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An Investigation of the Potential Interaction Between Paroxetine and Pindolol: Pharmacodynamic Assessment in Healthy Male Volunteers.

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Abstract

The increasing incidence of cardiovascular disease and subsequent depressive symptoms has highlighted the potential for concomitant treatment of β-blockers and antidepressant medication. It has been noted that both types of medications are associated with decrements in psychomotor and cognitive performance. Thus, the aims of this study were to characterise the psychomotor performance characteristics in a group of healthy male volunteers who received a single oral dose of paroxetine 10 mg (an SSRI), pindolol 5 mg (a β-blocker), a placebo and a combination of paroxetine and pindolol. It was hypothesised that concurrent administration of single doses of paroxetine and pindolol will result in a significant decrease in psychomotor performance.

The study was conducted as a double blind, placebo controlled, four-way cross over study. To assess the psychomotor effects of the administered drugs, the participants were required to perform the critical flicker fusion frequency task (CFF), choice reaction time task (CRT), Bond-Lader visual analogue scale of mood (VASM) and the digit-symbol substitution test (DSST). A significant effect between condition and time for CRT ($F(3)= 7.918$, $p<0.001$), CFF ($F(3)= 2.459$, $p<0.05$), and DSST($F(3)= 2.488$, $p<0.05$) tests was found, which indicated that a decrement in psychomotor performance over time had occurred after concurrent administration of paroxetine and pindolol together. The explanation for the drug-drug interaction is not clear from this study, but may be due to one or more factors, such as a pharmacokinetic or pharmacodynamic interaction.

Keywords

Antidepressants, paroxetine, beta-blockers, pindolol, psychomotor effects, cognitive effects

AN INVESTIGATION OF THE POTENTIAL INTERACTION BETWEEN PAROXETINE AND PINDOLOL : PHARMACODYNAMIC ASSESSMENT IN HEALTHY MALE VOLUNTEERS

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Introduction

Depression is a commonly diagnosed psychological disorder. It is estimated to affect 3-4% of the adult population at some point in their lives (Brick & Erickson, 1998). Affecting individuals of all ages, depression may be detected in patients who display changes in their social functioning, motor behaviour, emotional states, cognition and motivation. It is suspected that the onset of depression is due to excess neurotransmitter receptor sites, thus leading to intrinsically lower levels of specific monoamine neurotransmitters, namely serotonin (5-HT) and noradrenaline (NA) which normally contribute to producing an overall sense of well being (Nevid, Rathus & Greene, 2000). Therefore, in order to inhibit the reuptake and increase the release of NA and 5-HT, antidepressants work by decreasing the number and sensitivity of receptors, thus decreasing signs of depression in patients (Carvey, 1998). Several classes of antidepressants exist, each increasing neurotransmitter levels via different mechanisms. Selective serotonin-reuptake inhibitors (SSRIs), one of the newer, more potent and less toxic treatments, exert their effects by increasing levels of 5-HT specifically *in vitro* and *in vivo* (Leonard, 1992; Kerr, Fairweather, Mahendran & Hindmarch, 1992).

Cardiovascular disease has also increased in incidence in recent years. As a result of improved medical treatments for these disorders there is an increased incidence of survival after myocardial infarction and stroke. Beta-adrenergic receptor antagonists (β-blockers) are commonly prescribed to treat patients after myocardial infarction and also individuals with hypertension, arrhythmias and angina, and work to decrease the heart rate and blood pressure in individuals (Chavey, 2000; Smith & Ball, 2000). They are also currently used to treat other conditions such as performance anxiety, migraines and hyperthyroidism (Yudofsky, 1992).

Individuals suffering from cardiovascular disease quite often present with symptoms of depression following a myocardial infarction (Raskin, Veith, Barnes & Gumbrecht, 1982). Between 18%-60% of patients suffering coronary artery disease (CAD) also suffer from depression (Musselman, Evans and Nemeroff, 1998).

Furthermore symptoms of depression are both a risk factor contributing to the development of cardiovascular disease and influence survival following myocardial infarction (Frasure-Smith, Lesperance and Talajic, 1993). Co-occurrence of depression and heart disease is likely to be a relatively common presentation with both disorders requiring medication (Avorn, Everitt and Weiss, 1986). A drug-drug interaction, with adverse consequences, in such circumstances is a distinct possibility. This may occur by a variety of central and peripheral mechanisms.

Central Mechanisms of Interaction

The central nervous system plays a key role in coordinating sensory and motor systems, which in turn drive psychomotor performance behaviour (Hawley, McPhee, Quick & Smith, 1997). A decrement in functioning of psychomotor behaviours has been noted in individuals suffering psychological disorders such as depression. Administration of psycho-active drugs such as antidepressants can further exacerbate impairment of psychomotor performance. Furthermore, β-blockers directly affect central adrenergic activity and as a result are associated with central nervous system (CNS) effects such as insomnia, depressed mood, vivid dreams, cognitive impairment and sedation (Waal, 1967; Yudofsky, 1992).

Psychomotor performance encompasses skills and responses such as measures of central arousal, vigilance, reaction times and motor coordination. Tests such as critical flicker fusion (CFF) and choice reaction time (CRT) have been designed to test for differences on these parameters as a result of sedative drug administration. Drugs that impair psychomotor performance are said to be psychomotor toxic as they impair the organisational processes of the CNS, which works to integrate the sensory and motor systems (Hawley, McPhee, Quick & Smith, 1997). Antidepressants have been shown to impair psychomotor performance in healthy volunteers. For example, the tricyclic antidepressant (TCA) dothiepin had a sedative effect and impaired performance on psychomotor tests involving measures of CNS arousal, sensorimotor performance, short-term memory and psychomotor function in healthy volunteers (Fairweather, Ashford and Hindmarch, 1996).

Antidepressants impair visual selective attention as measured by delayed responses to peripheral and centrally placed targets in tracking tests (Weinstein,

Wilson, Bailey and Nutt, 1996; Smiley, 1987). This pattern of a decrement noted in detection of peripheral targets is replicated in individuals suffering Parkinson's disease. The SSRI paroxetine may be associated with an impairment in psychomotor performance, which is dose dependent (Kerr, Fairweather, Mahendran and Hindmarch, 1992; Hawley, McPhee, Quick and Smith, 1997; Dechant and Clissold,1991). As measured by visual analogue scales, paroxetine may lead to feelings of drowsiness. Furthermore, paroxetine associated feelings of fatigue, dizziness and visual disturbances, suggest such events may be associated with impairments in psychomotor performance (Hawley, McPhee, Quick & Smith, 1997; Preskorn, 1997).

The effects of the beta-blocker propranolol on psychomotor functioning have been investigated (Broadhurst, 1980a; 1980b; McDevitt, 1985; Betts et al.,1985), Decreased complex reaction times followed propanolol administration. However, this psychomotor performance impairment was dose dependent. McDevitt (1985) also indicated that lower doses of propranolol (40mg) have a greater effect on impairment of psychomotor performance than higher doses (320mg), that may reduce β-blockade effects on psychomotor functioning. Some of the main side effects elicited by beta blockers, such as lowered blood pressure, increased sedation and interference with the body's adrenergic stress response, all of which decrease sensory/cognitive awareness and reactions, may play key roles in the impairment of psychomotor behaviours (Dimsdale, Newton & Joist, 1989; Glaister, 1981). Furthermore, propranolol has been documented to be responsible for changes in mood and even the onset of hallucinations (Glaister, 1981; Hinshelwood, 1969).

