

# Escitalopram in a working population: results from an observational study of 2378 outpatients in Austria<sup>†</sup>

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**Objective** The aim of this observational study was to evaluate the effectiveness of escitalopram in a naturalistic sample of employed people with mood and anxiety disorders.

**Method** Days on sick leave 3 months prior and 3 months during treatment with escitalopram were recorded and compared (mirror study design) in 2378 patients (949 men and 1376 women). A further clinical examination including the clinical global impression of severity (CGI-S) and improvement (CGI-I) scales and assessments of tolerability were used to evaluate treatment effects in a subgroup of 807 study subjects.

**Results** Escitalopram treatment (mean final daily dosage:  $12.4 \pm 5.0$  mg) led to a significant reduction (baseline versus end of study) of sick leave ( $11.0 \pm 12.8$  days versus  $5.4 \pm 11.0$  days;  $p < 0.001$ ). CGI-S scores decreased from  $4.7 \pm 0.9$  at baseline to  $2.4 \pm 1.1$  after 3 months ( $p < 0.001$ ), the CGI-I after 3 months was  $1.9 \pm 0.9$ . The incidence of adverse events after initiation of treatment with escitalopram was 13.1%, with only 1.3% of patients experiencing severe adverse events interfering with patient functioning.

**Conclusion** Our results suggest that escitalopram is an efficacious and overall well-tolerated treatment in a naturalistic sample of working patients. A decrease in the days on sick leave is indicative of indirect cost-effectiveness of this treatment. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — escitalopram; major depression; antidepressants; sick leave

## INTRODUCTION

Mood and anxiety disorders are highly prevalent and disabling, making them a major global burden (Chrisholm, 2005). They are common in the community and often affect functioning to such an extent that it leads to absence from work. This kind of dysfunction is of extensive social and financial concern for the patient and for society. In Austria, the average cost of a single day of sick leave is 85 euro (Hauptverband der Österreichisches Sozialversicherungsträger, 2002; Statistik Austria, 2003), and patients with psychiatric disorders have a higher number of days on sick leave compared to the healthy, working population (Kessler *et al.*, 2001).

Antidepressants are the choice of treatment for mood and anxiety disorders. In Austria, escitalopram is registered for the treatment of major depressive disorder, panic disorder with or without agoraphobia, social anxiety disorder, and generalized anxiety disorder (Winkler and Kasper, 2004). Escitalopram has been termed a serotonin dual action antidepressant as it binds to both the primary site of the serotonin transporter and to the allosteric site, which increases the reuptake inhibition (Chen *et al.*, 2005). The efficacy of escitalopram has been shown in controlled clinical trials in primary care and in specialist settings, for the treatment of depression (Burke *et al.*, 2002; Gorman *et al.*, 2002; Auquier *et al.*, 2003; Lepola *et al.*, 2003; Llorca *et al.*, 2005; Moore *et al.*, 2005; Wade *et al.*, 2005b; Kasper *et al.*, 2006; Kennedy *et al.*, 2006) and anxiety disorders (Stahl *et al.*, 2003; Goodman *et al.*, 2005; Kasper *et al.*, 2005).

Observational studies fulfill an important function in assessing drug effectiveness (Hakkarainen *et al.*, 1984; Linden *et al.*, 1994). The patients included in

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controlled trials prior to drug registration comprise a homogenous group, and it is therefore often questioned whether the results of these trials can be directly transferred to the daily clinical practice that consists of a heterogeneous group of patients, including elderly patients, patients with comorbid diseases, and those on different concomitant medications. Observational studies are therefore important to test the results from controlled, clinical trials in a more naturalistic patient cohort. Escitalopram has been investigated in open-label studies as well as in naturalistic settings (Klein *et al.*, 2004; Rush and Bose, 2005; Anders *et al.*, 2006; Pjrek *et al.*, 2006), including the largest antidepressant trial to date, with 11 760 patients on escitalopram (Möller *et al.*, 2005).

The present study examined the effectiveness of treatment with escitalopram. In addition, it was investigated whether treatment with escitalopram would affect the number of days on sick leave, which represents an important part of the indirect costs of mental illness in a working population in Austria. The effect of treatment on work attendance was assessed as the number of days absent from work, prior to and during treatment with escitalopram.

