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# Comparative Study of Fluoxetine and Escitalopram : the Impact of SSRI's on Sleep and Anxiety

Medical Science

**KEYWORDS :** fluoxetine; escitalopram; depression; sleep; anxiety

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## ABSTRACT

*Fluoxetine (20 mg) was compared to escitalopram (10 mg) in a prospective, double blind, randomised clinical trial involving 125 patients with major depression treated for an initial phase of 6 weeks and then followed up for a further 6 months. There was no difference in the efficacy of the two drugs based on the results of established rating scales (MADRS, HAM-D, BPRS). The impact of both drugs on sleep measured using the Leeds Sleep Evaluation Questionnaire showed no significant differences between treatments, however drowsiness and disturbed sleep were reported more frequently as side effects with escitalopram. Symptoms of anxiety responded equally well to both treatments. Our study has confirmed that fluoxetine is as effective as escitalopram in the acute treatment of major depression and has shown that fluoxetine has a better tolerability profile without loss of the beneficial effect of normalising sleep. In addition fluoxetine has been shown to be as effective as escitalopram in relieving the symptoms of anxiety associated with depression*

## INTRODUCTION

The first report of the use of a tricyclic antidepressant was published over 40 years ago (Kuhn, 1957) and at that time the tricyclic antidepressants did indeed represent a major breakthrough in the pharmacotherapy of depression. However the tricyclic antidepressants, as a class, are characterised by considerable toxicity, especially on account of their autonomic and sedative side effect profile. In particular, anticholinergic side effects such as dry mouth, impaired accommodation and consti- pation may limit their potential efficacy because of poor compliance with treatment especially at therapeutic doses (Donoghue et al., 1996). The addition of a fourth ring to their structure has not eliminated these difficulties. The introduction of fluoxetine, an antidepressant with a more specific action on neurotransmitters, offered the possibility of better tolerated pharmacotherapy for depression (Chouinard, 1985; Laakman et al., 1988). This possibility has been confirmed by subsequent research (Judd et al., 1993; Montgomery et al., 1994).

There has been some debate about the usefulness of the impact of antidepressants on sleep (Montgomery, 1991; Tollefson et al., 1994). One of the possible advantages of selective serotonin re-uptake inhibitors, such as fluoxetine, is that they are less prone to cause drowsiness (Benfield et al., 1986; Pu ◎tler and Hajak, 1991): it is often assumed that this benefit may be achieved at a cost of less normalisation of the sleep pattern following the initiation of treatment but data from a study of fluoxetine in the elderly have suggested this may not be a problem (Kerr et al., 1993; Fairweather et al., 1993).

Escitalopram is a widely used SSRI marketed in India. Its efficacy has been demonstrated in major depression (Mendlewicz et al., 1980). The most widely used SSRI is fluoxetine, a drug which has been shown to be highly effective as a treatment for depression in numerous studies (Benfield et al., 1986; Silverstone, 1989). It is known to be less sedating than tricyclic antidepressants and its side effect profile has been characterised (Benfield et al., 1986). We therefore decided to investigate the relative efficacy and tolerability of these two antidepressants and to measure their impact on sleep patterns by using the Leeds Sleep Evaluation Questionnaire (Hindmarch, 1975; Parrott and Hindmarch, 1978, 1980) long established as the instrument best suited for use in this setting.

METHODS The study was approved by the Local Ethics Committee and was conducted in accordance with the Declaration of Helsinki (Hong Kong revision).

### Aim

The aim of the study was to compare the efficacy in depression and anxiety symptoms, tolerability, and impact on sleep of fluoxetine with that of escitalopram in the treatment of major depression. Patients were either treatment naı ◎ve or their antidepressant therapy in the previous month had proved inadequate or ineffective.

### Methodology

The study was designed as a randomised double blind, double dummy, comparator controlled clinical trial of fluoxetine vs escitalopram in patients with major depression. The trial had two phases; a single blind placebo controlled run-in phase lasting 1 week and a double blind acute treatment phase lasting 6 weeks, followed by a 6-month follow up period on treatment. Efficacy was evaluated using established rating scales for depression. Safety and tolerability were documented by collecting adverse event data and measuring sleep performance using the Leeds Sleep Evaluation Questionnaire (Hindmarch, 1975; Parrott and Hindmarch, 1978, 1980).