Peripheral Mechanisms of Interaction

Detrimental effects of pharmacokinetic drug interactions of SSRIs as a consequence of their effects on the metabolism of other drugs have been reported (Richelson, 1997). SSRIs are extensively metabolised and detoxified by cytochrome P450 (CYP) isoenzymes of the liver, however they also inhibit these enzymes. One of the main isozymes involved in the metabolism and clearance of psychoactive drugs is CYP2D6. Inhibition of CYP isoenzymes and CYP 2D6 in particular is the leading cause of drug-drug interactions, and since enzyme inhibition is dose-dependent, higher dosages result in greater inhibition. As a result of this inhibition, metabolism of other

drugs in the liver such as β- blockers (which are also metabolised by CYP2D6) would also be affected (Preskorn, 1997). Occurrence of increased drug concentrations indicates that potentially serious interactions may take place e.g., enhanced side effects of either or both drugs.

It has been well documented that paroxetine is a potent inhibitor of the CYP2D6 isoenzyme, and thus, of its own metabolism (Hiemke & Hartter, 2000; Jeppesen et al, 1996; Lane, 1996; Preskorn, 1997; Richelson, 1997). During chronic administration increased blood concentrations of paroxetine may occur resulting in increased side effects (Hiemke & Hartter, 2000).

Specific central interactions occur when β-blockers such as pindolol are co-prescribed with SSRI antidepressants like paroxetine. This is due to their effectiveness in augmenting the onset of action and efficacy of SSRIs through the enhancement of serotonergic transmission (Bordet, Thomas & Dupuis, 1998). Both drugs compete at 5-HT receptors blocking reuptake to increase release, with studies now indicating that pindolol has 5-HT1A receptor antagonistic properties along with its beta blocker activity ((Haddjeri, de Montiigny & Blier, 1999; Tome, Isaac, Harte & Holland, 1997; Zanardi et al, 1997). The readiness with which drugs cross the blood brain barrier further indicates ways in which clinically relevant drug-drug interactions may occur. Pindolol, along with paroxetine is lipophilic in nature, thus penetrating the blood brain barrier very efficiently and extensively. There is convincing evidence for a central action and the suggestion of more cognitive side effects such as sedation or lethargy occurring than noted in non-lipophilic sedative drugs or if the drugs were taken individually (Dimsdale, Newton & Joist, 1989; Gengo, Huntoon & McHugh, 1987).

Since both SSRIs and beta-blockers each significantly contribute to side effects relating to psychomotor impairment and are dose dependent, co-administration may further increase impairment of psychomotor performance due to the interactions occurring either in the liver (metabolic) or at 5-HT receptor sites (central). Few studies have been conducted on interactions between antidepressants and β-blockers, and the potential effect they may pose to psychomotor performance skills, notably driving a motor vehicle. Based on studies investigating the individual contributing effects of antidepressants and beta-blockers on impairment in psychomotor performance, it is

suspected that adverse effects could occur if the two treatments were taken simultaneously.

Aim

The aims of the current investigation were to characterise the psychomotor performance effects in a group of healthy male volunteers who received single oral doses of paroxetine, pindolol and placebo alone and together.

Hypothesis

Based on previous studies indicating the known metabolic profile of the SSRI antidepressant paroxetine and β-blocker pindolol, it was hypothesised that the concurrent administration of single paroxetine doses of 10mg and single pindolol doses of 5mg would result in a significant decrease in psychomotor performance.

Method

Participants

Healthy male volunteers aged 18-45, and a weight range within 15% of the mean weight considered ideal for height were recruited among the general public by recruitment posters. Volunteers must have presented with normal findings from pre-study laboratory tests and pre-study physical evaluations and have serum levels of ALAT, ASAT, gamma-GT and creatinine under the upper normal laboratory limit. As part of the selection procedure to determine volunteer suitability and eligibility for the study, completion of a battery of screening questionnaires covering emotional status and medical histories was required. These screening questionnaires comprised the General Health Questionnaire (GHQ), Life History Questionnaire and Subject Questionnaire. Exclusion criteria were psychiatric or medical disturbances. Once volunteers have been deemed suitable candidates for study participation, a written Statement of Informed Consent document was read and signed and participants were provided with a Participant Information Sheet and given the opportunity to ask questions regarding the study.

Volunteers were required to present as drug free, agree to refrain from taking any concomitant medications or recreational drugs throughout the testing period, and from consuming alcohol, caffeine or tobacco within 48hrs prior to testing. Women were not

included in the study due to the possible effects of menstruation. Ethics approval was obtained from the Drug Trials Sub-Committee and the Human Research Ethics Committee at Austin & Repatriation Medical Centre, Heidelberg. Volunteers were not naive to the aims and but were naive to the hypothesis of the study. At any time during the study, for any reasons, volunteers were free to withdraw. All information, including coded participant data collected during the course of the study was kept in a secured locked filing cabinet and stored under a password protected computer data base.

Materials

To test pharmacodynamics, a battery of four psychomotor and cognitive functioning tasks was administered to participants. The test battery included The Leeds Psychomotor Performance Tester, comprising Critical Flicker Fusion (CFF) and Choice Reaction Time (CRT) tasks. Subjective tasks included the Digit Symbol Substitution Test (DSST) and the Bond-Lader Visual Analogue Scale of Mood and Alertness (VAS) measuring intellectual ability (VASI), physical ability (VASP) and tranquillisation effects (VAST).

Pharmacodynamic Assessment: Tasks of Measurement and Materials

In order to assess psychomotor function and vigilance, all tests were specifically sensitive to the effects of sedative drugs. If there was to be an effect exhibited at the administered dose level, these tests were the most appropriate tests to indicate such an outcome. The Leeds Psychomotor Tester is an apparatus used to perform the CFF and CRT tests in healthy controls or patient samples (Hindmarch, 1994).

1. Critical Flicker Fusion (CFF)

Results obtained in the CFF task indicate central cortical arousal and alertness. A flashing red electroluminescent diode with varying frequency is presented to subjects. The speed of central nervous system information processing during the increasing frequency phase is measured via the threshold frequency (Hertz) or fusion frequency, the point at which volunteers perceive a flashing light to become a continual illumination (Hawley, McPhee, Quick & Smith, 1997). The volunteers are then required to indicate their flicker threshold, the point at which the flickering is again detected during the decreasing frequency phase. Both thresholds are constant amongst subjects. The test ran for three minutes and the result was evaluated based on the mean

value for six alternating increasing and decreasing phases. Psychomotor impairment was indicated via decrements within CFF threshold detection. Certain rules were applied during the course of the CFF test to ensure standard conditions were met:

(1) since physical characteristics of the stimulus (light source intensity, light/darkness ratio) vary from one apparatus to the next, the same apparatus was used throughout the study;

(2) artificial lighting conditions were kept constant in the test room;

(3) phonic insulation was adequate;

(4) volunteers wore corrective lenses if they had refraction disorders;

(5) a constant distance of 30cm was kept between the subject's eyes and the light source.

