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The Effects of Fluoxetine and Dothiepin on Cognitive Function in Depressed Patients in General Practice

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The objective of this study was to assess whether there are any differences between fluoxetine and dothiepin on cognitive function of patients with major depression (DSMIII-R). A randomized, double-blind, parallel group design, 6 week trial in patients in general practice was employed where patients were randomly allocated to one of two treatment groups, i.e. fluoxetine 20 mg *mane* or dothiepin 75 mg *nocte* (increasing to 150 mg in the 2nd week). Eighty-four depressed patients aged 18–70 (mean 43·8) years were admitted to the study. Cognitive function was assessed by a valid battery of tests before and during treatment. The severity of depression was assessed using the Hamilton Depression Rating Scale (HAMD) at the start and end of the study. Both treatments were similarly efficacious in reducing the HAMD and performance tended to improve with both drugs during treatment. There were significant differences between the drugs on the critical flicker fusion task where the fluoxetine group performed significantly better than the dothiepin group ($p < 0.05$). The fluoxetine group also had better scores on a mental arithmetic task. No significant differences were observed in the adverse event profiles. The results of this study show that fluoxetine and dothiepin cannot be differentiated in terms of efficacy manifest by changes in the HAMD, but do possess different profiles of action on the battery of cognitive tests.

KEY WORDS — fluoxetine; dothiepin; depression; cognitive function

INTRODUCTION

Patients suffering from depressive disorders often experience psychomotor and cognitive deficits (Miller, 1975; Widlöcher, 1983; Widlöcher and hozlan, 1989; American Psychiatric Association, 1987) and such impairments not only hinder the performance of activities of normal daily life, but also put the patient at increased risk of accident. As depression improves, so psychomotor performance and cognitive function improve along with the amelioration of affect (Szabadi *et al*., 1976; Davies *et al*., 1978; Siegfried *et al*., 1984; Austin *et al*., 1992); however it is possible that a given antidepressant may mask these improvements or even exacerbate existing disturbances, particularly in those patients who do not respond to treatment.

Most current antidepressants are equally efficacious in alleviating depression (Song *et al*., 1993), but there are differences between antidepressants in the extent to which they affect patients' psychomotor and cognitive abilities (Hanks, 1984; Fairweather *et al*., 1993; Hindmarch and Kerr, 1994; Hale and Pinninti, 1995). The British Association for Psychopharmacology (1993) guidelines for the treatment of depression suggest that following efficacy, the side effect profile of a drug should be the second most important aspect to be considered when choosing a prescription. This is particularly important in the present context where the unwanted effects of a drug have the potential to interfere with a patient's cognitive processes, and so this must be considered when deciding appropriate pharmacotherapy.

The unwanted effects of antidepressants can arise as a direct consequence of their intrinsic pharmacological properties. For example, tricyclic antidepressants (TCAs) have antihistaminic, anticholinergic and α-adrenoreceptor blockade properties (Richelson, 1987; Rudorfer and Potter, 1989), which can induce sedation, drowsiness, disturbance of memory, impairment of cognitive function,

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dizziness and poor sensorimotor co-ordination. In contrast, the specific serotonin reuptake inhibitors (SSRIs) have little anticholinergic action, no antihistaminic properties and low affinity for α-adrenoreceptors (Fuller and Wong, 1987), therefore having little or no potential for producing adverse effects on behaviour.

