The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

**Study No:** 29060/156 (HP/84/121)

**Title:** A study to assess the CNS effects of paroxetine, and haloperidol and any interaction of paroxetine with the sedative effects of haloperidol

**Rationale:** Previous studies have shown that paroxetine does not have a sedative effect on the quantitative electroencephalogram (EEG), or significant effects on psychomotor performance. It is likely that paroxetine will sometimes be co-prescribed with antipsychotic drugs such as haloperidol. This study was designed to assess any central nervous system (CNS) interaction between paroxetine and haloperidol after single dose administration.

**Phase:** I

**Study Period:** No dates specified in the report; report was issued in May 1986.

**Study Design:** Single-blind, double dummy, crossover study. The dose of haloperidol used in this study (3 mg) is within the usual recommended daily dose range of 1 to 200 mg.

**Centres:** One study centre in the UK.

**Indication:** None.

**Treatment:** paroxetine 30 mg tablets and matched placebo tablets; haloperidol 3 mg capsules and matched placebo capsules. All subjects received one dose of each of the following treatment combinations in a random order, with at least one week between each dose:

- **Treatment A:** paroxetine matched placebo + haloperidol matched placebo
- **Treatment B:** paroxetine + haloperidol matched placebo
- **Treatment C:** paroxetine matched placebo + haloperidol
- **Treatment D:** paroxetine + haloperidol.

Study treatments were administered at approximately 10 a.m. with 300 mL water.

**Objectives:** To assess the effects of co-administration of paroxetine and haloperidol on measures of CNS activity, and to assess the effects of paroxetine alone on measures of CNS activity in comparison with haloperidol and placebo.

**Statistical Methods:** Statistical methods not available. CNS monitoring consisted of: Tremor, EEG, digit span, subjective assessments (16 visual analogue scale of alert/drowsy, attentive/dreamy, energetic/lethargic, clear-headed/muzzy, well-coordinated/clumsy, quick-witted/mentally slow, strong/feeble, interested/bored, proficient/incompetent, happy/sad, amicable/antagonistic, tranquil/troubled, contented/discontented, gregarious/withdrawn, calm/excited, relaxed/tense), choice reaction time, continuous performance, flash fusion threshold, motor control and coordination, time estimation, tapping rate.

**Study Population:** Healthy male volunteers, aged 18-60 years; body weight 55-120 kg and who passed a comprehensive medical examination were eligible for this study.

**Number of Subjects:**

| Planned N | 12 |
| Dosed N   | 11 |
| Completed n | 10 |
| Total Number Subjects Withdrawn N | 1 |
| Withdrawn due to Adverse Events (AEs) n | 0 |
| Withdrawn due to Lack of Efficacy n | Not applicable |
| Withdrawn for Other Reasons n | 1 |

N = total number of subjects; n = subset of subjects (based on N).

**Demographics:**

| N | 12 |
| Males | 12 |
| Mean Age in Years (sd) | 36.42 (6.50) |
| Mean Weight in Kg (sd) | 79.96 (15.36) |
| Race n | Not available |

**Pharmacokinetic (PK) Endpoints:** Paroxetine plasma levels were monitored over 4-8 hour period after each dose, yielding nominal maximal concentration values ranging from 2.8 to 62.4 ng/ml when paroxetine was administered alone and from 2.6-31.7 ng/ml when it was co-administered with haloperidol.

**Pharmacodynamic (PD) Endpoints** Treatment A showed a reduction in the frequencies between 8 and 18 Hz.
dominant frequencies of essential tremor) at all post-dose recording times, with peak reduction at 6-8 hours post-
dose. Treatments B, C and D did not reveal any marked changes in the tremor power spectrum. There was a trend for
treatment B to reduce the amount of slow (<8 Hz) and fast (>18 Hz) frequencies with an increase in the intermediate
frequencies. The peak effect of these changes was observed at 24 hours post-dose.

Computer analysis of the majority of EEG recordings was not possible due to equipment malfunction. The remaining
EEG results were considered insufficient to average each treatment.

Compared to treatment A, significant increases in sagittal sway were observed at 4 hours post-dose with treatments B
(p<0.01) and D (p<0.05). No significant differences were observed in lateral sway when compared with treatment A.

No significant differences were observed in digit span when compared with treatment A. Treatments B, C and D
reduced performance slightly from 4 hours post-dose onwards.

Of the 16 visual analogue scales (VAS) completed for subjective assessment, statistically significant differences were
observed for 8 parameters.

A significantly different mean "attentive/dreaming" VAS score was observed with treatment D compared to the 3 other
groups at 8 hours post-dose.

