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A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance

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1 The acute and subchronic effects of dothiepin 75–150 mg and fluoxetine 20 mg on critical fusion frequency (CFF), sustained attention and actual driving performance were compared with those of placebo in a double-blind, cross-over study involving 18 healthy volunteers. Drugs and placebo were administered for 22 days in evening doses. Fluoxetine doses were constant but dothiepin doses increased on the evening of day 8. Performance was assessed on days 1, 8 and 22 of each treatment series. Subjective sleep parameters and possible side effects were recorded on visual analogue scales on alternate treatment days.

2 Dothiepin reduced sustained attention on day 1 by 6.7% (95% confidence interval (CI): −12.0 to −1.3%) and CFF on day 22 by 1.1 (CI: −2.2 to −0.1) Hz. Fluoxetine reduced sustained attention days 1, 8 and 22 of treatment by 7.4, 6.7 and 6.5% respectively (CI: −11.3 to −3.6; −14.3 to −1.5 and −9.5 to −3.4). CFF decreased linearly over days during fluoxetine treatment and significantly differed from placebo on day 22 with 1.2 Hz (CI: −2.3 to −0.2). Neither drug significantly affected driving performance. Whilst receiving dothiepin, subjects complained of drowsiness on days 1–3 of treatment (mean rank 5.6; CI: 2.0 to 9.2) and slept 43 min longer (CI: 8.2 to 76.2). After receiving fluoxetine, they reported dizziness (mean rank 2.8; CI: 0.1 to 5.5), shakiness (mean rank 1.9 and 4.2; CI: 0.5 to 3.3 and 1.5 to 6.9), nausea (mean rank 3.5 and 4.1; CI: 0.1 to 6.9 and 0.9 to 7.4) and concentration problems (mean rank 2.4; CI: 0.4–4.9) in the second or third week of treatment. Spontaneously reported adverse events resembled the side effects recorded on visual analogue scales but differed less between drug treatments.

3 It is concluded that both drugs possess similar but apparently small potentials for impairing performance.

Keywords dothiepin fluoxetine driving performance psychometric performance sleep side effects

Introduction

Dothiepin belongs to the group of tricyclic antidepressants (TCAs) that achieve their antidepressant efficacy through non-selective inhibition of monoamine uptake. TCAs are also antagonists of cholinergic, adrenergic and histaminergic receptors which may cause cognitive impairment, postural hypotention and sedation. Fluoxetine belongs to a different class of antidepressant drugs, the selective serotonin reuptake inhibitors (SSRI). They increase the availability of serotonin in the synaptic cleft by inhibiting its neuronal reuptake. In clinical trials, SSRIs and TCAs have been shown to possess similar antidepressant activities. SSRIs generally produce less side effects compared with TCAs owing to a greater selectivity for serotonin. Consequently, SSRIs are generally regarded as behaviorally safe drugs, whereas TCAs are classified as

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impairing, particularly because of their sedative effects.

Though behavioral impairment depends primarily on the drug's intrinsic sedative activity, seen most clearly after initial doses, other factors such as pharmacological tolerance and accumulation can influence its persistence with repeated dosing. Tolerance to the sedative activity of antidepressants is generally recognized to diminish the acute impairing effects [1–3]. Accumulation occurs for most antidepressants when taken according to therapeutic dosing regimens. Dothiepin and its metabolite nordothiepin have elimination half-lives of 14–24 h and 34–45 h, respectively, and accumulate for 2 weeks before reaching steady state. Fluoxetine and its main metabolite norfluoxetine have elimination half-lives of 1–3 and 7–15 days. With multiple doses the drug accumulates for 35 days [4]. The possible influence of tolerance and accumulation on the immediate and late occurrence of side effects affecting performance should therefore not be ignored when comparing the effects of antidepressants on performance.