Studies in populations of non-depressed subjects, i.e. the effects due to the drug alone without concomitant illness, demonstrate that the TCAs, e.g. amitriptyline and dothiepin, impair objective measures of cognitive function (e.g. critical flicker fusion threshold) and psychomotor speed (e.g. choice reaction time) (Hindmarch, 1987; Hindmarch and Bhatti, 1988; Kerr *et al*., 1992; Fairweather *et al*., 1995, 1996, 1997) and cause unsteady gait (e.g. Lord *et al*., 1995). Such impairments with these drugs are also found in patient populations treated for several weeks (Hanks, 1984; Fairweather *et al*., 1993; Hindmarch and Kerr, 1994) and months (Hale and Pinninti, 1995). Many similar studies have failed to show any significant impairment with SSRIs such as fluoxetine, sertraline, paroxetine and citalopram in healthy volunteers (Hindmarch, 1987; Hindmarch and Bhatti, 1988; Kerr *et al*., 1992; Fairweather *et al*., 1995, 1996, 1997) and depressed patients (Fairweather *et al*., 1993; Hindmarch and Kerr, 1994; Hale and Pinninti, 1995). Some authors, however, have reported performance impairments with SSRIs, e.g. fluoxetine (Saletu and Grünberger, 1985; Ramaekers *et al*., 1995). Although there are studies published in which the effects of antidepressants have been assessed in depressed patients, the majority of investigations have been performed in healthy volunteers.

The objective of the present study was to compare the effects of the SSRI fluoxetine and the TCA dothiepin on objective and subjective measures of cognition in depressed patients before and during 6 weeks of treatment.

METHODS

Patients

Eighty-four depressed patients (54 females, 30 males) aged between 18 and 70 (mean 43·8) years were recruited from patients attending G.P. surgeries in proximity to the University of Surrey. All patients at entry satisfied the DSMIII-R criteria for major depression and were not suffering from concurrent illness. Patients requiring concomitant use of psychotropic medication, or patients who had been receiving long term treatment with benzodiazepines were excluded from the study. Patients provided informed consent and were medically examined to ensure that they satisfied the inclusion/exclusion criteria.

Ethical approval was obtained from the ethics committees of each individual clinical investigator.

Design

The study was a randomized, parallel group, double-blind 6 week study. Patients were randomly allocated to the fluoxetine group or the dothiepin group.

Patients received either fluoxetine 20 mg *mane* and placebo *nocte* for 6 weeks, or placebo *mane* and dothiepin 75 mg *nocte* for the first week, rising to 150 mg for the remaining 5 weeks. Drugs and placebos were packaged in identical capsules.

Procedure

At initial diagnosis on DSMIII-R criteria, patients were also rated on the 17-item Hamilton Depression Rating Scale (HAMD) (all clinical investigators had received training prior to the study in order to standardize inter-investigator ratings). Patients were also familiarized with all the testing procedures and received training on all tests in order to preclude learning effects (Parkin *et al*., 1997). Following this, patients performed the test battery to provide baseline pre-treatment scores then returned to their G.P. on days 7, 14, 28 and 42 of treatment where the assessments were repeated. Adverse events and concomitant medication were also recorded at each visit.

Test battery

The tests described here have been shown to be valid and reliable indicators of the action of antidepressants in healthy volunteers (Hindmarch, 1980; Sherwood and Kerr, 1993) and clinical populations (Hanks, 1984; Fairweather *et al*., 1993; Hindmarch and Kerr, 1994).

Critical Flicker Fusion (CFF). This task was used to measure the information processing capacity of the central nervous system (Hindmarch, 1975, 1980). A decrease in CFF threshold is indicative of lowered CNS arousal and capacity for impairment of information processing. Patients were required

to discriminate flicker from fusion in a set of four light emitting diodes in binocular fixation at a distance of 1 m. The mean CFF thresholds were determined by the psychophysical methods of limits on three ascending and three descending scales (Woodworth and Schlosberg, 1958). CFF was measured under two conditions: once with binocular fixation at 1 m and once under the same viewing conditions using 2×1 mm artificial pupils.

Kim's Game. In this test of short term memory, patients were required to recall as many items as possible from a picture of 30 everyday objects shown to them for 1 min (Paes de Sousa *et al*., 1981). The number of items correctly recalled was the response measure.

Serial Subtraction of Numbers (SSN). A mental arithmetic task was used to provide an index of the integrity of the cognitive processing systems. Patients were asked to make consecutive subtractions of 3, 7 and 17 from an initial five figure number. The response measure were the number of errors made and the time taken to complete the task (Hindmarch, 1977).

Cognitive Failures Questionnaire (CFQ). The CFQ was used as a measure of self-reported failures in perception, memory and motor function (Broadbent *et al*., 1982). The response measures were the frequencies (i.e. very often, quite often, occasionally, very rarely or never) of each of 25 possible failures experienced by the patients.