2. Choice Reaction Time (CRT)

The CRT task measures the mean reaction times to stimuli via the speed of the subject's motor response (milliseconds) to a specific visual sensory cue. Volunteers are required to keep the index of their dominant hand on a switch, which they then quickly activate when a red diode is illuminated, whilst ignoring simultaneous and random presentation of twenty-one other misleading cues, with intervals of 1 to 3 seconds between stimuli (Hawley, McPhee, Quick & Smith, 1997). The test took about one minute to complete. Psychomotor impairments were indicated via increased reaction times.

3. Bond-Lader Visual Analogue Scale of Mood and Alertness (VAS)

The Visual Analogue of Scale Mood and Alertness (VAS) questionnaire is a subjective measure of 16 analogue scales comprising three factors to assess personal experiences/feelings of self-rated alertness (physical-VASP), self-rated calmness (tranquillity-VAST) and self-rated contentment (intellect-VASI). This test has proven sensitivity to a wide range of compounds (Bond & Lader, 1974).

4. Digit Symbol Substitution Test (DSST)

The DSST is a pencil/paper test that is administered to assess the number of correct digit/symbol substitutions the volunteer correctly allocates in a limited time 30 seconds. A legend of symbols with an allocated letter is displayed, and volunteers are

required to substitute as many symbols as possible with the correlated letter. Results were indicative of the number of substitutions, along with the number of correct substitutions (Wechsler, 1955). Thus, impaired individuals reflected increased errors and low substitution scores.

Study Design and Procedure

Drug treatments were administered according to a double blind, four-way, crossover trial design. Volunteers were given four experimental doses of placebo, pindolol (Visken 5mg tablets), paroxetine (Aropax 10mg tablets) and a combination of pindolol/paroxetine. All volunteers received each of the four oral doses in a counter-balanced order.

Once volunteers had satisfied selection criteria for the study, they were then required to travel to the testing venue at the Department of Psychiatry, Austin and Repatriation Medical Centre in Heidelberg, arriving 8am, having fasted after midnight the previous night and having not consumed breakfast on each day of study. A light breakfast and lunch were provided for all volunteers. Four one-day treatment sessions were scheduled over a four- week period, with a wash-out period of 7 days between testing days. Each session lasted approximately 9 hours, during which volunteers were required to participate in the four psychomotor tests.

Volunteers were then familiarised with the standard psychomotor performance tasks until a plateau in performance level was reached. The baseline data for each test was collected at the commencement of each session, half an hour prior to drug administration. Testing of psychomotor performance was then repeatedly assessed following randomised administration of drug doses of either placebo, pindolol (5mg), paroxetine (10mg) or pindolol/paroxetine at intervals 30 mins after breakfast and prior to dosing, then 2, 4 and 8 hours after dosing. Once the final test had been completed at the end of each day, volunteers were given taxi vouchers to return home until required for the next session. Subjects were not permitted to drive home under any circumstances. Following completion of 4 days of testing, a subsequent medical examination was conducted in order to determine that volunteers had no lasting effects from the drugs administered.

Safety

Prior to acceptance and within 72 hours following completion of the current study, haematology, blood biochemistry and urinalysis tests were performed on all individuals. Depending on clinical indications, tests were also performed outside of these given time frames.

Any abnormalities detected by volunteers or the investigator defined as adverse events, which encompass clinical symptoms/signs that may develop or worsen under treatment, as indicated in laboratory tests or in vital signs detected during routine evaluations, were promptly reported. An adverse event form was on hand to report such occurrences, whereby severity was to be evaluated on a three-point scale (1=mild; 2 = moderate; 3 = severe). The causal relationship between the event and the study drug would have been classified as excluded or not excluded.

Statistical Data Analysis

The current study implemented a randomised, double blind, placebo controlled, four-way crossover design. A four-factor repeated measures analysis of variance (ANOVA) statistical testing procedure with one grouping factor (psychomotor performance following sedative drug administration) and two repeated factors (treatment and time of testing) was used for the main analysis. Data was subjected to within-subject ANOVA. The completed model included psychomotor task, drug treatment and time of testing. Prior to analyses, the Visual Analogue Scale of Mood and Alertness (VAS) was log transformed in order to account for non-normal distribution of scores. Statistical testing for all analyses was conducted at alpha confidence levels of 0.05 and nomograms relating power, sample size and effect size for a two tailed test were available. At this level of significance and with a difference of 40% for the overall mean in psychomotor tests, it was calculated that a minimum of sample size of 12 subjects were required to detect this difference with a power of around 80%. Such a sample size also provided a statistically significant difference with a low probability of a Type II error.

The independent variables were the drug dosage amounts administered to participants during the course of testing, and the times at which tests were conducted (-0.5, 2, 4, and 8 hours). Dependent variables were the differences between the test

values for each of the four tasks at 2, 4 and 8hrs following drug administration and baseline performance.

Mauchly's tests of sphericity were used to test for normal variance. If violations within sphericity tests were detected, a Greenhouse-Geisser correction was used. Pair-wise comparison analyses were then conducted in order to determine where the differences lay.

Results

Critical Flicker Fusion

The CFF thresholds for each participant under each condition at each sample time were obtained. The data was collated and summary statistics including the means, standard deviations and standard errors of the means were determined. The CFF threshold means and standard errors for each condition at each time point are depicted in Figure 1.

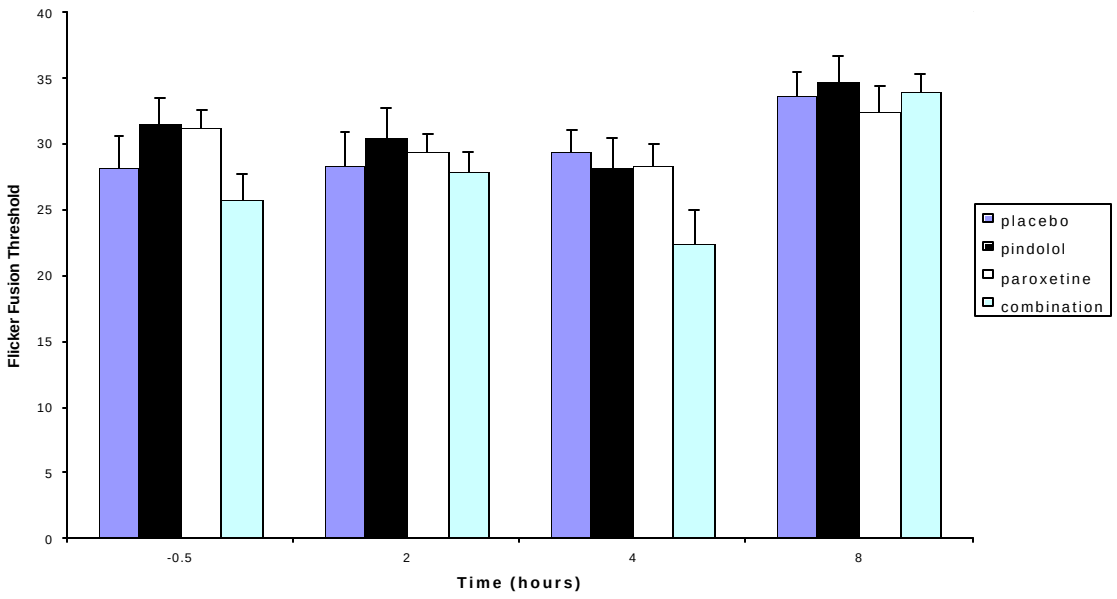

Figure 1. Means and standard errors for CFF threshold in relation to time of drug administration across drug conditions.