Little information concerning the acute and long-term effects of dothiepin or fluoxetine was available prior to this study. Single doses of dothiepin 50 mg impaired performance of healthy volunteers in several psychomotor and memory tests in one study [5] but not in another [6]. Several attempts have failed to show any impairing effects of fluoxetine 20 or 40 mg on the performance of volunteers [7, 8]. Multiple nightly doses of dothiepin, beginning at 75 mg and increasing to 150 mg after 1 week, generally had no effect on the performance of volunteers when measured on the 17th day [9]. They did however show a slight but significant impairment in a 'concentration' test. Allen *et al.* [10] administered a 40 mg dose of fluoxetine to healthy volunteers each morning for 1 week. It had no effect in any of a battery of psychomotor and memory tests. Fairweather *et al.* [11] reported that fluoxetine 20 mg day^{-1} elevated CFF in elderly depressed patients' beginning after 2 weeks of therapy and continuing for the subsequent month. The comparative antidepressant amitriptyline 75 mg day^{-1}, depressed CFF in a parallel group for 2 weeks, following which this measure returned to baseline. The difference in mean CFF between groups was always significant though their respective therapeutic responses were practically identical.

The current study was designed to measure and compare the acute and subchronic effects of dothiepin 75/150 mg and fluoxetine 20 mg on CFF, sustained attention and actual driving performance. Expectations based upon the studies mentioned above and similar studies with other TCAs and SSRIs [1, 3, 12, 13] were as follows. We hypothesized that dothiepin would cause mild impairment on day 1, with attenuation of the effect on day 8 as a result of tolerance. The impairment on day 22 would be greater if drug accumulation was the determining factor, and less if tolerance was the determining factor. We did not expect fluoxetine to cause impairment unless there was a hitherto unrecognized effect of accumulation of the parent drug or an active metabolite.

Methods

Subjects

Eighteen healthy volunteers, 10 males and 8 females, aged between 21–45 years, were recruited by means of newspaper advertisements. Initial screening was accomplished on the basis of replies to a medical history/driving experience questionnaire. Qualified individuals were physically examined and blood samples and a standard 12-lead electrocardiogram were obtained from each one. Standard blood chemistry and haematology tests were conducted on these samples. All volunteers were licenced drivers who had operated a vehicle for at least 5000 km/year during the previous 3 years. Exclusion criteria included the following: history of psychotic illness or drug abuse including alcoholism, history of cardiovascular disease including recent myocardial infarction, heart block or other cardiac arrhythmias, history of allergy to tricyclics, renal, hepatic, sensory or neurological disease or a history of serious disorders of these types, women of childbearing potential who were pregnant or lactating or failing to take medically acceptable contraceptive precautions, use of any psychoactive drug during the 4 weeks before entering the study, history of previous attempts at suicide.

The study was carried out in accordance with the World Medical Association's Declaration of Helsinki (Hong Kong Modification, 1989). It was approved by the standing Ethics Review Committee of the University of Limburg. Written informed consent was obtained from each subject prior to participation.

Experimental design and drug administration

Drugs and placebo were administered in separate 22-day series, according to a placebo controlled, 3-way, double-blind, cross-over design. Treatment orders were balanced and assigned to subjects by exhaustive random selection from six independent 3×3 Latin Squares. In the course of the three successive treatments, subjects' performance was tested after 1, 8 and 22 days of treatment. A minimum of 35 days elapsed between the end of one treatment series and the beginning of the next.

Daily doses of dothiepin were 75 mg during the first 8 treatment days and 150 mg from day 8 on. Fluoxetine was administered at a fixed daily dosage of 20 mg during the 22 treatment days. Dosing started the evening before the first test day. Drugs and placebo were always ingested at 21.30 h and 23.00 h by respective halves of the subjects. Blood samples were collected on day 8, 15 and 22 to determine mean plasma concentrations of both drugs by means of h.p.l.c. method.

Psychometric tests and driving

Subjects were individually trained to perform both driving tests and two laboratory performance tests over the course of a single day before entering the study. At day 1, 8 and 22 of each treatment series, subjects undertook a sequence of performance tests

scheduled at 12.00 h and 13.30 h for respective halves of the group.

Critical fusion frequency Critical fusion frequency (CFF) was measured in a computer-controlled system using a combination of the psychophysical Methods of Limits and Successive Approximations [14]. The subject was seated looking through an aperture of 2 mm (i.e. 'artifical pupil') into a visual tunnel that displayed a white light source in Maxwellian perspective. To begin, the computer alternatively increased and decreased the source flicker frequency (1:1 light/dark ratio) and the subject responded by pressing separate buttons whenever his perception changed from one state to the other. After three complete cycles, the approximate location of the subject's CFF was defined according to the Method of Limits. At that point, the programme identified two frequencies in 1 Hz steps above, two below and one at the suspected threshold. Each of the five stimuli were shown six times in separate, randomized presentations lasting 3 s each. The subject was instructed to withhold responding during the presentation period, and then give one of two responses indicating the perception of flicker or fusion. The proportions of each type of response were used to calculate intersecting linear functions in the frequency domain.