Leeds Sleep Evaluation Questionnaire (LSEQ). The LSEQ measures aspects of subjective assessment on factors of sleep, i.e. the ease of Getting to Sleep (GTS), Quality of Sleep (QOS) and the ease of Awakening from Sleep (AFS) using 100 mm line analogue rating scales (Hindmarch, 1975; Parrott and Hindmarch, 1980). Patients were required to rate how they perceived GTS, QOS and AFS at the time of rating compared to how they felt prior to starting treatment.

Milford Epworth Sleepiness Scale (MESS). The MESS is an adaptation of the Epworth Sleepiness Scale (Johns, 1991) using a visual analogue scoring technique. Patients were required to rate the likelihood of their falling asleep in a number of everyday situations, and the overall mean score gave a measure of daytime sleepiness.

Data analysis

The HAMD scores were analysed using Wilcoxon's matched pairs, sign-ranks test. The adverse event and drop-out data were analysed using Mann-Whitney U tests.

The data from the cognitive tests were analysed using independent groups repeated measures analyses of variance (ANOVA), with one between subject (drug) and one within subject (visit: either five or four levels, depending on the test) factor. *Post hoc* testing for differences between significantly different means were carried out using Tukey's HSD procedure. Statistical significance was set at $p < 0.05$.

RESULTS

Of the 84 patients recruited onto the study, 63 completed visit 5.

Hamilton Depression Rating Scale scores

Intention to treat. On entry the mean score for the 84 patients was 21·29 (SD 5·17; range 10–35). Those who completed the final HAMD ($n = 63$) scored an average of 10·25 (SD 5·81; range 0–28). A Wilcoxon Matched Pairs Test revealed that there was a highly significant difference between the initial and final scores ($n = 63$; $z = 6{\cdot}86$; $p < 0.000001$).

Responders. Thirty-six patients who completed the study responded to the medication, i.e. their HAMD scores decreased by 50 per cent or more. Of these, 15 were taking fluoxetine and 21 dothiepin.

No significant differences were found between the drugs at the initial or final assessments (Kolmogorov Smirnov Test) for both the intention to treat group and for those who completed the study. Also, there were no significant differences in initial or final HAMD scores between those who completed the study and those who dropped out or were withdrawn.

Adverse events

A total of 186 adverse events were reported by 77 patients. The most common adverse events (frequencies are presented in parentheses) with dothiepin were headache (11), dry mouth (14), dyspepsia (5) and somnolence (5). For fluoxetine these were headache (14), dizziness (6), nausea (6)

and diarrhoea (6). There were no significant differences between treatment groups.

Test battery

Two sets of analyses were carried out on the psychometric data: intention to treat ($n = 84$) and responders ($n = 36$). Both sets of analyses revealed similar results and the responders analysis is discussed in detail below.

For CFF, using the standard methodology (i.e. without artificial pupils), there was a significant drug effect ($F(1,29) = 5{\cdot}01$; $p < 0.05$) in the responders (Figure 1). *Post hoc* analysis revealed that fluoxetine produced significantly higher thresholds compared to dothiepin at all visits. As there were differences at the baseline assessment, an analysis of covariance (ANCOVA) was performed using baseline scores as the covariate. Significant differences were found ($p < 0.05$) at all subsequent visits.

With artificial pupils, CFF scores were similar to those obtained with the standard methodology, except that there were no differences between treatments at baseline. A time effect was also apparent where CFF increased over the course of the study with ($F(4,116) = 4{\cdot}33$; $p < 0.05$) and without ($F(4,116) = 5{\cdot}81$; $p < 0.05$) artificial pupils (Figure 1).

In the SSN test, both drugs improved performance over the duration of the study ($F(4,92) = 9{\cdot}43$; $p < 0.05$), however, those patients in the dothiepin group consistently scored significantly lower on the 17 s subtraction than the fluoxetine group ($p < 0.05$). When all of the SSN variables were added together, there were no significant differences, although there was a trend for dothiepin to appear worse than fluoxetine, but with both groups improving over time (Table 1). Performance on Kim's Game and the CFQ did not significantly differ between treatments, although the pattern was for those patients on fluoxetine to have better scores than those on dothiepin (Table 1).

