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The effect of escitalopram on sleep problems in depressed patients

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The results from three 8-week escitalopram studies in major depressive disorder are presented with respect to efficacy and the effect on sleep quality, both in the full population and the subpopulation of patients with sleep problems at baseline.

Analysis of pooled data from these randomized, double-blind, placebo-controlled, studies in which citalopram was the active reference, showed a significant improvement for escitalopram-treated patients ($n = 52{\cdot}0$) in the Montgomery-Åsberg depression rating scale (MADRS) item 4 ('*reduced sleep*') scores at weeks 6 and 8 compared with placebo ($n = 398$; $p < 0.01$) and at weeks 4, 6 and 8 ($n = 403$; $p < 0.05$) compared with citalopram.

Escitalopram-treated patients with sleep problems (MADRS item 4 score$\geq$4; $n = 254$) at baseline showed a statistically significant improvement in mean MADRS item 4 scores at weeks 4, 6 and 8 compared with patients treated with placebo ($n = 191$; $p < 0.05$) or citalopram ($n = 193$; $p < 0.01$). These patients also showed a statistically significant ($p < 0.05$) and clinically relevant improvement in MADRS total score after escitalopram treatment compared with citalopram at weeks 1, 4, 6 and 8 (observed cases) and endpoint (-2.45; last observation carried forward [LOCF]). Statistical significance in favour of escitalopram versus placebo treatment was found at all visits, including endpoint (-4.2; LOCF).

Thus, these post-hoc analyses suggest that escitalopram has a significant beneficial effect compared with placebo or citalopram in reducing sleep disturbance in patients suffering from major depressive disorder. The effect of escitalopram in improving '*reduced sleep*' scores was clearly seen in patients with more severe sleep disturbance at baseline. A further prospective study is needed to establish this useful clinical effect in insomniac depressives. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — escitalopram; sleep problems; MADRS; citalopram

INTRODUCTION

Over the past 40 years, it has become established that sleep is altered in patients with depression (Winokur and Reynolds, 1997). A pan-European survey of approximately 1900 patients who consulted a health-care professional about depression showed that 76% suffered from low mood, 73% complained of reduced energy and fatigue and 63% reported sleep problems (Tylee *et al*., 1999). The most common complaints related to sleeping problems are increased sleep latency, frequent awakenings after sleep onset, early morning awakening, and unrefreshing sleep, often particularly distressing symptoms. Polysomnographic sleep studies confirm that the sleep pattern of depressive patients is abnormal (Reynolds and Kupfer, 1987; Benca *et al*., 1992).

Many antidepressants (TCAs and some SSRIs) alter the sleep pattern in depressive patients by restoring rapid eye movement (REM) latency by suppressing REM sleep (Doghramji, 1989; Gursky and Krahn, 2000). An example is citalopram, which decreases REM sleep and lengthens significantly REM latency. However, no significant relationship was detected between REM suppression and clinical response (van Bemmel *et al*., 1993).

Other antidepressants, such as mirtazapine, the tricyclics and paroxetine are perceived as helpful due to

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a sedative effect. However, they often also induce daytime somnolence, as a side effect. The optimal antidepressant for patients presenting with sleep problems as a symptom of depression should improve sleep quality rather than causing somnolence. If effective, such a therapy would also minimize the need to augment the antidepressant medication with hypnotics or benzodiazepines. These have been used widely in the treatment of insomnia, but may induce daytime sedation with cognitive deficit and increased risk of falls and of motor vehicle accidents (Jindal *et al*., 2004). They may also result in rebound insomnia and tolerance, and they have an addictive potential.

Escitalopram is significantly more efficacious than citalopram in the treatment of depression when used in equivalent doses (Lepola *et al*., 2004). This is supported by two recent studies indicating an as least as good efficacy but better tolerability of escitalopram compared with venlafaxine XR mg (Montgomery *et al*., 2004; Bielski *et al*., 2004). This paper investigates the effect of escitalopram on sleep seen in clinical trials in the treatment of patients with depression, based on single item scores of the Montgomery Åsberg depression rating scale (MADRS; Montgomery and Åsberg, 1979) and reported treatment-emergent adverse effects, such as sedation and insomnia.