Sustained attention test This test has been extensively used in studies on human vigilance performance [15]. Subjects were seated in front of a computer screen displaying a circular arrangement of 60 dots simulating the second marks on a clock. Dots were briefly illuminated in clockwise rotation at a rate of one per second. Usually the rotation proceeded with a 6° 'jump'. Subjects were instructed that at rare, irregular intervals the target would proceed with a 12° jump by skipping one of the dots in the normal sequence. This 'double jump' was the signal to which subjects were required to respond by pressing a button. A response made within 4 s after the occurrence of a signal was registered as correct detection. A total of 30 signals were presented during the 45 min task. Ten signals occurred within each successive 15 min period. The distribution of the intersignal intervals (ISI) was skewed. It contained more short intervals than long intervals, ranging from 8 s to 7.20 min. Approximately 50% of the intervals fell in the range 8 s to 1 min, 25% in the range 1 to 2 min, 15% in the range 2–3 min and 10% in the range 3–7 min. The major dependent variables of the test were the number of Correct Detections (CD) and False Detections (FD). Because CD data were negatively and FD data positively skewed, they were subjected to conventional arcsin ($X' = 2 \arcsin X^{0.5}$) and logarithmic transformations, respectively, before statistical analysis [28].

Highway driving test This test has been used for drug screening purposes in The Netherlands since 1981 [16]. It was standardized the following year and has been applied in essentially the same manner ever since. The subject's task was relatively simple. He or she entered an 'actual' primary highway at the beginning of a 100 km circuit. He or she then proceeded to drive while attempting to maintain the vehicle at a constant speed (95 km) and steady lateral position between the delineated boundaries of the slower traffic lane. The subject was allowed to deviate from this procedure in order to pass slower vehicles travelling in the same lane. At an intersection halfway through the circuit, the subject drove off the highway and re-entered travelling in the opposite direction.

Lateral distance separating the vehicle and the left lane-line was continuously measured by an electro-optical device. Its signal was digitized at a rate of 4 Hz and stored on a computer disk for later editing and analysis. The off-line editing routine involved removal of all data segments that revealed signal loss, disturbance or the occurrence of passing manoeuvers. The primary measure is standard deviation of lateral position (SDLP). It measures continuous road tracking error during high speed travel on a highway.

The subject was accompanied by two investigators. A technician, whose task was to operate the equipment, was present in the rear passenger's seat. A licenced driving instructor was seated in the front passenger's seat with access to duplicate controls. His sole function was to ensure test safety. Subjects were informed that they would be asked to stop by the instructor if, in his opinion, their physical appearance or driving performance indicated the possibility of a control loss.

Car following test A preliminary version of this test was applied during a pilot study in 1985 [17]. The test begins with two vehicles travelling at 90 km h^{-1} in tandem separated by a distance of about 30 m. The leading vehicle's speed was automatically controlled and the subject controlled the speed of the following vehicle. Subjects were instructed beforehand that the purpose of the test was to measure their reactions to the movements of the leading vehicle. They were told to maintain an average headway of 30 m throughout the test. Furthermore they were informed to attend constantly to the leading vehicle since it might slow down then speed up at unpredictable times.

Headway was continuously measured by means of a DME 2000 optical distance sensor. This device was placed in the grill of the following vehicle and emitted laser signals in the direction of a reflection board that was mounted on the leading vehicle's towing bracket. Following emission, the laser signals were reflected from the board to the receiving end of the distance sensor. Distance was then deduced from the time lapse between transmission and receipt of the signal.