No differences were found in the GTS component of the LSEQ. There was a time effect in that both drugs improved QOS over the study ($F(3,84) = 6{\cdot}14$; $p < 0.05$), although this was to a lesser extent with fluoxetine (Table 1). Dothiepin impaired ratings of AFS, significantly so at visit 2 ($p < 0.05$) (Figure 2). No differences were detected in the MESS (Table 1).

DISCUSSION

The aim of this study was to investigate the effects of fluoxetine 20 mg and dothiepin 150 mg on cognitive function and activity in depressed patient treated in general practice. The results demonstrate that fluoxetine 20 mg and dothiepin 150 mg were similarly efficacious in alleviating depression as assessed by clinical rating scales (i.e. 50 per

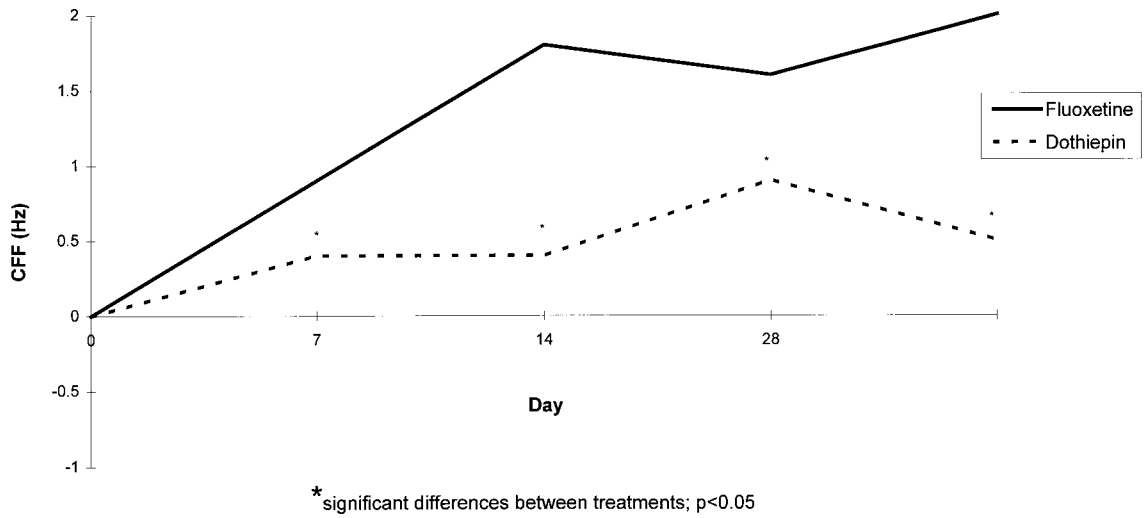

Figure 1. The effects of fluoxetine 20 mg and dothiepin 75–150 mg on Critical Flicker Fusion (CFF) — differences from baseline

