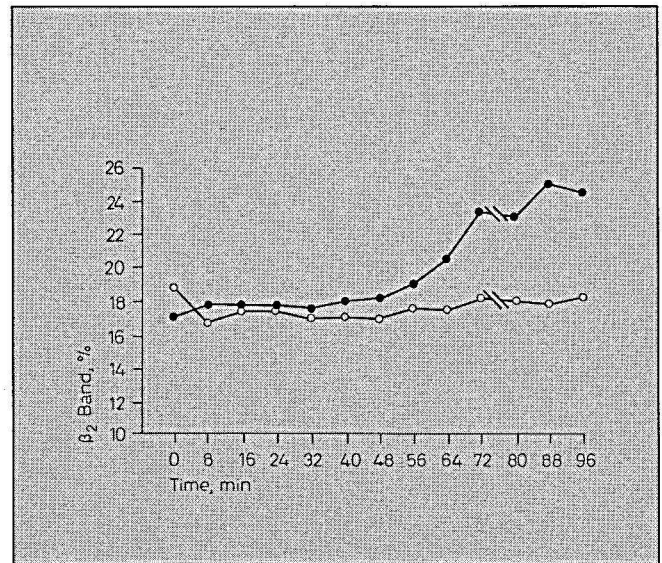


Fig. 2. Mean changes over time in the EEG $\beta_2$ band after a single intake of oxazepam 30 mg in either the regular (o) or the FDD (•) formulation.

## Results

### Anxiolytic Activity

Mean Hamilton Anxiety scores before and after drug intake were 28.0 (6.0) and 11.8 (4.4) for the FDDF oxazepam sessions; and 28.8 (7.5) and 17.0 (7.7) for the regular oxazepam sessions. These results indicate a significant improvement for both drugs combined [F $(1, 4)$ = 8.15; $p < 0.05$], without statistical difference between the two forms [F $(1, 4)$ = 2.49; NS]. The clinical improvement measured by the visual analogue scales was also significant for both forms combined [F $(9, 36)$ = 3.20; $p < 0.01$], but significantly faster with FDDF than with regular oxazepam [F $(9, 36)$ = 4.07; $p < 0.05$] (fig. 1). There was a significant relationship between the level of anxiolytic symptomatology assessed by Hamilton Anxiety Scale and by visual analogue scales both before and after treatment ($r = 0.91$; $p < 0.001$ and $r = 0.82$; $p < 0.01$).

### EEG Changes

In all sessions, the integrative parameter showed the highest sensitivity to benzodiazepine-induced changes. During the 5 individual sessions with FDDF oxazepam, the increase in $\beta_2$ band frequencies became statistically significant ($p < 0.1$) after: 64 min ($n = 3$), 72 min ($n = 1$), and 88 min ($n = 1$). This was different than the 5 sessions with regular oxazepam, where no significant change in $\beta_2$

frequencies was ever noted throughout the recording periods.

Mean changes over time in $\beta_2$ band frequency are displayed in figure 2. The increase in $\beta_2$ band was significant across all sessions [F $(12, 48)$ = 5.87; $p < 0.0001$], but significantly faster after FDDF oxazepam [F $(12, 48)$ = 5.37; $p < 0.0001$].

### Relationship between Anxiety Scale Scores and EEG Changes

There was a significant relationship between the evolution of anxiety scores on visual analogue scales and the percentage of $\beta_2$ band for the whole sessions ($r = -0.73$; $p < 0.01$). However, this relationship was only significant after FDDF oxazepam ($r = -0.59$; $p < 0.05$), and not after regular oxazepam ($r = -0.50$; NS). There was no significant relationship between Hamilton Anxiety Scale scores and $\beta_2$ band frequency percentage.

### Choice of Preference for Fastest Activity

In each of the 5 cases, the FDDF oxazepam session was preferred over the regular session, independently by the patient, the clinician who conducted the interview, the clinician who analyzed the visual analogue scales and the electrophysiologist who analyzed the changes in $\beta_2$ band. All these preferences were statistically significant ($p < 0.05$).

## Discussion

This study demonstrates a significantly more rapid onset of activity of a new galenic form of oxazepam (FDDF) compared with the standard tablet for both the self-ratings of anxiety and the specific EEG changes. These results support the discriminant power of using visual analogue scales and EEG recording analysis for the assessment of the latency of onset of benzodiazepine compounds. Indeed, the statistical differences are obtained with a sample of only 5 patients.

Visual analogue scales are particularly sensitive to assess short-term changes in subjective feelings and have been widely used as indicators of the time-effect curve of analgesic and sedative drugs [review in *Bond and Lader*, 1974]. Moreover, they are easy for the subjects to grasp, quick to fill out and do not require much subject motivation and, as the rater is not restricted to direct quantitative terms, permit as fine a discrimination as she/he wishes [*Freyd*, 1923]. In addition, they reduce the difficulties of response sets and the artificial distribution of positive and negative responses [*Aitken*, 1969]. The visual analogue scales especially designed for this study proved to be very sensitive to change, correlating highly with changes in the scores in the Hamilton Anxiety Scale, the standard rating instrument.