Speed of the leading vehicle was automatically regulated by a modified 'cruise control' system. It was activated by the investigator in the leading vehicle at the beginning of a test. In the initial phase and during intervals between manoeuvres the system maintained a constant speed of 90 km h^{-1}. To begin deceleration, the investigator activated a microprocessor that added to the speed signal which was interpreted by the cruise control as a deviation requiring a reduction in fuel flow. As the program continued, the microprocessor gradually ceased adding to the speed signal and began as gradually to subtract from it. When the vehicle's

actual speed reached the desired minimum the process was reversed until the leading vehicle recovered its original speed whereupon the microprocessor again became quiescent. In this manner the vehicle's speed described a sine function over time within each manoeuvre, dropping from 90 to 70 km h^{-1} and returning to 90 km h^{-1} within 50 s.

This manoeuvre was repeated five or six times. The entire test was conducted over a straight and level 18 km section of a secondary highway. The velocity of the leading vehicle was transmitted via telemetry to the following vehicle and stored on a computer disk along with the following vehicle's own velocity and headway. Speed signals collected during manoeuvres entered a power spectral analysis for yielding phase-delay between the vehicle's velocities at the manoeuvre cycle frequency (0.02 Hz). Phase-delay converted to a measure of the subject's average reaction time to the movements of the leading vehicle (RT), was then taken as the primary dependent variable from the car-following test. Headway (H) and standard deviation of headway (SDH) during deceleration/accelleration manoeuvres were taken as secondary dependent variables.

Subjective side effects and sleep

Side effects were measured on separate 100 mm visual analogue scales. The items included drowsiness, lack of concentration, memory disturbances, dizziness, nausea, weakness, headache, lack of coordination, nervousness and shakiness. Sleep was assessed using the Leeds Sleep Evaluation Questionnaire [18]. This questionnaire comprises a series of bipolar 100 mm visual analogue scale questions covering four aspects of sleep: ease of getting to sleep, quality of sleep, ease of awaking from sleep, and behaviour following waking. Estimated sleep duration was recorded additionally. All questionnaires were completed following waking on alternate days of treatment. For analytical purposes they were later averaged over days 1–3, 5–7, 9–11, 13–15 and 17–21. All adverse events reported spontaneously by the subjects or in response to questioning were recorded in a CRF.

Statistical methods

All dependent variables of the CFF, sustained attention and both driving tests were tested for overall effects of Drugs and Days and Drugs × Days using repeated measures, multivariate analysis of variance [19]. Sustained attention was also tested for the effects of Time on task and Drugs × Time on task. These were followed by univariate tests to compare treatment effects of dothiepin and fluoxetine with placebo.

Where the overall effect of Drugs or Drugs × Days was significant ($P \leq 0.05$), pairwise comparisons between drugs and placebo were performed using Fisher's protected LSD tests (one-tailed), to analyse differences on separate treatment days. In case of a significance, one-tailed, 95% confidence intervals (CI) of drug-placebo differences were calculated. If the overall Drugs × Days interaction was significant, Roy-Bargman stepdown F tests were conducted to check for linear or quadratic trends over days.

Leeds Sleep Evaluation Questionnaire and subjective side effects were analysed by means of the non-parametric Friedman test to detect an overall difference between treatments. These were followed by Wilcoxon's signed-rank test to compare the effects of drugs and placebo on separate treatment days. In contrast to Fisher's LSD tests, the latter were performed independently of the significant level of the overall difference between treatments. We used these different methods because within treatment series, subjective assessments were made every other treatment day and laboratory and driving assessments only on treatment days 1, 8 and 22. Because of the high number of observations, any overall test will accept H_0 if most of these observations are equal, although real differences between a few pairs of treatments may exist. The hypothesized side effects of dothiepin and fluoxetine were expected either shortly after acute dosing or towards the end of the drugs' accumulation phase. If so, these could easily go undetected if the remaining observations caused the overall test to be nonsignificant.