## METHODS

### *Patients*

The present observational study was conducted in accordance with Austrian Pharmaceutical Law (Arzneimittelgesetz §2a) (Bundesgesetzblatt für die Republik Österreich, 1983). It was an open-label, multi-center, naturalistic trial, including patients from 505 general practitioners or specialists in psychiatry or neurology across Austria. Patients were recruited between September 2004 and March 2005. They were included, if the physician judged them as being suitable for treatment with escitalopram. At least three visits were planned; one at inclusion, the second 4–6 weeks after inclusion, and a last visit after 3 months on medication. No restrictions were imposed concerning the treatment and dosage of escitalopram or the use of concomitant medication.

### *Assessments*

Basic demographic information and days on sick leave in the last 3 months before and during 3 months of treatment with escitalopram (mirror study design) were recorded in 2378 subjects. This information was derived by self-reports of the study subjects and was documented by the clinician. To derive a more detailed

picture on the course of illness, physicians were encouraged to perform an extended clinical interview with some of their patients: This examination was carried out in 807 study subjects and included the clinical global impression of severity (CGI-S) and improvement (CGI-I) (Guy, 1976), therapeutic efficacy (1: very good, 2: moderate, 3: poor, 4: unchanged), body mass index (BMI) before and after treatment, psychiatric diagnosis, duration of illness, previous antidepressive treatment, concomitant medication and escitalopram dosage, adverse events, patient compliance, and the choice of further treatment at the end of the study.

### *Statistical methods*

Data were analyzed with SPSS for Windows (SPSS Inc., 1989–2001). In addition to descriptive statistics, paired *t*-tests and repeated measures analysis of variance (ANOVA) with Bonferroni corrected *post-hoc* tests were utilized. A last observation carried forward (LOCF) approach was employed for missing data. The  $p \leq 0.05$  level of significance was adopted. All statistical comparisons were two-tailed.

## RESULTS

### *Patient characteristics at inclusion*

A total of 2378 patients (40.8% men, 59.2% women) was included in the study. The mean age ( $n = 2378$ ) was  $42.3 \pm 10.6$  years (range: 17–85 years, 2% over the age of 65) and the mean duration of illness ( $n = 807$ ) was  $2.5 \pm 5.0$  years. Mean BMI at baseline ( $n = 807$ ) was  $25.2 \pm 3.0 \text{ kg/m}^2$  for men and  $23.9 \pm 3.6 \text{ kg/m}^2$  for women (Table 1). Diagnostic characteristics for the subgroup of 807 patients participating in a more detailed clinical examination are reported in Table 2. While the gender distribution of these 807 patients was not different compared with the remaining 1571 patients ( $\chi^2 = 0.868$ ,  $df = 1$ ,  $p = 0.352$ ), the study subjects with the extended examination were slightly older ( $43.4 \pm 11.3$  vs.  $41.7 \pm 10.2$  years;  $t = 3.535$ ,  $df = 1501.585$ ,  $p < 0.001$ ). Details regarding how the patients were switched from previous antidepressants were not documented.

### *Treatment and clinical outcomes*

The mean initial daily dose of escitalopram was  $9.0 \pm 3.2$  mg ( $n = 805$ ). After 4–6 weeks of treatment the daily dosage increased to  $12.1 \pm 4.7$  mg ( $n = 794$ ), and to  $12.4 \pm 5.0$  mg at the last visit ( $n = 760$ ;

Table 1. Patient demographics

	Assessment of sick leave	Detailed clinical examination	Total
Number of patients	1571	807	2378
Men	637 (41.5%)	312 (39.5%)	949 (40.8%)
Women	898 (58.5%)	478 (60.5%)	1376 (59.2%)
Age (years)	41.7 ± 10.2	43.4 ± 11.3	42.3 ± 10.6
Illness duration since onset (years)		2.5 ± 5.0	
Height (cm)			
Men		178.0 ± 6.5	
Women		166.3 ± 5.8	
Weight (kg)			
Men		80.0 ± 10.2	
Women		66.0 ± 10.1	
BMI (kg/m <sup>2</sup> ) before treatment			
Men		25.2 ± 3.0	
Women		23.9 ± 3.6	
BMI (kg/m <sup>2</sup> ) after treatment			
Men		25.3 ± 3.1	
Women		24.0 ± 3.7	