Inspection of the data indicates that the combination condition resulted in lower CFF threshold scores compared to all other conditions over the first three time periods. A

repeated measures with-in subjects ANOVA showed a significant main effect of condition $F(3) = 3.731$, $p<0.05$, and time $F(3) = 21.554$, $p<0.001$ on CFF threshold values. The interaction observed between condition and time was also significant $F(3) = 2.459$, $p<0.05$. As there was a significant effect of the drug received on the participants' performance, pair-wise comparisons were performed to determine when these differences occurred. The mean CFF threshold score for the combination condition was found to be significantly lower than all other conditions at 4 hours after drug administration. At 8 hours, pindolol had a significantly higher CFF threshold than the paroxetine condition. A second pair-wise comparison was conducted to detect the effect of time within each of the conditions. The CFF threshold scores observed at 8 hours were significantly greater compared to all other time points within both the combination and placebo conditions. Scores at 4 hours were significantly lower than scores at baseline and at 8 hours for the paroxetine condition.

Choice Reaction Time

CRT scores for each participant under each condition at each sample time was obtained. Data was collated and summary statistics including the means, standard deviations and standard errors of the means were determined. The CRT score means and standard errors for each condition at each time point is depicted in Figure 2.

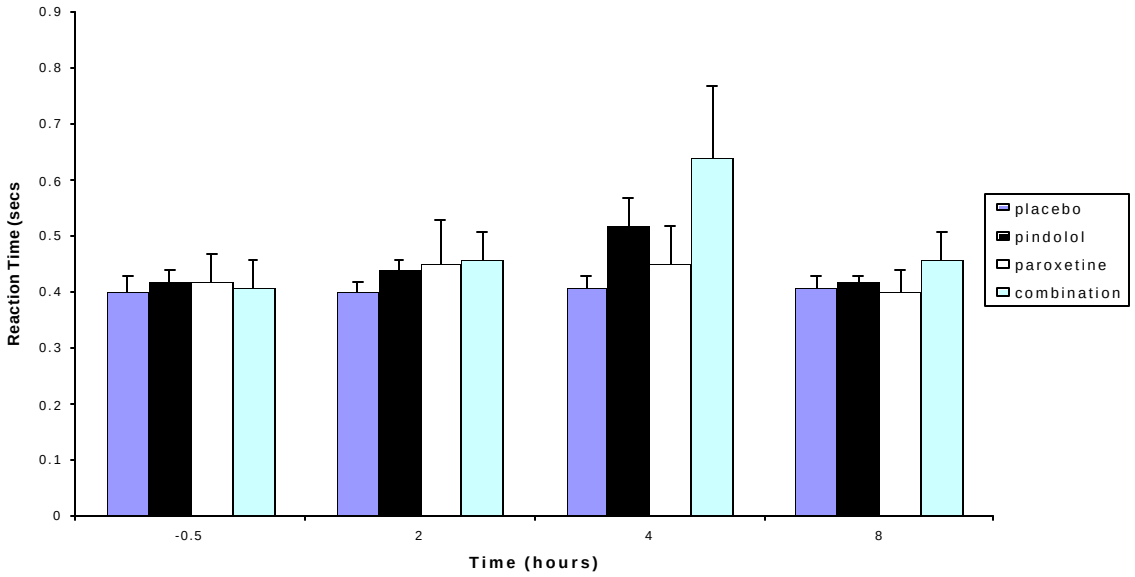

Figure 2. Means and standard errors for CRT scores in relation to time of drug administration across drug conditions.

Figure 2 suggests that at times 2, 3 and 4 reaction times were greater for the combination condition than all other conditions. To determine whether these differences were significant a repeated measures with-in subjects ANOVA was performed. A violation of the Mauchly's test of Sphericity for time was observed. The Greenhouse-Geisser correction was used for this measure. A significant main effect of condition on CRT was observed $F(3) = 4.661$, $p<0.05$, and a significant main effect of time was also observed $F(3) = 12.285$, $p<0.01$. Furthermore, the interaction between condition and time was also significant $F(3) = 7.918$, $p<0.001$. As there was a significant effect of condition on the participants' performance, pair-wise comparisons of condition across time were conducted to determine when these differences occurred. Reaction times were significantly longer for the CRT task for the combination condition compared to all other conditions at 4 hours. A second pair-wise comparison was conducted to detect the effect of time within each of the conditions. The CRT scores observed at 4 hours were significantly greater than all other time points within the combination condition. Reaction times recorded at 8 hours were also significantly greater to those at baseline within the combination condition.

Digit-Symbol Substitution Test

DSST scores for each participant under each condition at each sample time was obtained. Data was collated and summary statistics including the means, standard deviations and standard errors of the means were determined. The DSST score means and standard errors for each condition at each time point is depicted in Figure 3.

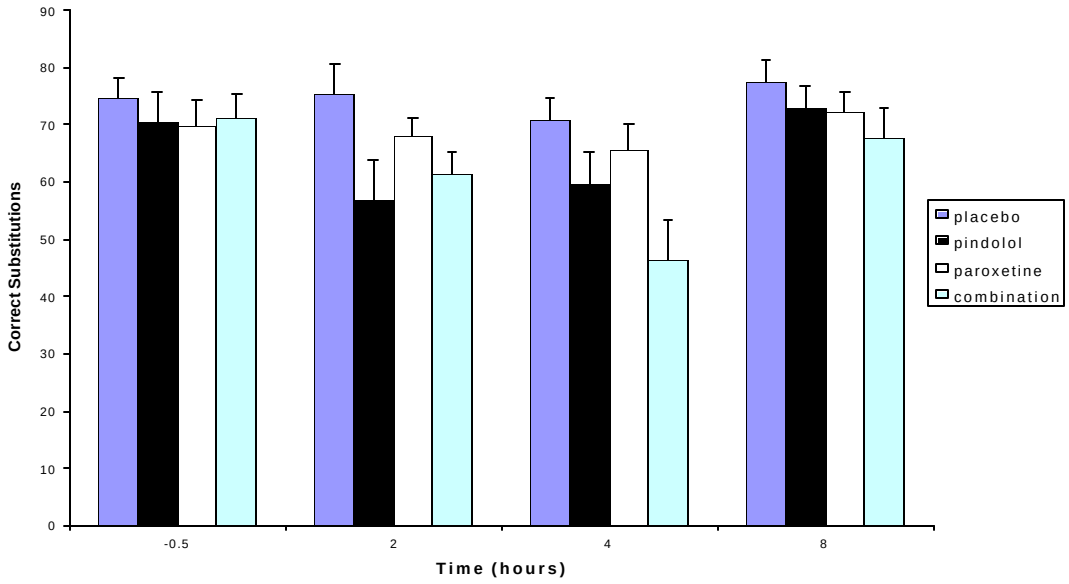

Figure 3. Means and standard errors for DSST scores in relation to time of drug administration across drug conditions.