Results

CFF

Overall, mean CFF (Figure 1) values were not affected by the factors Drugs and Days. The interaction of Drugs × Days was highly significant ($F_{4,9} = 8.60$, $P = 0.004$). Trend analysis showed a significant linear decrement of CFF during treatment with fluoxetine as compared with placebo ($F_{1,12} = 5.02$, $P = 0.045$). Separate comparisons between drug treatments and placebo showed no differences on day 1 and 8. On day 22 both dothiepin and fluoxetine significantly

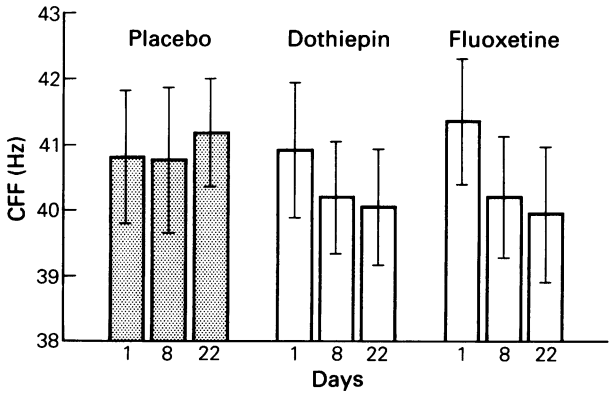

Figure 1 Mean (± s.e. mean) critical fusion frequency (CFF) in every treatment condition on treatment days 1, 8 and 22. On treatment days 8 and 22 mean (s.d.) plasma concentrations of dothiepin were 46.24 (52.48) and 71.70 (53.99) μg l^{-1} respectively. Mean plasma concentrations (s.d.) of fluoxetine and norfluoxetine were respectively 34.47 (14.41) and 42.47 (17.47) μg l^{-1} on day 8 and 57.83 (24.88) and 75.78 (28.29) μg l^{-1} on day 22 of treatment.

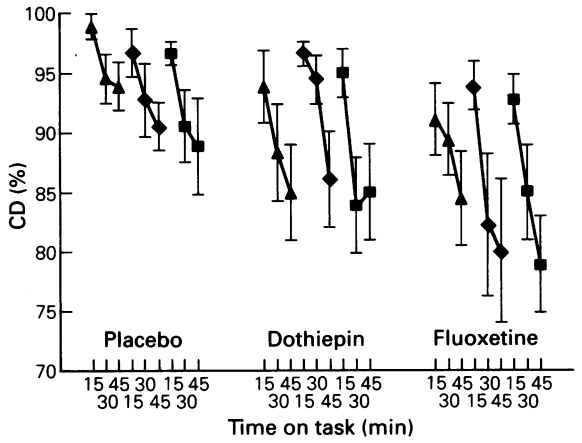

Figure 2 Mean (± s.e. mean) correct detections (CD) as a function of time on task on days 1 (▲), 8 (◆) and 16 (■) in every treatment condition. On treatment days 8 and 22 mean (s.d.) plasma concentrations of dothiepin were 46.24 (52.48) and 71.70 (53.99) μg l^{-1} respectively. Mean plasma concentrations (s.d.) of fluoxetine and norfluoxetine were respectively 34.47 (14.41) and 42.47 (17.47) on day 8 μg l^{-1} and 57.83 (24.88) and 75.78 (28.29) μg l^{-1} on day 22 of treatment.

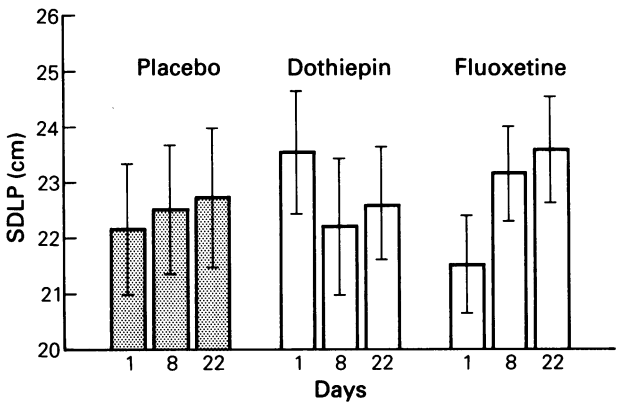

Figure 3 Mean (± s.e. mean) standard deviation of lateral position (SDLP) on treatment days 1, 8 and 22 in every treatment condition.

decreased CFF by 1.13 (CI: −2.14 to −12) and 1.24 Hz (CI: −2.25 to −0.23) respectively (t_{34} = 1.83 and 2.01; $P < 0.05$).