METHODS

Studies

There are three placebo-controlled studies with escitalopram that include citalopram as the active comparator that were used in this analysis (Burke *et al*., 2002; Lepola *et al*., 2003; Rapaport *et al*., 2004). For all three studies (Table 1), which were of similar design, the following applied:

- similar inclusion criteria were used for patients with MDD as defined by the DSM-IV criteria
- the studies were all double-blind, randomized, placebo-controlled 8-week studies with a 1-week single-blind placebo lead-in
- the MADRS total score was used as the primary efficacy measure, with a minimum total score of 22 for inclusion.

Eligible patients were male or female outpatients between 18 and 65 years of age. For one study (USII) the upper age limit was 80.

Concomitant therapy with any psychotropic drugs were not allowed except:

- in the US studies, zolpidem could be used for sleep problems at a maximum dose of 10 mg/day, up to three times per week.
- in the European study, benzodiazepines were allowed during the study if used for insomnia at a stabilized dose.

Statistical analyses

The statistical analysis was performed on the pooled modified *intent-to-treat* (ITT) population, comprising all patients from the three studies who received at least one dose of double-blind study medication and had at least one valid post-baseline MADRS assessment. Analyses were performed on adjusted mean changes from baseline in MADRS total score and on MADRS item 4 ('*reduced sleep*') (see Table 2).

Analyses were performed on the subsample of patients who had sleep problems at baseline (defined as a MADRS item 4 score of $\geq$4). The criterion for recovery from sleep problems was defined as a score on item 4 of 0 or 1 at endpoint. Further analyses were made on subgroups of the patients: the moderately

Table 1. Details of the individual studies used in the pooling

Reference	Inclusion criteria	Treatment group	No of patients per group	Withdrawal rate	Primary efficacy result[a]
USI	MADRS	Escitalopram 10 mg	118	20.2	−12.8
Burke *et al.*,	≥22	Escitalopram 20 mg	123	24.8	−13.9
2002	Age 18–65	Citalopram 40 mg	125	25.6	−12.0
		Placebo	119	25.4	−9.4
USII	MADRS	Escitalopram 10–20 mg	124	23.2	−12.9
Rapaport *et al.*,	≥22	Citalopram 20–40 mg	119	19.5	−13.0
2004	Age 18–80	Placebo	125	17.3	−11.2
Europe	MADRS	Escitalopram 10–20 mg	155	5.8	−15.0
Lepola *et al.*,	22–40	Citalopram 20–40 mg	159	5.0	−13.1
2003	Age 18–65	Placebo	154	9.7	−12.1

[a] The primary efficacy parameter in all studies was the mean change from baseline to week 8 in the MADRS total score (LOCF).

Table 2. MADRS sleep item

MADRS item
4. Reduced Sleep Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well. 0 Sleeps as usual 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep 4 Sleep reduced or broken by at least two hours 6 Less than two or three hours sleep

depressed patients (MADRS total score at baseline 22–29) and the more severely depressed patients (MADRS total score at baseline $\geq$30).

Both MADRS total score and MADRS item 4 scores were analysed by ANCOVA with study, treatment group, and centre as factors and baseline efficacy score as covariate. Remission rates were analysed by logistic regression, adjusting for the same factors as above. Since withdrawal rates were similar between treatments (Table 1), all analyses were conducted using observed cases (OC) data, with LOCF (last observation carried forward) data also shown at endpoint.

RESULTS

Study population

A total of 1321 patients were treated with placebo ($n = 398$), escitalopram ($n = 520$) and citalopram ($n = 403$). There were no demographic or clinically significant differences in the three treatment groups at baseline (Table 3). The mean MADRS total scores at baseline were 29.0, 28.7 and 28.9 for placebo, escitalopram and citalopram, respectively. The mean daily dose was 13.3 mg in the escitalopram group and 28.9 mg in the citalopram group, which represents comparable doses of the two drugs. Almost 50% of patients suffered from sleep problems, as defined by a baseline MADRS score on item 4 ('*reduced sleep*') of 4 or above [placebo (191), citalopram (193) and escitalopram (254)]. There were no significant differences between the treatment groups in the percentage of patients reporting sleep problems at baseline.