Patients aged between 18 and 70 years presenting with major depression (ICD-10 criteria) were entered into a single blind placebo controlled evaluation phase lasting 1 week (study visits 1–2). They were subsequently randomised to treatment with either fluoxetine or escitalopram if they met the following criteria at the end of the placebo controlled single blind run-in phase: confirmed diagnosis of major depression (ICD-10 criteria) with a rating of at least 22 on the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Patients were excluded from the study if they met the following criteria: concurrent treatment for depressive illness or with other drugs with psychopharmacological effects, serious risk of suicide, significant cardiac, renal or hepatic disease, and for women: pregnancy, lactation, inadequate method of contraception.

Patients who entered the randomised active treatment phase (study visits 2–5 at the ends of weeks 1, 2, 4 and 7) received either active fluoxetine 20 mg in the morning and placebo (resembling escitalopram) in the evening, or placebo (resembling fluoxetine) in the morning and active escitalopram in the evening. The acute treatment phase lasted for 6 weeks. Following the acute treatment phase patients who had responded remained on treatment for up to 6 months.

The evaluation of the patients involved the collection of the following data. At enrolment demographic data and a medical and psychiatric history and examination were carried out. At each visit the following psychiatric rating scales were completed: Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), Hamilton Depression rating scale (HAM-D) (Hamilton, 1967), Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), and the Clinical Global Impression scale (CGI) (Guy, 1976). The impact of the two treatments on anxiety symptoms was assessed by analysis of the subscales of the HAM-D and the BPRS. To measure the impact of study treatment on sleep the Leeds Sleep Evaluation Questionnaire was administered.

Safety and tolerability data were collected both in terms of vital signs and laboratory data, as well as by a symptom checklist designed to evaluate the common side effects of antidepressant treatments.

**Table 1. Patient Distribution**

| Population | Total | Fluoxetine | Escitalopram |
|---|---|---|---|
| Enrolled | 125 | - | - |
| Randomised | 107 | 51 | 56 |
| Treatment phase withdrawal | 30 | 14 | 16 |
| Due to adverse event | 6 | 2 | 4 |

The study was analysed using descriptive methodology. Inferential statistics were calculated only for those clinically relevant differences which emerged in the main end points. The population for the analysis comprised all patients who had received at least one dose of active medication and for whom there was at least one set of efficacy measurements. The safety analysis included all cases who had received at least one dose of study medication.

Data were analysed using appropriate summary statistics (mean, standard deviation, median, ranges) and frequency distributions were plotted. In addition efficacy data were analysed by comparing differences from baseline between treatment groups for the end of the acute treatment phase (6 weeks). Safety data from the follow up period were included in the analysis of tolerability of the two treatments.

The rating scales were analysed by determining the means, standard deviations, medians and ranges at each time point for each treatment group. Where appropriate, differences from baseline (randomisation visit) were calculated. The results were tabulated and appropriate graphs were drawn.

Safety data were tabulated and analysed using descriptive statistics. The relative frequencies of the common events were compared by calculating the ratio of the number of events occurring on fluoxetine to the number of events occurring on escitalopram (after adjusting the data for the actual number of patient visits documented for each treatment).

All statistical tests were two-tailed, and the limit of statistical significance was set at $\alpha = 0.05$ No adjustments were made for multiple testing (Perneger, 1998).

**RESULTS**

One hundred and twenty-five patients with major depression were enrolled into the study. Of these patients, 18 were withdrawn during the run-in phase because their condition did not meet the randomisation criteria. Therefore, 107 patients were randomised to treatment ( fluoxetine 51, escitalopram 56). The mean age of the study population was 43 (SD, 125) years (range 22–70 years) and there were more women (60) than men (47).

The disposition of patients is shown in Table 1. At the end of the acute treatment phase 73 per cent of the fluoxetine group remained on treatment compared to 71 per cent of the escitalopram group.

The mean MADRS scores at baseline were similar in both groups. The values fell sharply over the six weeks of the acute treatment phase but there were no significant differences between the two treatments (Table 2). The results of the Hamilton rating scale showed a similar pattern (Table 3) and no significant differences between the treatments were demonstrated using this instrument. Similar findings were observed using the BPRS (Table 4).

The impact of the two treatments on sleep, as measured by the Leeds Sleep Evaluation Questionnaire, was similar (Table 5). Both treatments were associated with normalisation of sleep as the patients became less depressed. The impact of both drugs on getting to sleep was apparent within the first week of active treatment after which it was maintained throughout the study.

