Br. J. clin. Pharmac. (1977), **4**, 167S-173S

REPEATED DOSE COMPARISON OF NOMIFENSINE, IMIPRAMINE AND PLACEBO ON SUBJECTIVE ASSESSMENTS OF SLEEP AND OBJECTIVE MEASURES OF PSYCHOMOTOR PERFORMANCE

I. HINDMARCH & A.C. PARROTT

Department of Psychology, University of Leeds, Leeds LS2 9JT, UK

1 Nine normal subjects volunteered to participate in a randomized single-blind crossover study of nomifensine 75 mg and two comparators, imipramine 75 mg and placebo.

2 Each volunteer received placebo for 3 d, then the first test drug for 4 days. This sequence was repeated twice more, so that each subject received each comparator. All medication was taken three times daily.

3 Assessments were made on days 3, 5 and 7 of each sequence, and consisted of a Sleep Evaluation Questionnaire, a test of Critical Flicker Fusion and a measurement of Complex Reaction Time (CRT).

4 There were no significant differences in the CRT. There was a significant increase in critical flicker fusion with nomifensine.

5 Although both nomifensine and imipramine disturbed the quality of sleep, only imipramine produced a hangover.

Introduction

Imipramine and related tricyclic compounds (amitriptyline, desipramine) might be regarded as the archetypal antidepressants and are currently widely prescribed for the treatment of depression, but not without the most frequently reported untoward reactions of an 'atropine-like' dryness of mouth, blurred vision, urinary retention, nausea and dizziness (Jarvik, 1970). Although imipramine is most effective in reducing the symptoms of depression in clinical populations, it does not produce euphoria or 'elevation' of mood and paradoxically engenders fatigue and impairment of cognitive processes (Grunthal, 1958). It has also been observed (Wheatly, 1972) that drowsiness is a concommitant side-effect of the clinical administration of antidepressants. The sedative effect of imipramine has been specifically reported (Benesova, 1970; Heller *et al.*, 1971) and the 'muscarinic' side-effects (nausea, dryness of mouth, dizziness, and so on) due to the anticholinergic activity of the tricyclic antidepressives shown to be most frequently reported in patients prescribed imipramine (Blackwell *et al.*, 1972). Imipramine has been shown to decrease Rapid Eye Movement (REM) sleep duration and to disrupt other electroencephalogram (EEG) sleep variables (Maclean & Knowles, 1972).

Nomifensine is a new isoquinoline derivative which preliminary clinical studies have shown (Angst *et al.*, 1974; Pecknold *et al.*, 1975) to possess pronounced antidepressant activity, without noticeable side-effects. Hoffman (1973) in laboratory studies found nomifensine to be well tolerated and to possess a mild centrally stimulating effect. Franchin (1973) showed that nomifensine did not reveal any changes on EEG parameters following repeated daily doses of between 75 and 125 mg.

A small percentage of patients administered nomifensine reported insomnia as a side-effect (Angst *et al.*, 1974), but with psychiatric populations it is difficult to distinguish insomnia as a drug effect from insomnia as a symptom of the underlying depression. Furthermore, as Klein & Davis (1969) indicate, subjective reports of drug effects are notoriously unreliable when taken alone. Care must also be taken when dealing with clinically depressed populations where symptoms commonly due to depression itself overlap the known side-effects of antidepressant drugs (Glassman & Perel, 1973).

This present study is a comparison of nomifensine and imipramine with placebo to investigate the effects of repeated doses of the drugs on: objective measures of psychomotor performance; subjective assessments of the quality of sleep and integrity of early morning behaviour; subjective ratings of the drug effects; and objective measures of sedation and CNS arousal.

To avoid the possibility that the side-effects reported in clinical studies may be due to the underlying depression of the subjects, a normal volunteer population was used. It could be argued that

any treatment with an antidepressant compound, particularly one with known central stimulating activity, would disrupt normal sleep; and, therefore, assessments of the quality of sleep were made in the early morning. Early morning assessments of psychomotor performance and sedation were also made to measure any possible 'hangover' effect which might assume importance in patient populations having to drive motor vehicles or operate complex machinery while under treatment with an antidepressant. Any changes in performance, sedation or sleep indices were to be demonstrated against a placebo to distinguish drug-induced changes from those of a daily or experimental nature.