This study also shows the discriminant power of pharmacoelectroencephalography in assessing the onset of central effects. Even if we have been accustomed to describing the bioavailability of substances in terms of blood levels, it might be necessary in the case of certain compounds (in particular those which are centrally active) to describe the dynamics on an efficacy measure [*Herrmann and Irrgang*, 1983]. This is especially true for benzodiazepine compounds, the activity of which is mediated by specific central receptors, so that the extent and duration of this specific binding should be assessed rather than plasma pharmacokinetics [review in *Möhler and Richards*, 1983]. Benzodiazepine plasma pharmacokinetics has demonstrated its limits: no evident relationship exists between plasma levels and anxiolytic activity [review in *Bellantuono* et al., 1980]; moreover, clinical experience with benzodiazepines shows that observable effects like sedation do not persist as long as predicted by plasma pharmacokinetic data [*Kurowski* et al., 1982]. Since it is currently impossible to assess central receptor binding in humans, the pharmaco-EEG represents an interesting way to demonstrate the presence of central nervous system effects of benzodiazepines [*Herrmann and Irrgang*, 1983]. The EEG changes induced by benzo-

diazepines clearly exhibit a dose-effect relationship and are also related to the relative potency of the compounds, allowing one to find equipotent doses in terms of their EEG influence [*Fink* et al., 1976; *Matejcek*, 1979; *Saletu and Grünberger*, 1979; *Saletu* et al., 1980; *Matejcek* et al., 1983]. This study demonstrates the correlation between EEG changes and clinical activity.

Anxiolytic and sedative properties of the benzodiazepines have been related to two different EEG changes: anxiolysis to an increase in β activity and sedation to a decrease in α activity (with a concomitant increase of θ and δ activity), two parameters which can exhibit a different evolution [*Matejcek*, 1979; *Kurowski* et al., 1982]. No significant change in the α (or θ–δ) band appeared after oxazepam 30 mg in this study, in good agreement with the absence of sedative effects experienced by the 5 patients (as evidenced by the specific items of the visual analogue scales). It must be stressed, however, that anxious patients are generally less sensitive to pharmacologic sedative effects than normal subjects [*Fabre* et al., 1984]. With regard to descriptors of EEG changes, the integrative parameter (reflecting the relative power of each frequency band) appeared to be the most sensitive in this experimental design, showing its superiority over frequency and centroid parameters.

Clinically, rapid onset benzodiazepines like FDDF oxazepam are particularly suitable as sleep-inducing agents, shortening the time before beginning of their sedative effect. Moreover, because it is specially designed to be taken without water, FDDF oxazepam could be used as an oral sedative premedication before anesthesia, eliminating the need to use injectable benzodiazepines. FDDF oxazepam could also represent some improvement in the symptomatic treatment of episodic anxiety, being taken 30 min or so before entering the anxiety-provoking situation. If the panic attack has already started, a compound like FDDF oxazepam could still be taken and will exert a fairly prompt action, aborting the panic attack, according to the general rules described by *Lader and Petursson* [1983]. Some patients could also be reassured by carrying some FDDF oxazepam tablets they could take immediately (without need to find some liquid) for such an eventuality, which might be dubbed a 'talismanic' use [*Lader and Petursson*, 1983].

Finally, this study also shows the importance of rigorous clinical selection in differentiating between anxiolytic pharmacotherapies. The patients selected in this study showed very consistent anxious symptomatology: the individual differences between the two sessions were only 3, 3, 1, 2, and 1 points on the Hamilton Anxiety Scale and

11, 25, 23, 46, and 17 mm (on a total of 1,000) on the visual analogue scales, corresponding to a Pearson correlation coefficient of 0.96 ($p < 0.005$) for Hamilton Anxiety Scale and 0.998 ($p < 0.001$) for the visual analogue scales. The use of crossover design decreases the coefficient of variation and allows a direct comparison of the clinical and EEG effects of the two compounds [*Kellner* et al., 1978; *Ansseau* et al., 1984]. This methodology permits one to obtain significant conclusions with a limited number of subjects, as shown in this study.

## Acknowledgments

## References

Aitken, R.C.B.: Measurement of feelings using visual analogue scales. Proc. R. Soc. Med. *62:* 989–993 (1969).

Ansseau, M.; Doumont, A.; Diricq, S.: Methodology required to show clinical differences between benzodiazepines. Curr. med. Res. Opin. *8:* suppl. 4, pp. 108–114 (1984).

Ansseau, M.; Doumont, A.; Thiry, D.; Cerfontaine, J.L.; Tjandramaga, T.B.; Verbesselt, R.; De Schepper, P.J.: Oxazepam bioavailability in healthy male volunteers after single dose (15 mg) oral administration: comparison between freeze-dried dosage (FDD) and tablet formulation (in press).

Bellantuono, C.; Reggi, V.; Tognoni, G.; Garattini, S.: Benzodiazepines: clinical pharmacology and therapeutic use. Drugs *19:* 195–219 (1980).