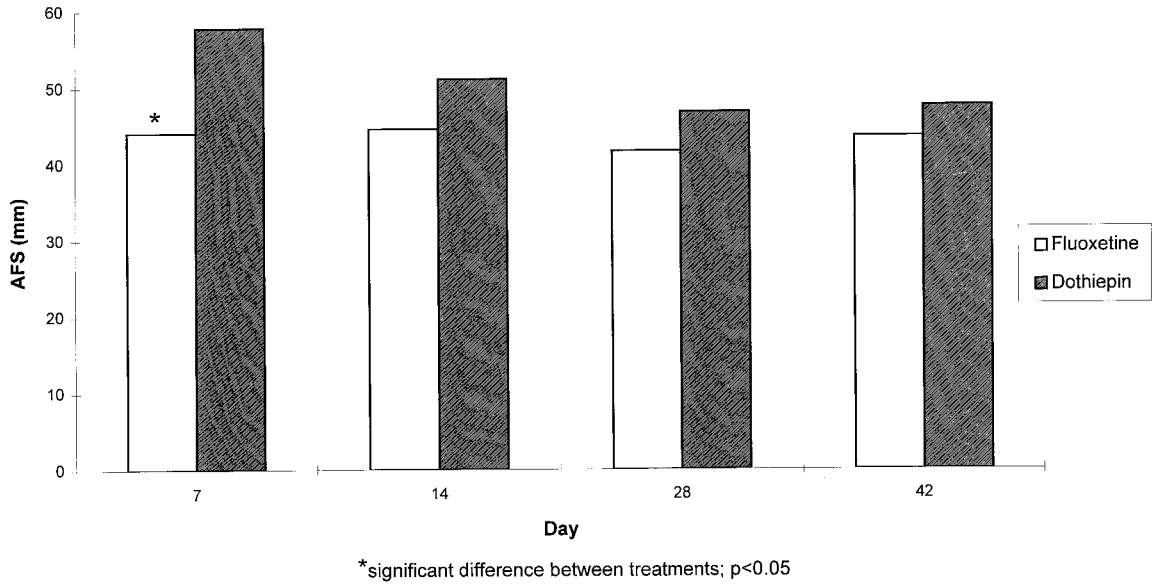

Figure 2. The effects of fluoxetine 20 mg and dothiepin 75–150 mg on subjective ease of Awakening From Sleep (AFS)

cent reduction in the HAMD) and had similar numbers of adverse events (though these were qualitatively different). However, there were differences between treatments on objective tests of cognitive function.

As CFF is an indicator of central processing ability, it would be expected that the drug-induced amelioration of the cognitive retardation associated with depression would be accompanied by an increase in CFF threshold. It may also be expected that if an antidepressant impaired cognitive function then any therapeutic effects on measures such as CFF would be masked. These effects were observed in this study, where the improvement in CFF scores in the fluoxetine group was significantly greater than that seen in patients treated with dothiepin. This finding is also in accordance with other studies employing similar batteries of tests with SSRIs (e.g. paroxetine, sertraline, fluoxetine, citalopram) and TCAs (e.g. amitriptyline, dothiepin) in a laboratory setting (Hindmarch, 1987; Hindmarch and Bhatti, 1988; Kerr *et al.*, 1992; Fairweather *et al.*, 1995, 1996, 1997) and with studies in patient populations (Fairweather *et al.*, 1993; Hindmarch and Kerr, 1994; Hale and Pinninti, 1995).

There is an argument that a change in CFF threshold is a result of changes in pupil size and that the decreased CFF observed with TCAs arises as a consequence of their anticholinergic action on pupil diameter and not due to impairment of cognitive function (Freeman and O'Hanlon, 1995). The CFF technique employed in the present study used binocular foveal fixation under controlled ambient lighting conditions (Hindmarch, 1975, 1980), thereby negating any effects of pupil size. In order to demonstrate this, CFF was measured under two conditions, i.e. with and without artificial pupils. There were no significant differences between the two conditions, and so it can be concluded that differences in thresholds using this particular CFF methodology are due to direct drug effects on the CNS which are independent of changes in pupil size.

Antidepressants which impair cognition not only reduce quality of life, but also increase the likelihood of accident (Ray *et al.*, 1991, 1992). This is borne out by the fact that a greater representation of TCAs were present in the bloods of perpetrators of accidents than in victims of accidents (Currie *et al.*, 1995) and Ray *et al.* (1992) showed that elderly patients taking TCAs equivalent to amitriptyline 125 mg/day were up to six times more likely to be involved in a road traffic accident than those taking non-TCA medication.