Sustained attention

MANOVA showed that CD (Figure 2) was significantly affected by Drugs ($F_{2,11}$ = 4.22; P = 0.044), Time on task ($F_{2,11}$ = $P < 0.005$) but not by Days and Drugs × Days or Drugs × Time on task. Univariate tests showed a significant main effect of fluoxetine on CD ($F_{1,12}$ = 9.09; P = 0.011) as compared with placebo. The effect of dothiepin approached significance ($F_{1,12}$ = 3.51; P = 0.086). The effect of Time on task was significant during both treatments ($F_{2,11}$ = 8.46 and 11.05; $P < 0.006$). Since no effects of Drugs × Time on task were found mean CD averaged over time were used for separate drug-placebo comparisons. They revealed that fluoxetine significantly decreased CD by 7.41 (CI: −11.33 to −3.56), 6.67 (CI: −14.27 to −1.50) and 6.48% (CI: −9.45 to −3.44) on days 1, 8 and 22 days of treatment respectively (t_{34} = 2.26, 3.11 and 1.97, respectively; $P < 0.05$). Dothiepin significantly decreased CD after day 1 of treatment by 6.67% (CI: −11.96 to −1.27, t_{34} = 2.54; $P < 0.05$). FD was not affected by any factor.

Driving tests

One subject was stopped by the driving instructor during the Highway Driving Test on day 8 of treatment with placebo after having completed 70% of the ride. No significant effects were found on any parameters in either the Highway Driving or the Car-Following Test. Nonetheless, mean SDLP were in opposite directions during dothiepin and fluoxetine treatment conditions (Figure 3).

Subjective sleep estimations

No significant overall differences between conditions were found for any sleep parameter. Differences in sleep duration approached significance (χ^2 = 22.68, df = 14, P = 0.066). Separate drug-placebo comparison revealed increased difficulty awakening during days 1–3 of dothiepin (Z = −2.03; P = 0.043) and days 17–21 of fluoxetine (Z = −2.30; P = 0.02) treatment. However mean differences from placebo were very small (−0.7 and −0.5%) and unlikely of practical relevance. Subjects estimated that duration of sleep on days 1–3 of dothiepin treatment was approximately 43 min (CI: 8.2 to 76.2) longer (Z = −2.30; P = 0.02) than during placebo treatment. Getting to sleep, quality of sleep, and behaviour following waking during treatment with fluoxetine or dothiepin did not differ from placebo.

Subjective side effects and adverse events

The major subjective side effects are summarised in Table 1. Overall, side effects did not significantly differ between treatments. Separate drug-placebo comparisons indicated that subjects felt more drowsy during days 1–3 of dothiepin treatment. Reported side effects increased throughout fluoxetine treatment. Relative to placebo, on days 9–11 subjects reported greater shakiness, and on days 13–15, more nausea. From day 17 on subjects reported more shakiness, nausea, concentration problems and dizziness after fluoxetine, than following placebo.

In total, 119 complaints were spontaneously reported by subjects. In 23 cases it was judged that they were not treatment related. Among them, headache (7 subjects) and symptoms of the common cold (5 subjects) were the most frequent. In 96 cases, complaints were judged to be treatment related. Treatment related adverse events are listed in Table 2. Adverse events were frequently reported by only one or two subjects per treatment. The type of adverse events differed among treatments. During fluoxetine treatment, adverse events reported by more than two subjects were: nausea (6 subjects), headache (5 subjects), fatigue and concentration problems

Table 1 Major results from Wilcoxon signed ranks test of subjective side effects during treatment with dothiepin and fluoxetine. Mean (drug-placebo), standard error, mean rank of differences, 95% confidence intervals, frequencies of positive and negative differences or ties and Z ratios are shown with the associated *P* values

	Days	*Mean (%)*	*s.e. mean*	*Mean rank*	*95% CI*	*>0*	*<0*	*ties*	*Z*	P
Dothiepin										
Drowsiness	1–3	5.08	2.10	5.61	2.04–9.19	11	5	2	−2.45	0.014
Fluoxetine										
Shakiness	9–11	7.03	3.39	1.89	0.46–3.32	7	1	10	−2.38	0.017
	17–21	7.26	4.00	4.17	1.45–6.88	11	2	5	−2.62	0.008
Nausea	13–15	2.69	1.58	3.50	0.13–6.87	10	4	4	−1.97	0.048
	17–21	2.59	1.19	4.16	0.93–7.39	11	3	4	−2.29	0.014
Concentration difficulty	17–21	6.35	4.71	2.44	0.42–4.85	8	3	7	−1.96	0.050
Dizziness	17–21	6.91	3.91	2.83	0.13–5.54	9	3	6	−2.00	0.046

(4 subjects). During dothiepin treatment they were: dry mouth (6 subjects), headache (5 subjects), shakiness (4 subjects), fatigue, concentration problems and difficulty waking up (3 subjects). During placebo treatment there were fewer reports of adverse events. Headache (6 subjects) and fatigue (3 subjects) were most common.