Bond, A.; Lader, M.: The use of analogue scales in rating subjective feelings. Br. J. med. Psychol. *47:* 211–218 (1974).

Cooley, J.W.; Tukey, J.W.: An algorithm for machine calculation of complex Fourier series. Maths Comput. *19:* 297–301 (1965).

Detti, I.: Benzodiazepines in the treatment of insomnia: pharmacokinetic considerations; in Costa, The benzodiazepines: from molecular biology to clinical practice, pp. 173–199 (Raven Press, New York 1983).

Fabre, L.F.; Johnson, P.A.; Greenblatt, D.J.: Drowsiness sedation levels in anxious neurotic outpatients. Psychopharmacol. Bull. *20:* 128–136 (1984).

Fink, M.: Cerebral electrometry – quantitative EEG applied to human psychopharmacology; in Dolce, Kunkel, Computerized EEG analysis, pp. 272–288 (Fisher, Stuttgart 1975).

Fink, M.; Irwin, P.; Weinfeld, R.E.; Schwartz, M.A.; Conney, A.H.: Blood levels and electroencephalographic effects of diazepam and bromazepam. Clin. Pharmacol. Ther. *20:* 184–191 (1976).

Freyd, M.: The graphic rating scale. J. educ. Psychol. *14:* 83–102 (1923).

Gibbs, F.A.; Gibbs, E.L.: Clinical and pharmacological correlates of fast activity in electroencephalography. J. Neuropsychiat. *3:* 573–578 (1962).

Greenblatt, D.J.; Shader, R.I.; Abernethy, D.R.: Current status of benzodiazepines. New Engl. J. Med. *309:* 410–416 (1983).

Hamilton, M.: The assessment of anxiety states by ratings. Br. J. med. Psychol. *32:* 50–55 (1959).

Herrmann, W.M.; Irrgang, U.: An absolute must in clinico-pharmacological research: pharmaco-electroencephalography, its possibilities and limitations. Pharmacopsychiat. *16:* 134–142 (1983).

Itil, T.M.: Quantitative pharmaco-electroencephalography; in Itil, Modern problems of pharmacopsychiatry, vol. 8. Psychotropic drugs and the human EEG, pp. 43–75 (Karger, Basel 1974).

Kaplan, S.A.; Jack, M.L.: Metabolism of the benzodiazepines: pharmacokinetic and pharmacodynamic considerations; in Costa, The benzodiazepines: from molecular biology to clinical practice, pp. 173–199 (Raven Press, New York 1983).

Kellner, R.; Uhlenhuth, E.H.; Glass, R.M.: Clinical evaluation of antianxiety agents: subject-own-control designs; in Lipton, DiMascio, Killam, Psychopharmacology: a generation of progress, pp. 1391–1400 (Raven Press, New York 1978).

Kurowski, M.; Ott, H.; Herrmann, W.M.: Relationship between EEG dynamics and pharmacokinetics of the benzodiazepine lormetazepam. Pharmacopsychiat. *15:* 77–83 (1982).

Lader, M.; Petursson, H.: Rational use of anxiolytic/sedative drugs. Drugs *25:* 514–528 (1983).

Lehmann, D.; Koukkou, M.: Computer analysis of EEG wakefulness-sleep patterns during learning of novel and familiar sentences. Electroenceph. clin. Neurophysiol. *37:* 73–84 (1974).

Marjerrison, G.: Effects of minor tranquilizers on the EEG; in Itil, Modern problems of pharmacopsychiatry, vol. 8. Psychotropic drugs and the human EEG, pp. 149–157 (Karger, Basel 1974).

Matejcek, M.: Pharmaco-electroencephalography: the value of quantified EEG in psychopharmacology. Pharmacopsychiat. *12:* 126–136 (1979).

Matejcek, M.; Neff, G.; Abt, K.; Wehrli, W.: Pharmaco-EEG and psychometric study of the effect of single doses of temazepam and nitrazepam. Neuropsychobiology *9:* 52–65 (1983).

Möhler, H.; Richards, J.G.: Benzodiazepine receptors in the central nervous systems; in Costa, The benzodiazepines: from molecular biology to clinical practice, pp. 93–116 (Raven Press, New York 1983).

Saletu, B.; Grünberger, J.: Evaluation of pharmacodynamic properties of psychotropic drugs: quantitative EEG, psychometric and blood level investigations in normals and patients. Pharmacopsychiat. *12:* 45–58 (1979).

Saletu, B.; Grünberger, J.; Linzmayer, L.; Stadler, R.: Classification and assessment of cerebral bioavailability of lopirazepam (D-12524) by quantitative EEG and psychometric analysis. Arzneimittel-Forsch. *30:* 513–518 (1980).

Spiegel, M.R.: Theory and problems of statistics (McGraw-Hill, New York 1972).

Spitzer, R.; Endicott, J.; Robins, E.: Research diagnostic criteria: rationale and reliability. Arch. gen. Psychiat. *34:* 773–782 (1978).

M. Ansseau, MD,
Psychopharmacology Unit,
University Hospital 'de Bavière',
B-4020 Liège (Belgium)