Figure 1). Initially, 28.1% of patients took 5 mg/day (decreasing to <4% after 4–6 weeks), with 71.5% of patients taking 10 mg/day. After 3 months of treatment, 67.6% of patients were taking 10 mg/day, 9.5% were taking 15 mg/day, and 17% were taking 20 mg/day.

Ratings with CGI-S and CGI-I were made for 805 patients at the start of treatment, for 798 after 4–6 weeks, and for 774 after 3 months. During treatment, there was a significant decrease in CGI-S score from  $4.7 \pm 0.9$  at baseline to  $3.4 \pm 1.0$  after 4–6 weeks, and  $2.4 \pm 1.1$  after 3 months of treatment ( $F = 2436.6$ ,  $df = 1.686$ ,  $p < 0.001$ ; *post-hoc* tests among all three time points:  $p < 0.001$ ; Figure 2). The improvement of the patients' clinical condition was measured by a significant decrease of the CGI-I from  $2.5 \pm 0.8$  after 4–6 weeks to  $1.9 \pm 0.9$  at the end of the study ( $p < 0.001$ ). The therapeutic efficacy was rated as  $1.8 \pm 0.9$  and  $1.4 \pm 0.7$  at the same time points.

Three months before treatment, the average number of days on sick leave ( $n = 2378$ ) was  $11.0 \pm 12.8$ , which significantly decreased to  $5.4 \pm 11.0$  days

during the 3 months of escitalopram treatment ( $t = 24.934$ ,  $df = 2298$ ,  $p < 0.001$ ; Figure 3). The 807 patients with the more detailed clinical examination had a higher number of days on sick leave than the remaining 1571 subjects before ( $12.6 \pm 18.6$  vs.  $10.3 \pm 8.5$  days;  $t = 3.249$ ,  $df = 910.286$ ,  $p = 0.001$ ) and after ( $7.4 \pm 16.7$  vs.  $4.3 \pm 6.0$  days;  $t = 5.120$ ,  $df = 880.691$ ,  $p < 0.001$ ) initiation of treatment with escitalopram. Of our patients, 45.4% ( $n = 807$ ) had previously been treated with antidepressants: these patients had significantly more sick leave days in the 3 months before the study ( $15.1 \pm 19.9$  days) than patients without previous antidepressant treatment ( $10.5 \pm 17.1$  days;  $t = -3.337$ ,  $df = 665.173$ ,  $p =$

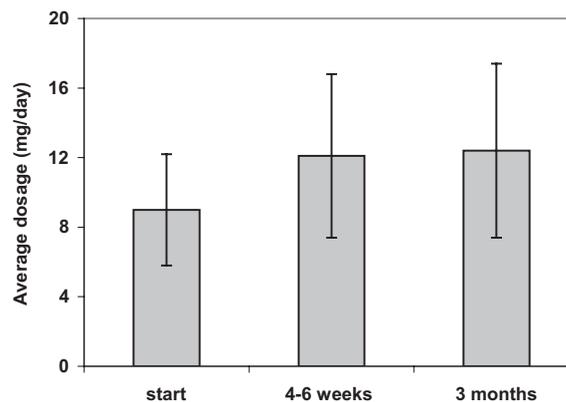


Figure 1. Daily dosage of escitalopram (mean ± SD) at baseline ( $n = 805$ ), 4–6 weeks ( $n = 794$ ), and after 3 months ( $n = 760$ ) of escitalopram treatment. Analysis of variance (ANOVA) with repeated measures and *post-hoc* tests with Bonferroni correction were used for comparison of the three visits ( $p < 0.001$  for differences between all visits)

Table 2. Diagnostic characteristics of patients at baseline

	<i>n</i> (%)
Baseline diagnosis <sup>1</sup>	807
Affective disorders (F3)	617 (76.5)
Anxiety disorders (F40, F41)	87 (10.8)
Adjustment disorder (F43.2)	49 (6.1)
Somatoform disorders (F45)	38 (4.7)
Other psychiatric disorders	66 (8.2)

<sup>1</sup>According to ICD-10 (WHO, 1991).