Methods

Subjects

Nine (5 female, 4 male) informed consenting volunteers with ages in the range 20–48 yr, were used. All subjects were in normal physical health without a history of hepatic, renal or cardiac disease or psychiatric disturbance. Concurrent treatment for illness and actual or possible pregnancy excluded subjects from the study. For the duration of the study all subjects refrained from excessive alcohol and used public transport. Subjects were informed as to the general aims of the study and made aware of the possibility of untoward side-effects, it being made clear that they could break off their participation at any time should the 'side-effects' be too obnoxious.

Design and medications

Placebo, imipramine and nomifensine were all presented in identical capsules, with the daily dose of each compound being 75 mg presented as three 25-mg capsules.

The substances were administered in accordance with the following schedule. For 3 consecutive d one placebo capsule was taken three times daily followed by 4 d when active compounds were taken (1 capsule three times daily) followed by a further 3 d when 1 placebo was taken three times daily. The sequence was repeated until each subject had received each of the three treatment conditions (imipramine, placebo and nomifensine). The order of presentation of the treatment conditions was counterbalanced and, since the placebo and active preparations were presented in matching capsules, the experimental design was blind to the subject. Subjects were tested on the morning of the third placebo day (following the first capsule of the day), on the morning of the second drug day, and finally on the morning of the last drug day. Each drug condition thus had three test values—a placebo pretest level, a drug post-test following initial doses, and a drug post-test following the repeated dose of active compound. The testing sessions were at identical times for each subject on each test day and ranged from 0830 to 1100. On each test day subjects completed each of the assessments described below.

Measures and assessments

There were three measures used in this experiment:

Sleep evaluation questionnaire (SEQ) This is a set of 10-cm analogue scales which allows subjects to rate their perceived evaluation of the ease of getting to sleep (GTS), quality of sleep (QOS), ease of awakening from sleep (AFS) and the integrity of behaviour following wakefulness (BFW). The subjective ratings are thus measures of the quality of induced sleep (GTS + QOS) and 'hangover' the morning following (AFS + BFW). Although the polarity of the scales in the questionnaire is changed to avoid series effects, the scores are arranged so that a tendency to score towards 10 cm represents an increasingly positive trend. The SEQ is detailed elsewhere (Hindmarch, 1975); also contained in the questionnaire is provision for the rating of side-effects and their perceived severity.

Complex reaction time (CRT) Six stimulus lights were matched to six response buttons arranged in an arc about a central resting template. The distance from each response button to the central point was the same. The lights were illuminated at random and the subject had to respond as quickly as possible by raising his finger from the template and touching the appropriate response button. Two partial response measures were recorded—movement and recognition time. The movement latency is the time taken to move the finger from the resting template to the correct response button. The recognition time is the time difference, between the stimulus light onset and the finger leaving the resting template. The total response latency was also recorded, that is, the sum of the individual recognition and movement times. The response used was the performance scores on 25 stimulus presentations. This task was computerized and controlled on line using a Nova 1b, thus ensuring standard methods of stimulus presentation and data recording, as was also the critical fusion measure detailed below.

Critical flicker fusion (CFF) The critical flicker fusion threshold is used as an index of sedation and drug-induced drowsiness. The subject was required to discriminate flicker in a set of four light-emitting diodes set at a metre from his eyes in a daylight viewing tube. The assessment measure used was the threshold point at which the diodes appeared stable. The subject was required to view the diodes for 2 s and then indicate whether or not they were subject's

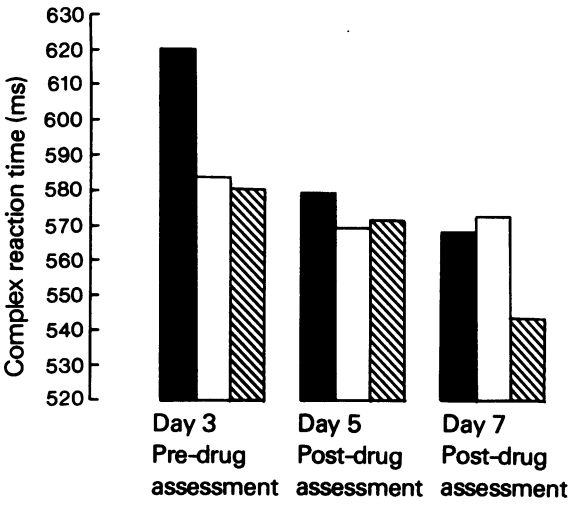

Figure 1 Mean changes in psychomotor performance on CRT for all treatment conditions. Open columns, Placebo; solid, nomifensine; hatched, imipramine.