**Table 2. Montgomery–Asberg Depression Rating Scale: overall mean scores**

| | W1 | W2 | W4 | W |
|---|---|---|---|---|
| Fluoxetine | | | | |
| Mean | 28.0 | 23.9 | 17.3 | 13.0 |
| SD | 5.0 | 9.1 | 9.9 | 10.0 |
| Number of Patients | 50 | 48 | 45 | 37 |
| Escitalo-pram | | | | |
| Mean | 29.9 | 25.7 | 20.0 | 16.0 |
| SD | 7.3 | 9.2 | 9.7 | 9.0 |
| Number of Patients | 56 | 53 | 47 | 39 |

W = week
SD = Standard Deviation

**Table 3. Hamilton Depression rating Scale : overall mean scores**

| | W1 | W2 | W4 | W7 |
|---|---|---|---|---|
| Fluoxetine | | | | |
| Mean | 19.8 | 15.8 | 12.5 | 9.2 |
| SD | 4.6 | 6.4 | 7.9 | 7.1 |
| Number of Patients | 51 | 48 | 47 | 37 |
| Escitalo-pram | | | | |
| Mean | 21.0 | 18.0 | 18.8 | 11.3 |
| SD | 5.7 | 6.5 | 7.2 | 6.3 |
| Number of patients | 56 | 53 | 47 | 39 |

W = week
SD = Standard Deviation

A greater improvement in getting to sleep was noted with fluoxetine at week 7 Quality of sleep improved more gradually and more consistently with both treatments throughout the study .The results for hangover effects of treatment

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showed that there was a marginal advantage for fluoxetine over escitalopram but this difference was not statistically significant.

**Table 4. Brief Psychiatric Rating Scale**

| | W1 | W2 | W4 | W7 |
|---|---|---|---|---|
| Fluoxetine | | | | |
| Mean | 12.9 | 10.8 | 8.6 | 6.8 |
| SD | 7.6 | 6.0 | 5.9 | 5.1 |
| Number of Patients | 51 | 47 | 46 | 37 |
| Escitalo-pram | | | | |
| Mean | 15.6 | 14.5 | 12.5 | 10.1 |
| SD | 7.3 | 8.0 | 8.2 | 7.3 |
| Number of Patients | 56 | 51 | 46 | 38 |

W = week
SD = Standard Deviation

**Table 5. Leeds Sleep Evaluation Questionnaire**

| Week | | Fluoxetine | Escitalo-pram | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Getting to Sleep score | | | | |
| 1 | 54.7 | 20.53 | 44.6 | 25.25 |
| 2 | 47.22 | 20.51 | 49.95 | 23.94 |
| 4 | 42.09 | 20.21 | 40.83 | 16.47 |
| 7 | 44.15 | 18.14 | 44.16 | 17.94 |
| Quality of Sleep Score | | | | |
| 1 | 34.05 | 8.75 | 33.19 | 15.79 |
| 2 | 32.15 | 11.24 | 30.86 | 13.36 |
| 4 | 29.98 | 11.87 | 29.05 | 12.47 |
| 7 | 30.24 | 10.36 | 29.08 | 13.25 |
| Hangover Score | | | | |
| 1 | 55.25 | 17.75 | 55.28 | 17.74 |
| 2 | 57.68 | 15.61 | 54.79 | 12.51 |
| 4 | 53.62 | 18.42 | 50.13 | 16.11 |
| 7 | 52.74 | 15.57 | 49.42 | 20.17 |

The number of patients dropping out of the study due to side effects during the acute phase was small and similar on both treatments (Table 1) but in the long term follow up the drop out rate on escitalopram increased more than that on fluoxetine. Thus by the end of the 6-month follow up period the drop out rate was markedly higher in the escitalopram group 42/56 (75 per cent) than in the fluoxetine group 32/51 (63 per cent).

## DISCUSSION

Our study has provided several important clarifications as to the relative safety and efficacy of escitalopram and fluoxetine. Whilst both drugs are effective as antidepressants fluoxetine is better tolerated than escitalopram. Furthermore despite its non-sedating profile fluoxetine has both anxiolytic and sleep normalisation properties which are demonstrably similar to those of escitalopram.

The impact of the two drugs on sleep is interesting. Both drugs had an early impact on getting to sleep with a noticeable improvement in the relevant sub-scale of the Leeds Sleep Evaluation Questionnaire in the first 2 weeks. The sedating property of escitalopram is consistent with the greater frequency with which drowsiness was reported as a side effect (Figure 1). Both drugs improved sleep quality and there was little evidence of a hangover after awakening on the basis of the Leeds Sleep Evaluation Questionnaire.

Our study has confirmed that fluoxetine is as effective as escitalopram in the acute treatment of major depression and has shown that fluoxetine has a better tolerability profile without loss of the beneficial effect of normalising sleep. In addition fluoxetine has been shown to be as effective as escitalopram in relieving the symptoms of anxiety associated with depression.

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