Table 3. Patient baseline characteristics

	Placebo ($n = 398$)	Escitalopram ($n = 520$)	Citalopram ($n = 403$)
Percentage female	64	67	61
Mean age (years)	42	41	42
Mean weight (kg)	80	77	79
Baseline MADRS mean total (SD)	29 (4.6)	28.7 (4.5)	28.9 (4.6)

Treatment of depression (MADRS total score)

All patients (ITT). The use of zolpidem and benzodiazepines was not significantly different between the treatment groups, and is therefore not likely to be a source of bias (in total, 6.3% escitalopram-, 5.6% citalopram- and 5.5% placebo-treated patients received zolpidem or benzodiazepines).

The mean change from baseline in the MADRS total score in the total population (ITT, LOCF) was −11.2 (placebo), −13.1 (citalopram) and −13.8 (escitalopram) (Gorman *et al*., 2002). The change from baseline to last assessment in MADRS total score (ITT, OC) was −12.0 for placebo-, −15.3 for escitalopram-, and −14.3 for citalopram-treated patients. Escitalopram treatment was statistically significantly superior to citalopram treatment at endpoint ($p < 0.05$, OC analysis), however, not for LOCF. Additionally, escitalopram and citalopram treatments were both significantly superior to placebo at endpoint ($p < 0.05$, LOCF).

Patients with sleep problems. For patients with sleep problems (i.e. with a baseline score of 4 or above on MADRS item 4), the improvement from baseline to week 8 on MADRS total score (OC analysis) was −12.2 for placebo, −16.47 for escitalopram, and −14.02 for citalopram-treated patients (Figure 1).

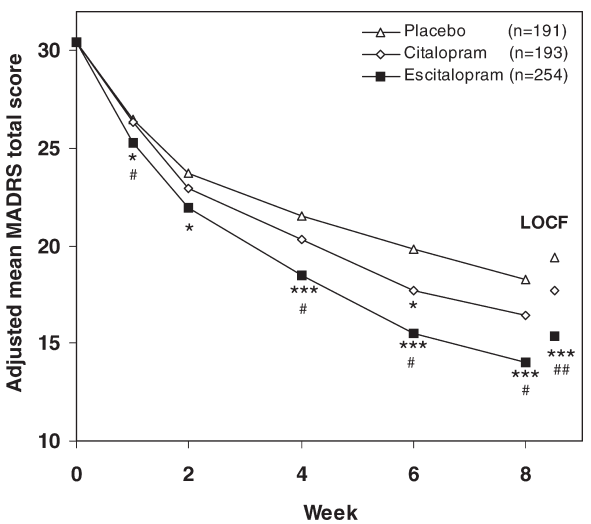

Figure 1. MADRS total score in patients suffering from sleep problems (defined as a baseline MADRS item 4 score $\geq$4). $^{*}p < 0.05$, $^{***}p < 0.001$: escitalopram vs placebo; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$: escitalopram vs citalopram

The improvement for the patients treated with escitalopram was significantly larger than placebo at all time points ($p < 0.05$). Citalopram-treated patients improved significantly more than placebo only at week 6 ($p < 0.05$), whereas escitalopram-treated patients improved significantly more than citalopram-treated patients at weeks 1, 4, 6 and 8 ($p < 0.05$).

Effect on MADRS item 4

The adjusted mean difference from baseline to week 8 in the MADRS item 4 score for all patients was significantly greater for the escitalopram group (−1.65 points) than both placebo (−1.26 points, $p < 0.01$) and citalopram (−1.31 points, $p < 0.01$; Figure 2). Analysis of MADRS item 4 for the subgroup of patients who suffered from sleep problems at baseline showed that escitalopram treatment also improved sleep quality significantly better than placebo and citalopram from week 4 and onwards, whereas citalopram did not separate from placebo (Figure 3).

Moderately versus severely depressed patients with sleep problems. The improvement in MADRS total score in the subgroup of patients who suffered from sleep problems might be because they were more severely depressed at baseline. Accordingly, patients with sleeping problems at baseline were divided into moderately depressed [MADRS 22–29: placebo ($n = 82$), escitalopram ($n = 106$) and citalopram ($n = 89$)] and severely depressed [MADRS > 30; placebo ($n = 109$), escitalopram ($n = 148$) and citalopram ($n = 104$)] patients.