Blood assays

Mean (s.d.) plasma concentrations of dothiepin on treatment days 8, 15 and 22 as determined by an h.p.l.c. method were 46.2 (52.5), 76.5 (80.1) and 71.7 (54.4) $\mu g\ l^{-1}$ respectively. Mean plasma (s.d.) concentrations of fluoxetine and its metabolite norfluoxetine were respectively 34.5 (14.4) and 42.5 (17.5) $\mu g\ l^{-1}$ on day 8, 51.1 (19.1) and 68.7 (25.9) $\mu g\ l^{-1}$ on day 15 and 57.8 (24.9) and 75.8 (28.3) $\mu g\ l^{-1}$ on day 22 of treatment.

Table 2 Spontaneously reported adverse events in every treatment condition and their rate of occurrence

	Placebo	*Dothiepin*	*Fluoxetine*
Pruritis	1		
Dry mouth	2	6	
Dyspepsia	1		1
Borborygmi	1		1
Shakiness	2	4	2
Fatigue	3	3	4
Headache	6	5	5
Weakness		1	
Nervousness	1	1	1
Concentration problems		3	4
Dizziness	1	1	2*
Nausea	2	1	6
Abdominal pains			2
Memory lapse			2
Diminished libido			1
Parethesia			1
Diarrhoea		1	
Insomnia			2
Muscle tension			1
Difficulty waking up	2	3	
Rash on abdomen	1		
Palpitations		1	
Perspiration	1	1	1
Drowsiness		1	1
Depressed			1
Coordination problems			1
Difficulty falling asleep	1		1
Total complaints	25	32	39
Total subjects complaining of any symptoms	11	13	14

*In this case the same complaint was reported twice during a single treatment period by the same subject. All other complaints were reported once per treatment by different subjects.

Discussion

The 3-week treatment periods in this study appear to be the longest ever undertaken by healthy volunteers for assessing antidepressant drug effects on performance. Moreover the doses of dothiepin and fluoxetine were those normally used for treating depressed patients. Higher doses of both drugs are occasionally prescribed in clinical practice but only to patients who fail to respond to those given in the present study. Thus these treatments closely approximated those of depressed patients up until the time when dothiepin and fluoxetine plasma concentrations closely approach steady-state. Performance changes measured in any of the test should therefore indicate drug properties of relevance to patients during their first 3 weeks of treatment. Drug effects on the performance of healthy volunteers would be only difficult to generalize to patients if their exposure extended beyond the therapeutic latency period, since the drug's net effects on them could then be predominantly determined by a therapeutic response.

The results did not entirely confirm expectations. Dothiepin's effects on performance were more or less as expected. The drug decreased sustained attention on day 1 and CFF on day 22. It had no significant effects on performance on day 8. Fluoxetine's effects were more than expected and comparable in magnitude with those of dothiepin. A reduction in sustained attention was seen throughout treatment. CFF decreased linearly over days and differed significantly from placebo on day 22. Side effects differed between drug treatment conditions, relative to placebo. Dothiepin increased the feeling of drowsiness and lengthened sleep duration. Fluoxetine increased feelings of shakiness, nausea and dizziness and decreased concentra-

tion. Spontaneously reported adverse events followed the same pattern as recorded side effects but the former were less clearly divided between drug conditions. Together, these results indicate that dothiepin and fluoxetine possess about the same modest potential for impairing performance and produce about the same incidence of side effects when taken in these doses over a 3-week period.

Neither drug had any significant effect on driving performance. Mean SDLP suggested an initial dothiepin effect that diminished over the treatment period and the opposite for fluoxetine. The suggested effects were small in both cases. The failure to find any significant drug effects on driving performance indicates that the use of either dothiepin or fluoxetine would not be expected to seriously compromise patients' abilities to undertake such activities in real life.