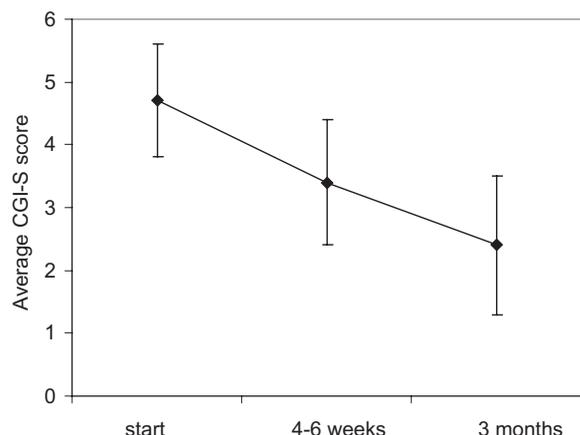


Figure 2. Clinical global impression of severity (CGI-S; mean  $\pm$  SD) for 796 patients at baseline, after 4–6 weeks, and after 3 months of escitalopram treatment. Analysis of variance (ANOVA) with repeated measures and *post-hoc* tests with Bonferroni correction were used for comparison of the three visits ( $p < 0.001$  for differences between all visits)

0.001). In both groups, there was a statistically highly significant decrease of days on sick leave during the 3 months of escitalopram treatment (patients with previous antidepressant treatment:  $7.6 \pm 16.0$  days;  $t = 7.995$ ,  $df = 317$ ,  $p < 0.001$ ; patients without previous antidepressant treatment:  $6.5 \pm 15.9$  days;  $t = 4.562$ ,  $df = 390$ ,  $p < 0.001$ ). There was no significant difference between the two groups in regard to sick leave days during escitalopram treatment ( $t = -0.878$ ,  $df = 734$ ,  $p = 0.380$ ).

#### Tolerability

Tolerability was assessed in the subgroup of 807 patients by recording adverse events. The initial incidence of adverse events after starting treatment with escitalopram was 13.1% ( $n = 106$ ), with only 1.3% ( $n = 10$ ) of patients experiencing severe adverse events that interfered with patient functioning. After 4–6 weeks of escitalopram treatment, 14.3% ( $n = 115$ ) of patients reported adverse events (2.8% [ $n = 23$ ]