Figure 3 suggests that at all times DSST scores were the greatest for the placebo condition compared to all other conditions. To determine any significant differences between drug conditions a repeated measures with-in subjects ANOVA was conducted which showed a significant main effect of condition on DSST scores $F(3) = 10.081$, $p<0.001$, and also time on this measure $F(3) = 9.610$, $p<0.001$. The interaction observed between condition and time was also significant $F(3) = 2.488$, $p<0.05$. As there was a significant effect of drug on the participants' performance, pair-wise comparisons of condition across time were performed to determine when these differences occurred. DSST scores were found to be significantly lower for the combination condition compared to all other conditions at 4 hours. Pindolol was found to have resulted in significantly lower DSST scores than paroxetine and placebo at 4 hours. An additional difference was found between the placebo and combination conditions both at 2 and 8 hours, where the combination of drugs resulted in a significant decrease in DSST scores compared to placebo. A second pair-wise comparison was conducted to detect the effect of time within each of the conditions. Scores at 4 hours were significantly lower than all other time points within the combination condition. For pindolol, scores at 4 hrs were significantly lower than were those at baseline and at 8 hours. Scores were significantly

lower at 4 hours compared to 8 hours for the placebo group, and at 4 hours compared to baseline for the paroxetine condition.

Visual Analogue Scale of Mood – Intellectual Ability (Factor 1)

Scores for the VASI factor were obtained for each participant under each condition at each test time. Data was collated and summary statistics including the means, standard deviations and standard errors of the means were determined. The Visual Analogue Scale score means and standard errors for the Intellectual ability factor for each condition at each time point is depicted in Figure 4.

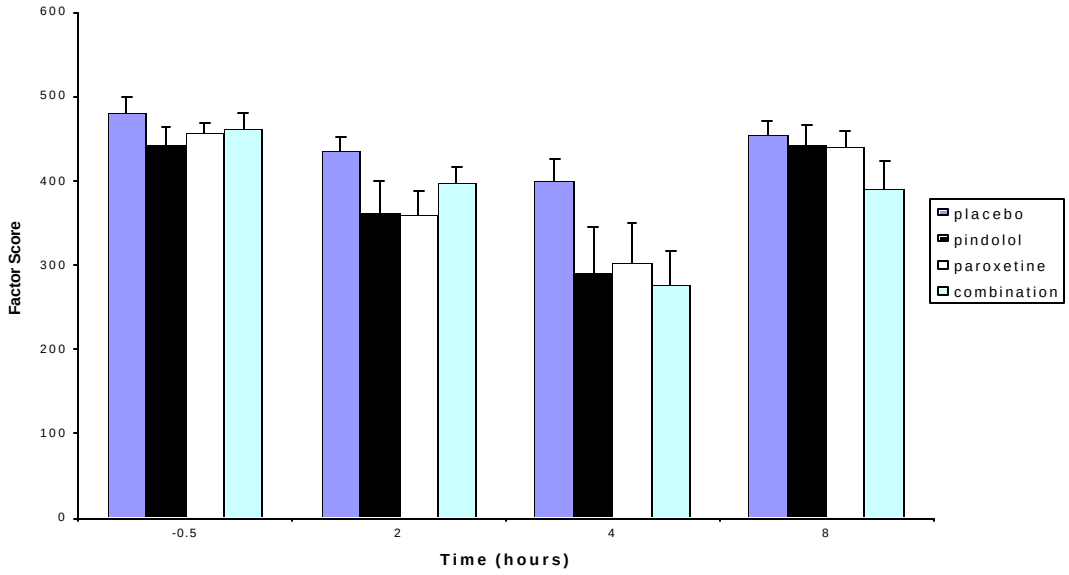

Figure 4. Means and standard errors for Visual Analogue Scale scores (Factor 1) in relation to time of drug administration across drug conditions.

The data suggest that the placebo condition resulted in increased Visual Analogue Scale ratings for the Intellectual Ability Factor compared to all other conditions over all sample times. A repeated measures with-in subjects ANOVA showed a significant main effect of time on VASI $F(3) = 19.779$, $p<0.001$. Furthermore no significant main effect of condition $F(3) = 2.430$, $p>0.05$, or interaction between condition and time $F(3) = 0.734$, $p>0.05$ were observed. A pair-wise comparison was conducted to detect the effect of time within each of the conditions. The VASI scores were found to vary significantly

across time for all drug conditions including placebo. At 4 hours scores were significantly lower than scores at 8 hours for all drug conditions. Scores at 4 hours were significantly lower than baseline scores for the pindolol, paroxetine and combination conditions.

Visual Analogue Scale of Mood – Physical Ability (Factor 2)

Scores for the VASP factor were obtained for each participant under each condition at each test time. Data were collated and summary statistics including the means, standard deviations and standard errors of the means were determined. The Visual Analogue Scale score means and standard errors for the physical ability factor for each condition at each time point is depicted in Figure 5.

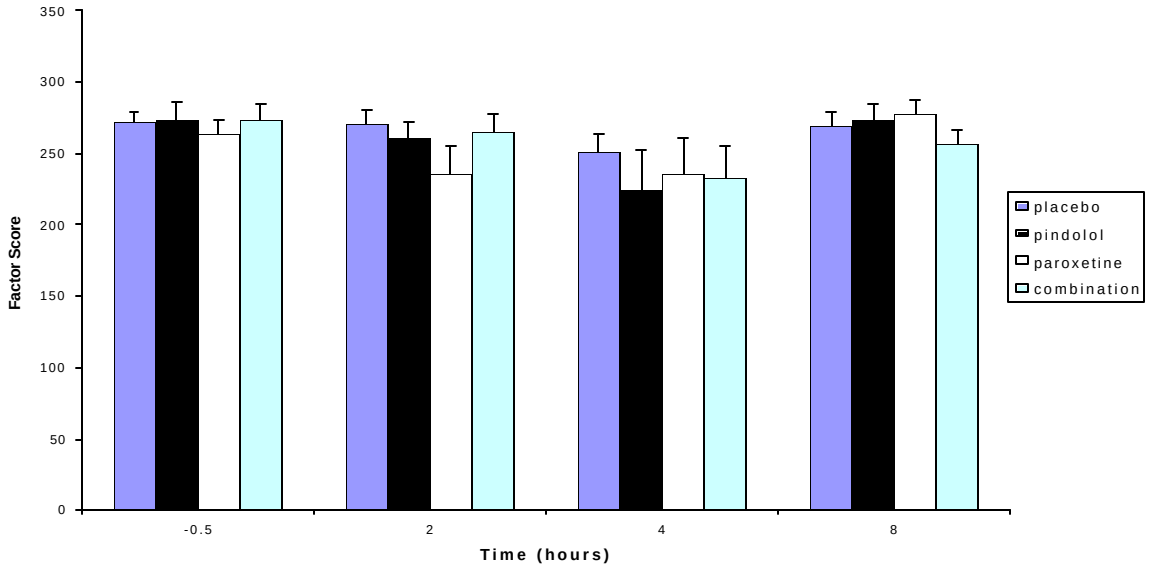

Figure 5. Means and standard errors for Visual Analogue Scale scores (Factor 2) in relation to time of drug administration across drug conditions.