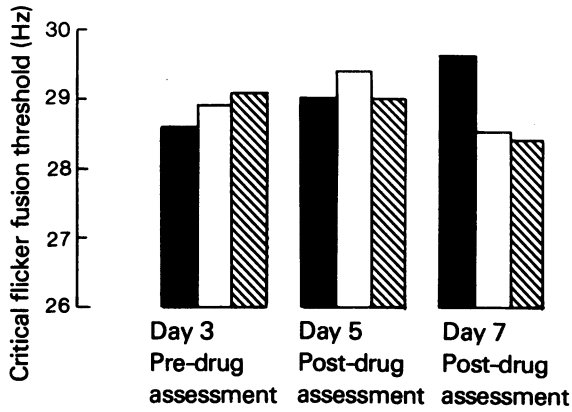

Figure 2 Mean changes in arousal level as measured using CFF threshold for all treatment conditions. Open columns, Placebo; solid, nomifensine; hatched, imipramine.

Table 1 Mean values obtained for pre- and postdrug assessments on all treatment conditions

	Nomifensine			*Placebo*			*Imipramine*		
	Pre	*Post 1*	*Post 2*	*Pre*	*Post 1*	*Post 2*	*Pre*	*Post 1*	*Post 2*
CRT (s)	0.620	0.579	0.568	0.584	0.569	0.573	0.580	0.571	0.544
CFF (Hz)	28.6	29.0	29.6	28.9	29.4	28.5	29.1	29.0	28.9
CTS	47	45	41	45	48	50	51	44	48
QOS	46	41	39	44	42	45	54	35	40
AFS	49	49	54	50	52	47	46	38	49
BFW	52	53	49	49	50	49	50	45	51

Table 2 Values of the normal deviate paired *t* test computed between pre- and postdrug scores for all treatment conditions

	Nomifensine		*Placebo*		*Imipramine*	
	Pre post 1	*Pre post 2*	*Pre post 1*	*Pre post 2*	*Pre post 1*	*Pre post 2*
RT	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
FF	1.16	4.25 $P < 0.001$	2.41 $P < 0.05$	1.52	<1.0	<1.0
TS	1.37	1.94	1.28	2.44 $P < 0.01$	1.65	1.87
QOS	2.25 $P < 0.05$	2.14 $P < 0.01$	1.0	1.80	4.43 $P < 0.001$	5.47 $P < 0.001$
HFS	<1.0	1.68	<1.0	0.87	2.13 $P < 0.05$	<1.0
BFW	<1.0	<1.0	<1.0	<1.0	1.61	<1.0

Levels of confidence (*P*) given for a two-tailed test with d.f.: CRT 269; QOS 17; CFF 35; AFS 17; GTS 26; BFW 26.