In order to prevent drug-induced accidents, it is essential that antidepressants do not cause sedation nor further impair psychomotor performance and

Table 1. The effects of fluoxetine 20 mg (Fluox) and dothiepin 75–150 mg (Dot) on a battery of tests in depressed patients. Standard deviations are given in parentheses

	Day 0	Day 7	Day 14	Day 28	Day 42
CFF (Hz)					
Fluox	29·8 (3·0)	30·7 (3·5)	31·6 (2·8)	31·4 (3·1)	31·8 (3·8)
Dot	28·9 (3·2)	29·3 (3·0)	29·3 (2·7)	29·8 (3·3)	29·4 (3·1)
CFF + artificial pupils (Hz)					
Fluox	27·5 (3·4)	29·3 (4·0)	29·6 (3·1)	29·5 (3·8)	30·4 (4·2)
Dot	27·5 (3·9)	28·0 (3·7)	27·7 (3·8)	28·2 (3·8)	27·6 (3·0)
SSN (score)					
Fluox	1·20 (0·39)	1·03 (0·18)	1·05 (0·21)	0·93 (0·15)	0·98 (0·23)
Dot	1·49 (0·54)	1·37 (0·56)	1·20 (0·35)	1·28 (0·45)	1·15 (0·42)
KIM (score)					
Fluox	13·0 (2·0)	12·2 (2·0)	12·5 (2·6)	13·7 (3·2)	13·8 (2·0)
Dot	11·1 (3·3)	12·0 (2·5)	11·8 (3·6)	11·7 (3·3)	12·0 (3·9)
CFQ (score)					
Fluox	50·9 (16·0)	48·3 (17·1)	46·9 (13·6)	41·7 (11·6)	42·1 (10·6)
Dot	55·8 (16·8)	54·3 (16·2)	50·5 (14·6)	46·8 (14·2)	47·1 (17·2)
LSEQ — Getting to Sleep (mm)					
Fluox	–	34·2 (13·5)	34·9 (12·2)	38·0 (18·4)	32·4 (10·8)
Dot	–	35·7 (17·3)	34·0 (14·7)	31·6 (11·9)	27·9 (13·8)
LSEQ — Quality of Sleep (mm)					
Fluox	–	43·0 (14·8)	39·2 (10·6)	36·5 (15·9)	35·0 (9·7)
Dot	–	37·0 (17·3)	36·7 (18·3)	29·8 (18·5)	28·7 (12·7)
LSEQ — Awakening From Sleep (mm)					
Fluox	–	44·1 (10·7)	44·6 (11·3)	41·7 (10·3)	43·6 (15·0)
Dot	–	57·8 (14·9)	51·1 (14·2)	46·8 (19·0)	47·6 (16·0)
MESS (mm)					
Fluox	–	48·2 (13·3)	45·6 (13·5)	48·2 (13·8)	50·6 (13·6)
Dot	–	51·5 (10·3)	47·1 (11·6)	47·6 (13·2)	50·3 (15·7)

CFF = critical flicker fusion; SSN = mental arithmetic ability; KIM = Kim's Game; CFQ = Cognitive Failures Questionnaire; LSEQ = Leeds Sleep Evaluation Questionnaire; MESS = Milford Epworth Sleepiness Scale.

cognitive function. Although there is little to choose between the two antidepressants used here in terms of clinical efficacy, the results from the present study demonstrate that fluoxetine 20 mg is beneficial to patients in terms of lack of impairment on objective measures of cognitive function. This is in contrast to the impairment of cognitive function found with dothiepin 150 mg. Of relevance is that impairments were found even after the first week of treatment with dothiepin 75 mg. As many as 88 per cent of prescriptions for TCAs are below the recommended dose (Donoghue and Tylee, 1996) and so it follows that patients who are prescribed these sub-therapeutic doses may be suffering adverse cognitive effects without the benefit of therapeutic efficacy.

CONCLUSION

Deteriorations in psychological functions not only reduce compliance to treatment regimens but also increase general accident liabilities. Furthermore, the increased sedation and compromised aspects of cognition found with TCAs such as dothiepin can cause an augmentation of these pre-existing features of untreated depression. The results from this study show that fluoxetine appears to be free from such detrimental effects on cognition.

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REFERENCES

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition. American Psychiatric Association, Washington, DC.

Austin, M. P., Ross, M., Murray, C., Carroll, R. E., Ebmeier, K. P. and Goodwin, G. (1992). Cognitive function in major depression. *Journal of Affective Disorders*, **25**, 21–30.