The data suggest that similar Visual Analogue Scale ratings for the Physical Ability Factor were observed for each drug condition at each test administration time. A repeated measures with-in subjects ANOVA showed a violation of the Mauchly's test of Sphericity for time, condition and time by condition. A Greenhouse-Geisser correction was used for these measures. No significant main effects of condition $F(3) = 0.978$,

p>0.05, time F(3) = 1.157, p>0.05, or the interaction between condition and time F(3) = 1.123, p>0.05 on VASP scores was observed.

Visual Analogue Scale of Mood – Tranquillisation Effects (Factor 3)

Scores for the VAST factor were obtained for each participant under each condition at each test time. Data was collated and summary statistics including the means, standard deviations and standard errors of the means were determined. The Visual Analogue Scale score mean and standard error for each condition at each time point is depicted in Figure 6.

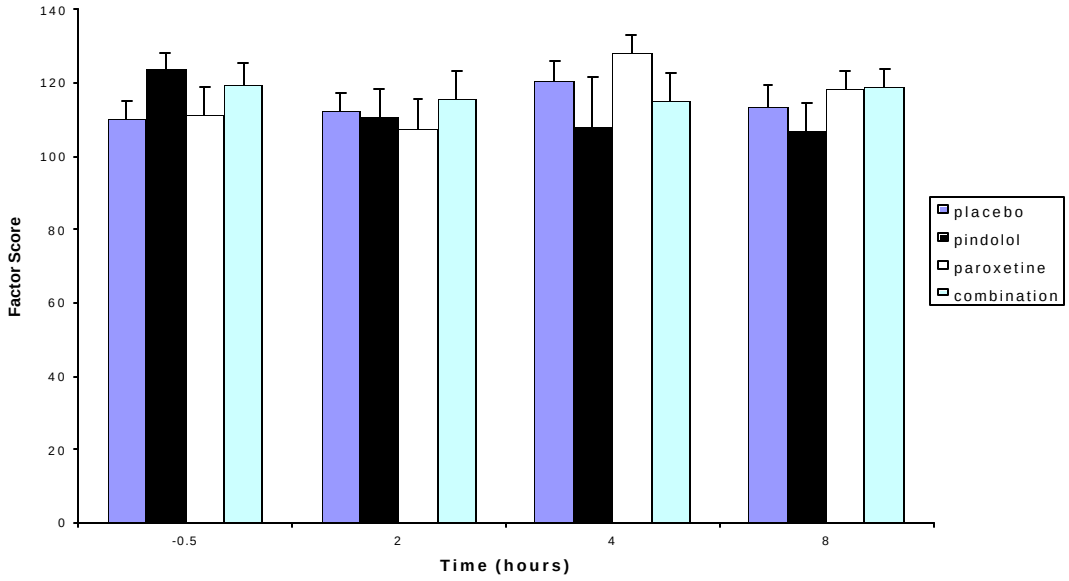

Figure 6. Means and standard errors for Visual Analogue Scale scores (Factor 3) in relation to time of drug administration across drug conditions.

The data suggest no real trend in Visual Analogue Scale ratings for the Tranquillisation Effects Factor between conditions over test administration times. A repeated measures with-in subjects ANOVA showed no significant main effect of condition on VAST F(3) = 0.404, p>0.05. Furthermore, no significant main effect of time F(3) = 0.742, p>0.05, or the interaction between condition and time F(3) = 1.454, p>0.05 was observed.

Discussion

The hypothesis that the concurrent administration of paroxetine and pindolol would result in a significantly greater decrement in psychomotor performance than exclusive single doses of the two drugs was supported by the results of the CFF task, the CRT task and the DSST. All factors of the Visual Analogue Scale failed to demonstrate any significant differences between drug conditions at any time. The results indicated that reaction times were significantly increased for the CRT task, CFF thresholds were significantly reduced and more errors were made on the DSST, 4 hours after the administration of the combination of drugs when compared to the placebo, paroxetine and pindolol conditions. The total number of substitutions and correct substitutions made in the DSST were also significantly decreased in the pindolol condition, 4 hours after drug administration, compared to the placebo and paroxetine conditions.

The results of the CFF task indicate that central arousal is decreased more significantly by the combination of drugs then by pindolol, paroxetine or placebo administered alone. The decreased CFF threshold scores observed are indicative of impairments in information processing, visual sensitivity and CNS arousal. The results of the CRT task also indicate that the combination of drugs has a significantly greater sedative effect than pindolol and paroxetine when they are administered alone. Sensorimotor coordination and attentional monitoring abilities are significantly impaired by the combination of drugs again indicating that such polypharmacy has pronounced central effects. The results of the DSST indicate that the combination of paroxetine and pindolol has a deleterious central sedative effect, with cognition being significantly altered. Interestingly pindolol, while not affecting psychomotor performance as much as the combination of drugs, resulted in a significantly greater decrement in DSST scores than paroxetine and placebo. Without pharmacokinetic information, a tentative explanation is that paroxetine potentiated the effect of pindolol when the drugs were administered concurrently. Paroxetine may potentiate the already greater deficit due to pindolol by inhibition of the CYP2D6 isoenzyme, effectively inhibiting the metabolism of pindolol. Alternatively the absorption of pindolol or its total body clearance may be affected, resulting in an increase in the plasma concentration of pindolol, and greater psychomotor effects in the combination condition.

Although pharmacokinetic parameters were not measured some further tentative conclusions can be made from the data. Most of the significant differences in psychomotor performance due to drug conditions occurred 4 hours (time 3) after administration. This is at or near the known maximum plasma concentration for pindolol and/or paroxetine. Pindolol, which is a lipophilic molecule, is able to cross the blood brain barrier with relative ease and speed and therefore the maximum CNS disturbances are expected to occur proximal to the maximum plasma concentration of the drug (Rosen & Kostis, 1985).

An alternative explanation for the pattern of results obtained is based on pharmacodynamic effects at central receptor sites of action. Impaired psychomotor performance from the combination may be due to synergistic effects of pindolol and paroxetine on central serotonin receptors. One potential site of action is the 5-HT_{1A} receptor. Pindolol acts as an antagonist at this auto-receptor, which results in an accumulation of 5-HT in the synaptic cleft. Although this drug interaction has been noted to increase the antidepressant effect of paroxetine (Tome et al., 1997; Zanardi et al., 1997), the effect on psychomotor performance has not been established. Without blood plasma concentration levels of either drug it is impossible to confirm or rule out any pharmacokinetic or pharmacodynamic explanations.