At 4 hours post-dose, subjects receiving treatments B, C and D were significantly less well coordinated compared to
those receiving treatment A. This trend was observed from 2 to 6 hours post-dose.

Subjects felt significantly less quick-witted at 4 hours post-dose with treatments B, C and D compared to treatment A.
At 4 hours post-dose, subjects were significantly less interested with treatments B, C and D compared to treatment A.

Also at 4 hours post-dose, subjects felt significantly less interested with treatment D compared to treatment B.

At 4 hours post-dose, treatments C and D made the subjects feel significantly less proficient than treatment A.

At 4 hours post-dose, subjects receiving treatments C or D were significantly less amicable. This effect was also
observed at 6 and 8 hours post-dose for treatment D.

At 4 hours post-dose, treatments C and D made the subjects feel significantly less tranquil than treatment A.
At 8 hours post-dose, treatment D made the subjects feel significantly less relaxed than treatment C. No significant
differences were observed when compared with treatment A.

Choice reaction time: no statistically significant effects were observed on either the number of errors made or button
release time. When compared with treatment B, the movement time following a misleading auditory cue was
significantly increased by treatments C and D at 8 hours post-dose. No significant effects were observed on movement
time with a consistent auditory cue.

Continuous performance: treatment C significantly reduced the number of correct responses at 4 hours post-dose
compared to treatments A and B. At 6, 8, and 24 hours post-dose, treatments C and D significantly reduced the
number of correct responses, compared to treatments A and B. No statistically significant effects on reaction time were
observed.

No statistically significant effects were observed on flash fusion threshold, time estimation or tapping rate.

Motor control and co-ordination: treatments C and D significantly increased the time taken to complete the motor task
compared to treatment B at 4 hours post-dose. At 6 hours post-dose, treatments C and D significantly increased the
time taken to complete the motor task compared to treatments A and B.

No significant treatment-related changes or statistically significant differences were observed in pulse rate or blood
pressure between treatments at any time during the study.

There was a trend for small (<1 mm) increase in pupil size after treatments B and D. At 8 hours post-dose, pupil size
was significantly increased with treatment C and at 30 hours post-dose pupil size was significantly increased
with treatment D (<0.05 mm compared to treatment A in both cases).

Nystagmus was not observed in any subject at any time during the study.

No obvious treatment-related effects were observed in tendon reflexes.

Safety Results: Subjects were asked to report all symptoms experienced during the study. Symptoms were checked
at 4, 8, 24 and 30 hours post-dose.

<table>
<thead>
<tr>
<th>Adverse Events:</th>
<th>paroxetine + placebo + haloperidol</th>
<th>paroxetine + haloperidol + placebo</th>
<th>paroxetine + haloperidol placebo</th>
<th>paroxetine + haloperidol placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>No. subjects with AEs n (%)</td>
<td>7 (63.6)</td>
<td>10 (90.9)</td>
<td>11 (100)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Most Frequent AEs (n≥2) n (%)</td>
<td>Drowsiness</td>
<td>1 (9.1)</td>
<td>4 (36.4)</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>4 (36.4)</td>
<td>4 (36.4)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td></td>
<td>Tiredness</td>
<td>2 (18.2)</td>
<td>2 (18.2)</td>
<td>1 (8.1)</td>
</tr>
</tbody>
</table>
Difficulty concentrating | 0 (0.0) | 2 (18.2) | 1 (9.1) | 3 (27.3) |
Lethargy | 2 (18.2) | 0 (0.0) | 1 (9.1) | 2 (18.2) |
Thirst | 1 (9.1) | 3 (27.3) | 0 (0.0) | 0 (0.0) |
Flatulence | 0 (0.0) | 2 (18.2) | 0 (0.0) | 2 (18.2) |
Appetite | 2 (18.2) | 0 (0.0) | 0 (0.0) | 1 (9.1) |
Feel unwell | 1 (9.1) | 2 (18.2) | 0 (0.0) | 0 (0.0) |
Sweating | 2 (18.2) | 0 (0.0) | 1 (9.1) | 0 (0.0) |
Diarrhoea | 0 (0.0) | 0 (0.0) | 1 (9.1) | 2 (18.2) |
Leg pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (27.3) |
Nasal congestion | 2 (18.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
Unsteady feeling | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (18.2) |
Dry mouth | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (18.2) |
Unpleasant taste | 0 (0.0) | 2 (18.2) | 0 (0.0) | 0 (0.0) |

Serious Adverse Events, n (%):
Subjects with serious adverse events
(includes fatal and non-fatal events) | 0 | 0 | 0 | 0 |

Publications:

Date Updated: 10-Oct-05