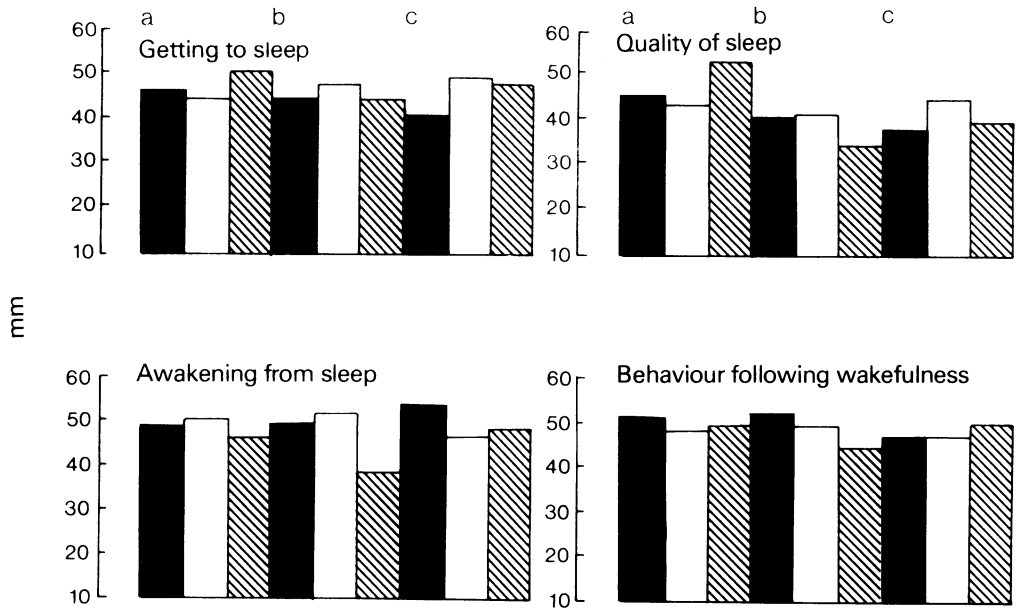

Figure 3 Mean scores obtained by all subjects on analogue rating scales of the subjective QOS and early morning behaviour. a. Pre-test values; b, post-test 1; c, post-test 2. Open columns, Placebo; solid, nomifensine: hatched, imipramine.

button response to a particular frequency, that is, 'flicker' or 'not 'flicker', determined the frequency of the next stimulus presentation.

By presenting a series of increasingly smaller frequency differences an approximate threshold was obtained. Then further frequencies about this threshold were presented in ascending and descending scales until an accurate threshold value was computed using the psychophysical method of limits (Woodworth & Schlosberg, 1958).

Table 3 Values of the normal deviate *t*, computed from paired *t* tests between the treatment conditions for both acute and chronic doses

	Acute dose comparisons			*Chronic dose comparisons*		
	N x *P*	*P* x *I*	*N* x *I*	*N* x *P*	*P* x *I*	*N* x *I*
CRT	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
CFF	1.74	1.12	<1.0	3.61 $P < 0.001$	1.22	2.33 $P < 0.05$
GTS	1.15	1.01	<1.0	2.721 $P < 0.02$	<1.0	1.58
QOS	<1.0	1.678	<1.0	1.98	1.82	<1.0
AFS	<1.0	3.48 $P < 0.005$	2.649 $P < 0.02$	2.43 $P < 0.05$	1.12	1.966
BFW	1.41	1.86	4.25 $P < 0.001$	<1.0	1.21	1.01

Levels of confidence (*P*) given for two-sided test with d.f.: CRT 269; CFF 35; GTS 26; AOS 17; AFS 17; BFW 26. N, Nomifensine; P, placebo.

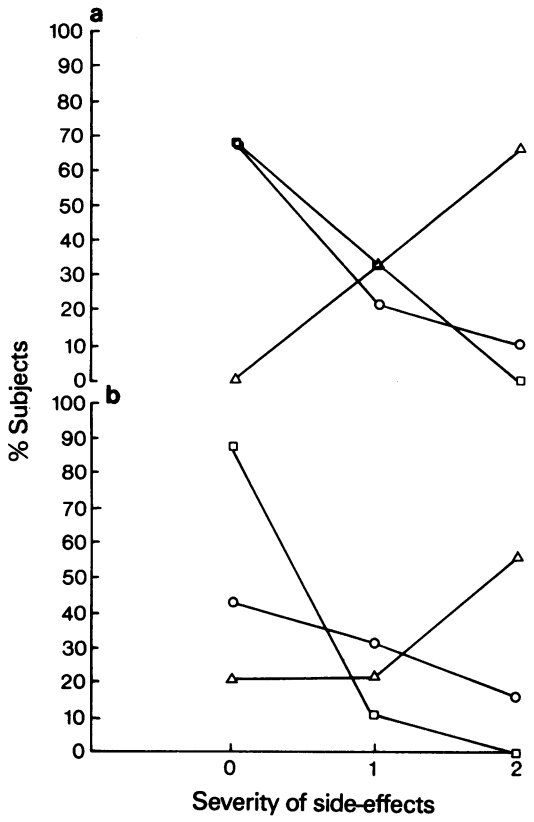

Figure 4 Frequency distribution of side-effect ratings following repeated doses of imipramine, placebo and nomifensine a, Acute administration; b, chronic administration.

Results

Objective measured and subjective assessments

Table 1 shows the mean values obtained for each treatment condition on CRT, CFF and the four SEQ parameters, and Figures 1, 2 and 3 present the same information graphically. A preliminary perusal of the results revealed that there were no significant changes in the two component parts of the CRT task; only the total response latency is presented.

Discussion

None of the change in psychomotor performance, as measured using the CRT task, proved significant. As can be seen in Figure 1, there is a tendency for the total CRT latency to decrease with both imipramine and nomifensine as the test proceeds; this is tentative evidence for a learning effect, although the changes in CRT performance with placebo do not confirm this hypothesis. It is therefore assumed that repeated doses of either imipramine 25 mg or nomifensine 25 mg do not significantly impair psychomotor performance.