This is not to say that either drug would never affect any patient's performance in an untoward manner. Dothiepin was given to the subjects according to the manufacturer's recommendation in evening doses. The reason for that recommendation is that dothiepin possesses sedative properties. It would almost certainly cause sedation and performance impairment if taken over the day, at least before the occurrence of tolerance mitigates this effect. Tolerance was apparently sufficient in the present study to largely attenuate the drug's acute effects on sustained attention by the eighth day of treatment. Escalating the dothiepin dose from 75 to 150 mg at night on the same night may have been followed by some residual sedation on day 9 and subsequently, but testing was not scheduled after the dose escalation. We cannot exclude the possibility that the subjects reacted to it adversely but no sign of this was observed in their reported side effects which did not differ between dothiepin and placebo conditions on days 9–11. Except for a significant difference in CFF between these conditions, no sign of a high dose effect was seen in tests given on day 22. These results do not contradict the commonly held belief that dothiepin is a sedating antidepressant, nor that under some conditions it can impair performance. Rather they indicate that the drug's sedating activity can be controlled so as to minimize its effects on performance by gradually increasing therapeutic dosing regimen with nocturnal drug administration.

Fluoxetine was also given at night. Though not contrary to its manufacturer's recommendation, this procedure is contrary to the usual practice of administering the drug in the morning. This is normally done to avoid disturbing patients' sleep since insomnia is a relatively frequent fluoxetine side effect in clinical practice [20, 21]. Nonetheless, the subjects' sleep did not seem unduly affected by nocturnal fluoxetine administration: on the average, their total estimated sleep duration was about the same as after placebo and only two individuals reported insomnia on one occasion apiece as an adverse event. It seems unlikely therefore that sleep disturbance was the factor responsible for the significant fluoxetine effects on performance in this experiment. Rather, those effects occurred in spite of the fact that they were measured at times other than when the drug's plasma concentrations were highest after repeated doses. If fluoxetine had been given in morning doses, one might expect to measure more rather than less impairment.

A methodological point should be made concerning the demonstration of a drop in mean CFF that occurred during fluoxetine treatment. Several investigators have reported the opposite, a rise in CFF, after single and multiple doses of fluoxetine and other SSRIs [11, 13, 22]. The apparent contradiction may be resolved by noting that whereas subjects viewed the flickering light through an artificial pupil (2 mm) in the present study, no such device was employed to control the luminance falling on the retina in previous studies showing SSRI effects on CFF. The reason why this is important is that drugs that affect serotonergic neurotransmission can cause either pupillary miosis or mydriasis which can, respectively, lower or raise CFF according to the Ferry-Porter Law [23].

The influence of serotoninergic drugs on pupillary diameter was first noted by Millson *et al.* [24] and confirmed by Danjou *et al.* [25] who respectively gave subjects single doses of 5-HT_2 receptor agonists; ICI 139 369 and ritanserin, respectively. The former investigators directly measured subjects' miosis after the drug while the latter inferred it from a large drop in subjects' CFF unaccompanied by any changes in their performance in a battery of highly sensitive psychomotor tests. Theoretically, SSRIs should have the opposite effect on pupillary diameter by increasing serotonin concentrations at post-synaptic receptors known to exist in the ciliary muscles [26]. This was confirmed in subjects treated for 7 days with paroxetine 20 mg day^{-1} [27]. Mydriasis occurred both after the first dose and at the end of the series as the subjects were tested while viewing a traffic film. The average degree of mydriasis they experienced on both occassions was 2 mm or about 50% of the total range of pupillary diameters. Had these subjects CFFs been measured, the same change in pupil diameter would almost certainly have led to elevated values. This finding underscores the need for controlling pupillary diameter when measuring serotonergic drug effects on CFF. When this is done, as in the present experiment, CFF changes can be taken as an index of the drug's central activity. Without this control, CFF changes under the influence of serotonergic drugs might not be a valid index of their central effects.

H.p.l.c. analyses showed that mean plasma concentrations of both drugs rose throughout treatment. On day 22, some drug effects on performance could still be found and some side effects persisted. It seems appropriate for future research on antidepressants to concentrate more on persistant or late-developing effects that influence performance and their correspondence with drug accumulation.

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