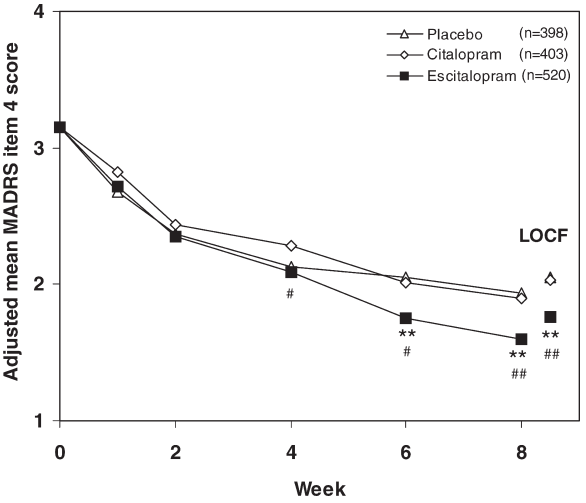

Figure 2. Change in MADRS item 4 ('*reduced sleep*') for all patients (ITT). $^{**}p < 0.01$: escitalopram vs placebo; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$: escitalopram vs citalopram

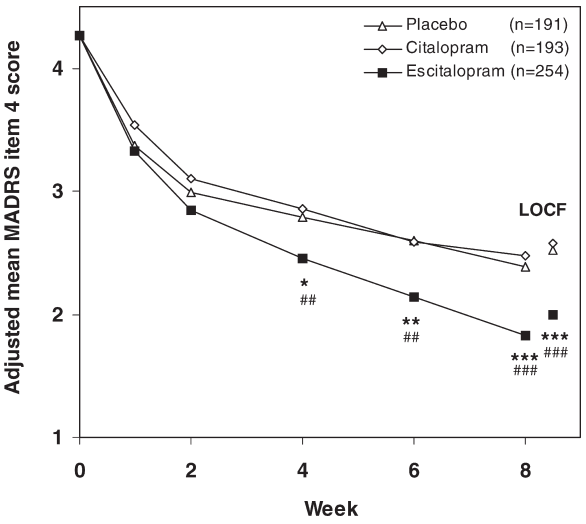

Figure 3. Change in MADRS item 4 ('*reduced sleep*') for the subpopulation of patients suffering from sleep problems (defined as a baseline MADRS item 4 score ≥4). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$: escitalopram vs placebo; $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$: escitalopram vs citalopram

Based on MADRS total score at endpoint (week 8, OC), escitalopram treated-patients improved significantly more than placebo-treated patients, for both moderately and severely depressed groups. The difference to placebo at endpoint in the mean MADRS total score was −3.16 ($p < 0.05$) and −5.15 ($p < 0.001$) for moderately and severely depressed patients, respectively. In contrast, there was no significant difference between citalopram- and placebo-treated patients in either the moderately depressed subgroup (mean difference = −2.02 points) or the severely depressed subgroup (mean difference = −1.5 points) at endpoint. In the severely depressed subgroup, escitalopram-treated patients separated significantly from the citalopram-treated patients at week 1 ($p < 0.05$), week 6 ($p < 0.01$), and week 8 ($p = 0.0195$) (data not shown).

Remission

All patients (ITT). There was no statistically significant difference in the median time to achieve remission (defined as achieving a single item score of 0 or 1 by week 8) for escitalopram-treated patients (ITT) for any of the single MADRS items. The onset of effect for the single items, measured as the visit at which statistically significant separation from placebo first occurred, was week 1 for items 1, 2, 3, 6 and 9

Table 4. Incidence of treatment-emergent adverse events[a]

Preferred term	Placebo $n=592$	Escitalopram $n=715$	Citalopram $n=408$
Insomnia	3.9%	9.2%	8.6%
Somnolence	2.2%	6.9%	4.7%

[a] Data from the four registration studies.

(*apparent sadness, reported sadness, inner tension, concentration difficulties* and *pessimistic thoughts*, respectively), week 4 for items 8 and 10 (*inability to feel* and *suicidal thoughts*, respectively), and week 6 for items 4 and 7 (*reduced sleep* and *lassitude*, respectively).