The changes in CNS arousal level as measured by the CFF threshold confirm the earlier reports (Hoffman, 1973) that nomifensine possesses central stimulating properties, since there is a noticeable increase in CFF threshold following administration of the drug (Figure 2). This increase in CFF proves significant for within treatment comparisons at $P<0.001$ when pre-drug assessments are compared with subchronic dose levels. Although there is an increase in CFF values with placebo medication following initial doses ($P<0.05$), it can be seen that the increases due to nomifensine are significant both when compared with placebo ($P<0.001$) and when compared with imipramine ($P<0.05$) (Table 3).

The subjective appraisals of the ease of getting to sleep indicate that the mean values for both active compounds are below the values obtained with placebo. Paradoxically, the subjective assessments of the GTS parameter improve as the experiment progresses; when baseline levels are compared with those following the subchronic dose assessments a significant improvement ($P<0.01$) in GTS scores are noted (Table 2 and Figure 3). At the same time there is a significant impairment ($P<0.02$) in the GTS when

Table 4 Frequency of side-effects reported following acute and chronic treatment with nomifensine, imipramine and placebo

		Nomifensine		*Placebo*		*Imipramine*	
	Severity of side-effect	*Number of subjects*	*%*	*Number of subjects*	*%*	*Number of subjects*	*%*
Following acute dose	0	6	67	6	67	0	0
	1	2	22	3	33	3	33
	2	1	11	0	0	6	67
Following chronic doses	0	4	44	8	89	2	22
	1	3	33	1	11	2	22
	2	2	22	0	0	5	56

compared with pre-drug assessments, following subchronic treatment with nomifensine. This is certainly consistent with the drug's central stimulating properties; at the same time, it cannot be regarded as a true drug effect since the ease of getting to sleep significantly improves following treatment with placebo.

Both active compounds significantly impair the perceived QOS, both at acute and subchronic dose levels (Table 2). These reductions in subjects ratings are further confirmation that the administration of antidepressant compounds may have adverse effects on sleep. Although the changes in QOS ratings achieved significance for the within treatment comparisons detailed in Table 2, they do not reach significance when compared with placebo assessments (Table 3). The impairment in QOS ratings noted for both active compounds, however, is regarded as a true drug effect since the ratings produced under repeated administration of a placebo show little change from baseline values.

The two subjective assessments of AFS and BFW show that following initial doses, imipramine impairs AFS assessments when compared with placebo ($P<0.005$). On the other hand, nomifensine seems to be better than placebo ($P<0.05$) following chronic doses of the drug (Table 3) on this (AFS) measure. The BFW values show no significant changes from within treatment comparisons; but when the changes in this parameter are compared between conditions, nomifensine is rated as better than placebo (Figure 3) and significantly better ($P<0.001$) than imipramine, following initial doses of the drugs.

The SEQ findings as a whole suggest that nomifensine interferes with QOS and GTS commensurate with its centrally stimulating properties, but does so without any apparent hangover of detrimental effects the morning following medication. Imipramine significantly disturbs QOS and also produces a significant 'hangover' effect when compared with placebo, following initial doses of the drug.

The findings with respect to imipramine are commensurate with previous work on the drug, where lethargy and drowsiness were found to be necessary side-effects of drug administration. The lethargy and clumsy behaviour noted in this study occur in the early morning when they could interfere with car driving or other complex psychomotor performance tasks.

Nomifensine is shown to possess a central stimulating activity and produces significant increases in CFF thresholds following subchronic presentation of the drug. This increase in CFF is matched by increases in the subjective assessments of the integrity of early morning behaviour—that is, individuals tend to feel more alert the morning following treatment with nomifensine than with either placebo or imipramine.

A consideration of Table 4 and Figure 4 shows that the frequency of reports of persistent side-effects due to administration of nomifensine is not noticeably different from placebo. Following administration of imipramine, however, nearly two-thirds of the subjects report debilitating side-effects following both the acute and subchronic doses of the drug.

The low incidence of side-effects reported for nomifensine compared with the high frequency of debilitating somatic effects noted with imipramine, indicates that nomifensine is better tolerated than imipramine.