British Association for Psychopharmacology (1993). Guidelines for treating depressive illness with antidepressants. *Journal of Psychopharmacology*, **7**, 19–23.

Broadbent, D. E., Cooper, P. F., Fitzgerald, B. and Parkes, K. R. (1982). The cognitive failures questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology*, **21**, 1–16.

Currie, D., Hashemi, K., Fothergill, J., Findlay, A., Harris, A. and Hindmarch, J. (1995). The use of antidepressants and benzodiazepines in the perpetrators and victims of accidents. *Occupational Medicine*, **45**(6), 323–325.

Davies, G., Hamilton, S., Hendrickson, D. E., Levy, R. and Post, F. (1978). Psychological test performance and sedation thresholds of elderly dements, depressives and depressives with incipient brain change. *Psychological Medicine*, **8**, 103–109.

Donoghue, J. M. and Tylee, A. (1996). The treatment of depression: prescribing patterns of antidepressants in primary care in the UK. *British Journal of Psychiatry*, **168**, 164–168.

Fairweather, D. B., Kerr, J. S., Harrison, D. A., Moon, C. A. and Hindmarch, I. (1993). A double blind comparison of the effects of fluoxetine and amitriptyline on cognitive function in elderly depressed patients. *Human Psychopharmacology*, **8**, 41–47.

Fairweather, D. B., Patat, A., Rosenzweig, P., Curson, V. H., Dunmore, C., Dubruc, C. and Hindmarch, I. (1995). The psychomotor and cognitive effects of litoxetine in young and middle aged volunteers. *British Journal of Clinical Pharmacology*, **40**, 119–125.

Fairweather, D. B., Ashford, J. and Hindmarch, I. (1996). The effects of fluvoxamine and dothiepin on psychomotor abilities in healthy volunteers. *Pharmacology, Biochemistry and Behavior*, **53**, 265–269.

Fairweather, D. B., Dal Pozzo, C., Kerr, J. S., Lafferty, S. V. and Hindmarch, I. (1997). Citalopram compared to dothiepin and placebo: effects on cognitive function and psychomotor performance. *Human Psychopharmacology*, **12**, 119–126.

Freeman, H. L. and O'Hanlon, J. F. (1995). Acute and sub-acute effects of antidepressants on performance. *Journal of Drug Development and Clinical Practice*, **7**, 7–20.

Fuller, R. W. and Wong, D. T. (1987). Serotonin reuptake blockers in vitro and in vivo. *Journal of Clinical Psychiatry*, **7**(suppl. 6), 36S–43S.

Hale, A. S. and Pinninti, N. R. (1995). Critical flicker fusion threshold and anticholinergic effects of chronic antidepressant treatment in remitted depressives. *Journal of Psychopharmacology*, **9**(3), 216–224.

Hanks, G. W. (1984). The effects of amitriptyline and nomifensine on critical flicker fusion threshold in an elderly patient population. *Royal Society of Medicine International Congress and Symposium Series*, No. 70, 95–97.

Hindmarch, I. (1975). A 1,4-benzodiazepine, temazepam: its effect on some psychological parameters of sleep and behaviour. *Arzneimittel-Forshung (Drug Research)*, **25**(11), 1836–1839.

Hindmarch, I. (1997). A repeated dose comparison of three benzodiazepine derivatives (nitrazepam, flurazepam and flunitrazepam) on subjective appraisals of sleep and measures of psychomotor performance the morning following night-time medication. *Acta Psychiatrica Scandinavica*, **54**, 373–381.

Hindmarch, I. (1980). Psychomotor function and psychoactive drugs. *British Journal of Clinical Pharmacology*, **10**, 189–209.

Hindmarch, I. (1987). Three antidepressants (amitriptyline, dothiepin and fluoxetine) with and without alcohol compared with placebo on tests of psychomotor ability related to car driving. *Human Psychopharmacology*, **2**(3), 177–183.

Hindmarch, I. and Bhatti, J. Z. (1988). Psychopharmacological effects of sertraline in normal healthy volunteers. *European Journal of Clinical Pharmacology*, **35**, 221–223.