For the CFF and CRT tasks, no differences were observed between the pindolol, paroxetine and placebo conditions. The DSST however, indicated deficits in psychomotor performance in the pindolol condition compared to the paroxetine and placebo conditions 4 hours after drug administration. The literature surrounding the sedative effects of antidepressants contains varying results. While significant deficits in psychomotor performance have been observed in a number of studies using antidepressants, the findings that the newer SSRIs have a reduced side effect profile appear to be supported by the current study (Hawley et al., 1997). Similarly, β-blockers have been found to consistently impair psychomotor performance but only in a dose and temporally dependent fashion (Dimsdale et al., 1989). It appears that the psychomotor deficits due to the administration of pindolol might be so small as only to be evident in the most sensitive test used.

The results suggest that there is evidence for decreased psychomotor performance due to the combination of paroxetine and pindolol. However, this is not evident in all tests of psychomotor performance used. Only the objective tests, rather than the subjective analogue scales, showed any difference between drug conditions. It may be that the alternative tests measured different aspects of psychomotor performance and therefore care must be taken in generalising the results from the particular tests used to all areas of psychomotor performance. The CRT task, which measures sensory and motor system coordination and attentional monitoring ability, is a good objective measure of sedative effects. Likewise, the DSST is sensitive to changes in cognition due to sedative effects, and is perhaps the most sensitive test, as differences between the combination condition and placebo were additionally observed at 2 and 8 hours after drug administration. Also, differences between the pindolol condition and paroxetine and placebo were also observed using this test. The CFF test also measures sedative effects on information processing and CNS arousal and is more contingent on visual sensitivity. It appears that the visual system may also be significantly altered by the combination of drugs and, lower CFF thresholds have previously been found with the lipophilic β-blockers, metoprolol and propranolol, 2-5 hours after drug administration (Gengo et. al., 1987; McDevitt, 1985). This is consistent with the current results and suggests that the larger effect found from the combination of drugs might be due to poteniation of the effects of pindolol by paroxetine. The extent to which each test measures peripheral and central effects could also have had a bearing on the results obtained. β-blockers have been shown to impair muscle activity and thus the results of the CRT task and the DSST may have simply reflected a deficit in the muscle-activated response rather than CNS effects (Broadhurst, 1980b). However, β-blockers have also been found to have pronounced central depressant actions such as depression, disruption of sleep architecture, hallucinations and subjective sedation (Broadhurst, 1980a; Glaister, 1981; Kostis et al., 1990). This, together with the fact that pindolol and paroxetine are both lipophilic, suggests that they access the CNS readily and that deficits in psychomotor performance can be explained, at least in part, by central effects.

Although other studies have found the Bond-Lader Visual Analogue Scale to be a good indicator of changes in subjective sedation (Kerr et al., 1992) no changes were

detected in this study. Perhaps these measures are not sensitive enough to detect changes in sedation of the magnitude detected by the CFF, CRT and DSST tasks. Although there was a significant increase in subjective intellectual impairment for the VAS-M (intelligence factor) over time with each drug, this decrease was also observed in the placebo group suggesting that the significant main effect of time was simply a reflection of diurnal variation. The trend of greater subjective reports of intellectual impairment 4 hours after drug administration may have had more to do with boredom and diurnal variation in lethargy and fatigue then the drugs themselves. It cannot be concluded that the lack of significant findings for the VAS-M is due to a lack of interaction, and it is possible that this observation was due to the acute low doses administered (as discussed below). It could be that the DSST, CRT and CFF tests are more sensitive to the peripheral changes that occur as a result of sedative drug administration and the subjective analogue scales are only sensitive to CNS alterations. These tests may also prove more useful over a longer time frame. Another consideration when using subjective ratings is the influence of social desirability and experimenter expectations on the participant's responses. If the participant believed that the drugs taken were sedative in nature and the experimenter expected them to show signs of increased drowsiness, a higher degree of subjective sedation may have been reported.

Some of the inconsistencies in the present studies findings may be due to methodological problems. The first potential problem of the experimental design was the doses of paroxetine and pindolol used. The doses used are sub-therapeutic. Doses of 15-20mg as opposed to the present 5mg for pindolol and 20mg as opposed to 10mg for paroxetine are commonly used therapeutically (Dechant and Clissold, 1991; Dimsdale et al., 1989). Doses in the normal therapeutic range were not used in the present study in order to minimise the major side effects of nausea, vomiting and hypotension. While it has been found that only doses of paroxetine higher than the normal therapeutic range impair psychomotor performance (Robbe & O'Hanlon, 1995), some studies suggest that lower doses of lipophilic β-blockers result in more significant deficits in psychomotor performance than higher doses (McDevitt, 1985). These findings are consistent with the results from the DSST. The dose used in the present study was an acute dose unlike the chronic dosing that occurs therapeutically. It may be that with chronic dosing, whereby

steady state plasma concentrations are attained, greater psychomotor deficits than reported here may occur. Alternatively, chronic dosing may result in an increase in tolerance to the drug and a reduced side effect profile over time, as observed with the β-blocker propranolol in the study by Broadhurst (1980b). A further methodological problem could be the small sample size utilised resulting in a low power and an increased probability of a Type II error, which may provide an explanation of the non-significant findings where graphical representation has suggested an effect of drug condition on psychomotor performance. Although strict exclusion criteria were used, this list was not exhaustive and could not have ruled out every possible confounding factor. No consideration of differing levels of the CYP2D6 enzyme in participants was taken which could have significantly affected the inter-individual metabolism of the drugs, significantly altering the results in such a small sample. A 40-fold or greater variation between individuals in drug plasma concentrations has been demonstrated for most psychotropic drugs (Lane, 1996). There are genetic differences in hepatic metabolism with a small proportion (5-10%) of poor metabolisers, with reduced rates of metabolism for substrates metabolised by the CYP2D6 isoenzyme, in the Caucasian population. If the present sample contained one of these individuals the results may have been significantly biased (Leonard, 1992). Poor metabolisers would have greater plasma concentrations and would be expected to have an exaggerated pharmacologic response (Nemeroff, DeVane & Pollock, 1996).

The frequency of testing may also have limited the conclusions that can be drawn. Although significant differences between drug conditions on psychomotor performance were consistently detected at 4 hours after drug administration, the duration of performance deficits either side of this time cannot be accurately determined from the present studies data. As significantly greater deficits in psychomotor performance for the combination condition compared to placebo were detected at 2, 4, and 8 hours after drug administration, significant differences in the pindolol and paroxetine conditions may also have occurred shortly after 2 hours and immediately prior to 8 hours. The peak plasma concentration for paroxetine has been found to occur at approximately 5 hours after administration, so it is possible that deficits in psychomotor performance may have been

detected at around this time if pharmacodynamic tests were performed (Dechant and Clissold, 1991).