Patients with sleep problems. The percentage of depressed patients with sleep problems whose sleeping problems successfully improved during treatment (defined as achieving a score of 0 or 1 on MADRS item 4 at week 8) was significantly higher for the escitalopram (43.6%) than the citalopram (28.4%) or placebo groups (24.4%) ($p < 0.001$). A significant difference between escitalopram and placebo in mean MADRS total scores was seen at week 1 (and subsequently) (Figure 1), whereas for MADRS item 4 scores, a statistically significant difference between for escitalopram and placebo was seen at week 4 (Figure 2).

Sleep problems reported as adverse events

The incidence of spontaneously reported sleep-related treatment-emergent adverse events as a proxy for causing sleep problems, is shown in Table 4, which includes patients from a fourth pivotal study (Wade *et al*., 2002). Relatively few patients (11/194) reported daytime somnolence as well as insomnia.

DISCUSSION

Sleep is an important part of depression (Tylee *et al*., 1999) and it is important to cure this symptom (Doghramji, 1989; Thase *et al*., 1992). However, many medications used to treat depression may interfere with sleep. For example, some SSRIs and venlafaxine tend to decrease sleep quality (Lustberg and Reynolds, 2000; Rudolph *et al*., 1998). These changes include reduced sleep time and increased night-time awakenings, as well as inducing somnolence. In order to evaluate whether escitalopram affects sleep positively or negatively in depressive patients treated with the drug, this *post-hoc* analysis of the fourth item of the MADRS was made. A single item analysis of the MADRS scale is justified, as this scale was designed to be sensitive to change (Montgomery and Åsberg, 1979).

The analyses show that escitalopram is better than both placebo and citalopram in improving the sleep item of the MADRS scale. This confirms previous results from individual studies for escitalopram compared with placebo (Wade *et al*., 2002; Lepola *et al*., 2003). Although escitalopram is effective in treating sleep problems among depressive patients, some patients did report sleep-related adverse events (insomnia and somnolence). While present in the escitalopram group at a higher incidence than in the placebo group, these AEs have a relatively low incidence, are core symptoms of MDD, and are therefore considered of minimal clinical importance. These symptoms were mainly reported by different patients, with only 11/194 reporting both insomnia and somnolence. This argues against daytime somnolence arising as the result of insomnia.

A further consideration is whether sleep problems remit in parallel with other depressive symptoms. For escitalopram, there is an approximate 4-week delay in achieving a significant difference from placebo for MADRS item 4 ('*reduced sleep*') compared with MADRS total score as well as many other single MADRS items. However, after 8 weeks the improvement in the sleep item was significantly better for escitalopram compared with both placebo and citalopram. This indicates that depressive symptoms and sleep problems are both treated during the acute phase of the treatment, which is clinically relevant in order to avoid relapse or recurrence of the depression. This is often not the case, and sleep problems may persist after the depression has remitted. In a fluoxetine study of the subgroup of depressive patients who achieved remission (total score HAMD ≤ 7 after 8 weeks treatment), 44% considered that they were still not sleeping well and 38% considered themselves to remain fatigued (Nierenberg *et al*., 1999). While co-therapy with clonazepam may partially suppress fluoxetine's side effects of anxiety and sleep disorder, the results with benzodiazepine augmentation were not as compelling as the short-term therapeutic effect of clonazepam alone on presenting symptoms of anxiety and sleep disorder (Londborg *et al*., 2000). Since patients with residual symptoms of insomnia have a higher risk of relapsing (Doghramji, 1989; Thase *et al*., 1992) or committing suicide (Agargun *et al*., 1997; Hall *et al*., 1999) than those without, it is important that sleep problems are also successfully treated.

These empirical post-hoc analyses suggest that escitalopram is an efficacious treatment for the

component symptom of poor quality of sleep in depressive patients. Since citalopram, despite being an effective antidepressant, does not show an improvement in sleep, this would suggest that the effect of escitalopram could be a specific one on sleep and not just part of a general antidepressant effect. This putative efficacy is particularly important in the more severely insomniac patients, who are often very distressed by sleep problems.

The results from these trials demonstrate that escitalopram was efficacious in treating depressive symptoms in both moderately and severely depressed patients suffering from poor sleep quality. The beneficial effect of escitalopram on sleep seemed to be independent of the severity of the patient's sleep problems at baseline. This finding needs to be confirmed in a prospective study using specific sleep rating scales, complemented ideally by a polysomnographic evaluation.

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