Hindmarch, I. and Kerr, J. S. (1994). Effects of paraoxetine on cognitive function in depressed patients, volunteers and elderly volunteers. *Medical Science Research*, **22**, 669–670.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*, **14**, 540–545.

Kerr, J. S., Fairweather, D. B., Mahendran, R. and Hindmarch, I. (1992). The effects of paroxetine, alone and in combination with alcohol on psychomotor performance and cognitive function in the elderly. *International Clinical Psychopharmacology*, **7**, 101–108.

Lord, S. R., Anstey, K. J., Williams, P. and Ward, J. (1995). Psychoactive medication use, sensori-motor function and falls in older women. *British Journal of Clinical Pharmacology*, **39**, 227–234.

Miller, W. R. (1975). Psychological deficit in depression. *Psychological Bulletin*, **82**, 238–260.

Paes de Sousa, M., Figuiera, M. L., Loureiro, F. and Hindmarch, I. (1981). Lorazepam and clonazepam in anxious elderly patients. *Royal Society of Medicine*

International Congress and Symposium Series, **No. 43**, 119–124.

Parkin, C., Kerr, J. S. and Hindmarch, I. (1997). The effects of practice on choice reaction time and critical flicker fusion threshold. *Human Psychopharmacology*, **12**, 65–70.

Parrott, A. C. and Hindmarch, I. (1980). The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations — a review. *Psychopharmacology*, **71**, 173–179.

Ramaekers, J. G., Muntjewerff, N. D. and O'Hanlon, J. F. (1995). A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *British Journal of Clinical Pharmacology*, **39**(4), 397–404.

Ray, W. A., Griffin, M. R. and Malcolm, E. (1991). Cyclic antidepressants and the risk of hip fracture. *Archives of International Medicine*, **151**, 754–756.

Ray, W. A., Fought, R. L. and Decker, M. D. (1992). Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *American Journal of Epidemiology*, **136**, 873–883.

Richelson, E. (1987). Pharmacology of antidepressants. *Psychopathology*, **1**, 1–12.

Rudorfer, M. V. and Potter, W. Z. (1989). Antidepressants, a comparative review of the clinical pharmacology and therapeutic use of the newer versus the older drugs. *Drugs*, **37**, 713–738.

Saletu, B. and Grünberger, J. (1985). Classification and determination of cerebral bioavailability of fluoxetine: pharmacokinetic, pharmaco-EEG and psychometric analyses. *Journal of Clinical Psychiatry*, **46**(3), 45–52.

Sherwood, N. and Kerr, J. S. (1993). The reliability, validity and pharmacosensitivity of four psychomotor tests. In *Human Psychopharmacology, Measures and Methods*, Vol. 4, Hindmarch, I. and Stonier, P. D. (Eds), John Wiley, Chichester, pp. 1–14.

Siegfried, K. R., Jansen, W. and Pahnke, K. (1984). Cognitive dysfunction in depression: difference between depressed and nondepressed elderly patients and differential cognitive effects of nomifensine. *Drug Development Research*, **4**, 533–553.

Song, F., Freemantle, N., Sheldon, T. A., House, A., Watson, P., Long, A. and Mason, J. (1993). Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *British Medical Journal*, **306**, 683–687.

Szabadi, E., Bradshaw, C. M. and Besson, J. A. O. (1976). Elongation of pause-time in speech: a simple objective measure of motor retardation in depression. *British Journal of Psychiatry*, **129**, 592–597.

Widlöcher, D. J. (1983). Psychomotor retardation: clinical, theoretical and psychometric aspects. *Psychiatric Clinics of North America*, **6**, 27–39.

Widlöcher, D. J. and Ghozlan, A. (1989). The measurement of retardation in depression. In *Human Psychopharmacology, Measures and Methods*, Vol. 2, Hindmarch, I. and Stonier, P. D. (Eds), John Wiley, Chichester, pp. 1–22.

Woodworth, R. S. and Schlosberg, H. (1958). *Experimental Psychology*. Methuen, London.