Conclusions

Repeated doses of imipramine 25 mg impair subjective assessments of QOS and AFS. The reported 'hangover' is confirmed in objective assessments of CFF thresholds which show a tendency for central alerting mechanisms to be dulled the morning following treatment with imipramine. The drug also produces noticeable and debilitating somatic side-effects characteristic of a tricyclic antidepressant.

Repeated doses of nomifensine 25 mg show an impairment on subjective ratings of QOS and GTS. This reported 'insomnia' is indicative of a drug with central stimulating activity disrupting the process of normal sleep. Moreover, there is a tendency for behaviour in the early morning to be rated as more integrated and aroused following treatment with nomifensine than that following either placebo or imipramine. These subjective assessments are confirmed by the findings from CFF thresholds which show elevations of threshold following medication with nomifensine. The drug is well tolerated with few side-effects.

It must be emphasized that the population used here is not culled from patients and so the clinical relevance of the findings is limited. It is important, however, to note that the reports of side-effects and insomnia can thus be regarded as true drug effects and not the product of some underlying symptomatology. In this respect, nomifensine was better tolerated than imipramine, which was found to produce a high frequency of persistent side-effects.

References

ANGST, J., KOUKKOU, M., BLEULER-HERZOG, M. & MARTENS, H. (1974). Ergebnisse eines offenen und eines Doppelblind versuches von Nomifensin im Vergleich zu Imipramin. *Arch. Psychiatr. Nervenkr.*, **219**, (3), 264-276.

BENESOVA, O. (1970). Neurophysiological and biochemical aspects in the action of antidepressant drugs. *Activ. Nerv. Sup. Praha*, **12**, 226-234.

BLACKWELL, B., LIPKIN, J.O., MEYER, J.H., KUZMA, R. & BOULTER, W.V. (1972). Dose response and relationship between anticholinergic activity and mood with tricyclic antidepressants. *Psychopharmacologia Berl.*, **25**, 205-217.

FRANCHIN, E.A. (1973). Clinical trial in 30 patients with nomifensine, a new antidepressant drug. *Rev. bras. clin. Terap.*, **2**, (7), 317-322.

GLASSMAN, A.H. & PEREL, J.M. (1973). The clinical pharmacology of imipramine. Implications for therapeutics. *Arch. gen. Psychiat.*, **28**, 649-653.

GRÜNTHAL, E. (1958). Untersuchungen über die besondere psychologische Wirkung des Thymoleptikums Tofranil. *Psychiatr. Neur. Wschr.*, **136**, 402-408.

HELLER, A., ZAHOŬREK, R. & WHITTINGTON, H.G. (1971). Effectiveness of antidepressant drugs: a triple blind study comparing imipramine, desipramine and placebo. *Am. J. Psychiat.*, **127**, 1092-1095.

HINDMARCH, I. (1975). A 1,4, benzodiazepine, temazepam (K3917), its effect on some psychological parameters of sleep and behaviour. *Arzneimittel.-Forsch.*, **25**, (11), 1836-1839.

HOFFMANN, I. (1973). 8-amino-2-mthyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, a new antidepressant. *Arzneimittel-Forsch.*, **23**, 45-50.

JARVIK, M.E. (1970). Drugs used in the treatment of psychiatric disorder. In *Pharmacological Basis of Therapeutics*, fourth edition, ed. Goodman, L.S. & Gillman, A. London: Collier-Macmillan.

KLEIN, D.F. & DAVIES, J.M. (1969). *Diagnosis and drug Treatment of Psychiatric Disorders.* Baltimore: Williams and Williams.

KLINE, N.S. & SHAH, B.K. (1973). Comparable therapeutic efficacy of tryptophan and imipramine: average therapeutic ratings versus 'true' equivalence—An important difference. *Curr. ther. Res.*, **15**, (7), 484-487.

MACLEAN, A.W. & KNOWLES, J.B. (1972). Behavioural effects of a tricyclic antidepressant. *NATO Symposium on Drugs, Sleep and Performance.* Mimeograph: Aviemore.

PECKNOLD, J.C., BAN, T.A., LEHMANN, H.E. & KLINGER, A. (1975). A clinical trial with nomifensine, a new antidepressant drug. *Int. J. clin. Pharmac. Biopharm.*, **11**, (4), 304-308.

WHEATLEY, D. (1972). Drowsiness and antidepressant drugs in mild depressive illness. *Br. J. Psychiat.*, **120**, (558), 507-509.

WOODWORTH, R.S. & SCHLOSBERG, H. (1958). *Experimental Psychology.* London: Methuen.