Future studies should aim to resolve some of the methodological problems encountered in the present study in order to fully characterise the drug interaction of pindolol and paroxetine in terms of pharmacokinetics as well as pharmacodynamics. Studies that measure the pharmacokinetic profile of each drug, including plasma concentration, peak concentration, time of peak concentration and bioavailability, should be undertaken to definitively clarify when the maximum blood concentrations of the drugs occur. Both pharmacokinetic and pharmacodynamic tests should be undertaken more frequently than in the present study to further elucidate the temporal components of the drug interaction. Studies using a larger number of subjects would minimise the chance that a confounding factor, such as differences in hepatic metabolism, might bias the results. Alternatively, participants could be screened genotypically or phenotypically for CYP2D6 activity. This task could prove rather expensive and arduous because of the large degree of variance between individuals in the population (Lane, 1996). Longer-term studies should also be conducted whereby the drugs are chronically administered in therapeutic doses. Despite the complexities in using females in such pharmacokinetic studies due to their menstrual cycle, the differential alterations in sedation due to drug administration in females is another area that warrants investigation, as there is some evidence that plasma concentrations of SSRIs are lower in males (Preskorn, 1997). The differential increases in plasma concentrations of paroxetine in the elderly is another consideration with increases of 50-100% having been observed in populations of 65-75 year olds (Preskorn, 1997). This has important implications as it is this group who are more likely to be receiving concomitant β-blocker treatment and more likely to be adversely affected by the elevated concentration of drugs.

It appears from this study that there is a significant drug interaction when pindolol and paroxetine are administered concurrently which results in a significant degree of CNS depression when compared to administration of the drugs alone. This has important implications for the population as the prescription of antidepressants and β-blockers becomes more common. Physicians should be aware of the dangers involved in concurrent administration of such agents. Impaired psychomotor performance may

significantly affect the execution of skilled movements involved in everyday life. Cognitive, sedative and motor impairments and changes in visual sensitivity may affect driving abilities and those skills involved in the operation of machinery. Different combinations of these classes of drugs should be fully explored to establish if there is an efficacious and safe combination of the two. If studies continue to reveal impaired psychomotor performance due to this drug interaction alternative anti-hypertensive drugs, with reduced side effect profiles, may need to be considered for patients already receiving antidepressants.

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Summary Statistics for CFF Threshold Scores.

Drug	Time (hrs)	Mean	S.D.	S.E.M.	N
Placebo	0	28.13	7.14	2.52	12
	2	28.35	7.27	2.57	12
	4	29.46	4.59	1.62	12
	8	33.64	5.15	1.82	12
Pindolol	0	31.56	5.36	1.89	12
	2	30.48	6.50	2.30	12
	4	28.14	6.58	2.33	12
	8	34.79	5.60	1.98	12
Paroxetine	0	31.21	4.13	1.46	12
	2	29.41	3.98	1.41	12
	4	28.37	4.58	1.62	12
	8	32.53	5.29	1.87	12
Combination	0	25.82	5.52	1.95	12
	2	27.84	4.53	1.60	12
	4	22.46	7.13	2.52	12
	8	33.99	3.94	1.39	12

Summary Statistics for CRT Scores.

Drug	Time (hrs)	Mean	S. D.	S.E.M.	N
Placebo	0	0.40	0.07	0.03	12
	2	0.40	0.06	0.02	12
	4	0.41	0.06	0.02	12
	8	0.41	0.07	0.02	12
Pindolol	0	0.42	0.06	0.02	12
	2	0.44	0.07	0.02	12
	4	0.52	0.15	0.05	12
	8	0.42	0.04	0.01	12
Paroxetine	0	0.42	0.05	0.02	12
	2	0.45	0.08	0.03	12
	4	0.45	0.07	0.03	12
	8	0.40	0.04	0.02	12
Combination	0	0.41	0.05	0.02	12
	2	0.46	0.05	0.02	12
	4	0.64	0.13	0.04	12
	8	0.46	0.05	0.02	12

Summary Statistics for DSST Scores.

Drug	Time (hrs)	Mean	S.D.	S.E.M.	N
Placebo	0	74.88	9.25	3.33	12
	2	75.25	15.01	5.31	12
	4	70.75	11.31	4.00	12
	8	77.50	10.86	3.84	12
Pindolol	0	70.50	14.96	5.29	12
	2	56.88	19.65	6.95	12
	4	59.75	15.46	5.47	12
	8	73.00	11.16	3.95	12
Paroxetine	0	69.75	12.62	4.46	12
	2	68.00	8.85	3.13	12
	4	65.75	12.50	4.42	12
	8	72.25	9.88	3.49	12
Combination	0	31.38	11.31	4.00	12
	2	61.50	10.78	3.81	12
	4	46.38	19.86	7.02	12
	8	67.75	14.39	5.09	12

Summary Statistics for VAS-M Intellectual Ability Scores.

Drug	Time (hrs)	Mean	S.D.	S.E.M.	N
Placebo	0	481.47	56.43	19.95	12
	2	435.21	50.21	17.75	12
	4	400.39	75.13	26.56	12
	8	456.04	47.08	16.64	12
Pindolol	0	442.46	59.50	21.04	12
	2	362.72	108.94	38.52	12
	4	291.21	156.64	55.38	12
	8	443.10	66.90	23.65	12
Paroxetine	0	456.29	34.45	12.18	12
	2	359.95	84.08	29.73	12
	4	302.74	131.80	46.60	12
	8	440.19	57.85	20.45	12
Combination	0	461.84	55.44	19.60	12
	2	398.54	50.50	17.85	12
	4	276.41	118.12	41.76	12
	8	391.48	91.19	31.89	12

Summary Statistics for VAS-M Physical Ability Scores.

Drug	Time (hrs)	Mean	S.D.	S.E.M.	N
Placebo	0	272.24	19.62	6.94	12
	2	270.17	29.84	10.55	12
	4	251.69	34.34	12.14	12
	8	269.02	30.32	10.72	12
Pindolol	0	273.90	36.63	12.95	12
	2	261.31	30.53	10.79	12
	4	224.12	79.89	28.25	12
	8	273.34	33.22	11.74	12
Paroxetine	0	263.79	28.57	10.10	12
	2	234.97	59.36	20.99	12
	4	236.15	70.77	25.02	12
	8	277.58	28.20	9.97	12
Combination	0	273.80	29.78	10.53	12
	2	265.53	33.07	11.69	12
	4	233.53	62.27	22.02	12
	8	256.69	29.00	10.25	12

Summary Statistics for VAS-M Tranquillisation Effect Scores.

Drug	Time (hrs)	Mean	St. Dev	St. Error	N
Placebo	0	110.35	12.93	4.57	12
	2	112.53	13.39	4.73	12
	4	120.24	15.60	5.52	12
	8	113.22	18.07	6.39	12
Pindolol	0	123.64	13.39	4.73	12
	2	110.85	21.04	7.44	12
	4	107.98	39.03	13.80	12
	8	106.82	21.87	7.73	12
Paroxetine	0	111.22	21.59	7.63	12
	2	107.43	23.75	8.39	12
	4	128.02	14.16	5.01	12
	8	118.44	13.94	4.93	12
Combination	0	119.56	16.94	5.99	12
	2	115.79	21.26	7.52	12
	4	114.90	21.68	7.67	12
	8	118.89	14.12	4.99	12