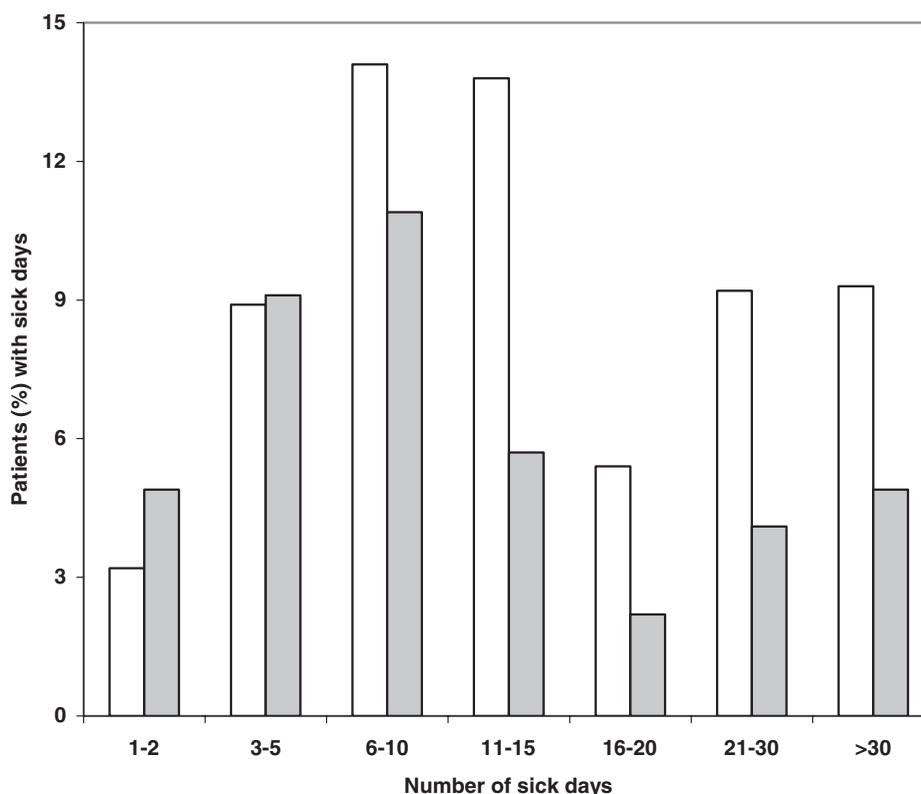


Figure 3. Percentage of patients ( $n = 754$ ) with different numbers of days on sick leave due to psychiatric morbidity; comparison of 3 months before (white bars) and 3 months during (grey bars) escitalopram treatment ( $p < 0.001$ )

Table 3. Most common adverse events ( $n = 807$ )

Adverse event	Start (%)	4–6 weeks (%)	3 months (%)
Patients with adverse events	13.1	14.3	7.3
Nausea	5.8	2.5	1.2
Inner tension	1.9	1.5	0.6
Ejaculation disorders	1.1	0.9	0.9
Dizziness and cardiovascular problems	1.0	1.1	0.5
Fatigue	1.0	1.4	0.5
Insomnia	1.0	0.9	0.6
Increased sweating	1.0	1.0	0.7
Headache	0.6	0.4	0

of which were regarded as severe), and 7.3% after 3 months treatment (1.0% of which were regarded as interfering with daily functioning). The incidence of the most common adverse events showed a trend wise decline during the course of the study (Table 3).

The BMI recorded in 807 patients before ( $24.4 \pm 3.4 \text{ kg/m}^2$ ) and after treatment with escitalopram ( $24.5 \pm 3.5 \text{ kg/m}^2$ ) was not statistically significantly different ( $t = -1.899$ ,  $df = 784$ ,  $p = 0.058$ ).

A total of 8.1% of patients ( $n = 807$ ) were concomitantly treated with another antidepressant at some point during the 3 months. Anxiolytic medication was prescribed in 34.9% of the patients at the beginning of the study, but only in 18.7% after 3 months of treatment. The most commonly prescribed anxiolytic substance was alprazolam (12.6% of patients). Antipsychotic medication was used in 10.4% of patients.

Of all patients, 95.2% ( $n = 2378$ ) completed the study. Reasons for withdrawal were not recorded.

#### Patient satisfaction with treatment

Physicians assessed compliance with medication as good in 91.6% of patients ( $n = 807$ ). Of the patients, 96.2% were still treated with escitalopram and continued treatment at the end of the study. During the 3 months of this study, 1.3% of the patients in this sample were switched to venlafaxine or milnacipran, 0.7% to mirtazapine or trazodone, and 0.5% to another SSRI.

#### DISCUSSION

The present observational study shows that the number of sick leave days decreased by more than 50% in a group of employed outpatients receiving escitalopram for 3 months. Furthermore, a large percentage (58.3%) of the patients had no sick leave days after 3 months of escitalopram treatment,

compared to 35.9% prior to treatment. It is important to note that the patients with previous antidepressant treatment, who had a much higher amount of sick leave before the study, had a similar reduction of days on sick leave during treatment with escitalopram compared to previously untreated patients. In this context, it is of interest that in Austria all employees with social insurance receive a sickness benefit from the fourth day onward for at least 26 weeks after becoming ill as a partial compensation for the lost income.

Most of the patients in this study were treated with 10 mg of escitalopram per day (68% at the last visit). The benefits of receiving escitalopram for 3 months can also be demonstrated by the decrease of CGI scores. Initially, patients were moderately- to markedly-ill, and ended with having mild or no symptoms at all. This decrease was comparable with the therapeutic efficacy of escitalopram reported in several randomized, controlled, clinical trials (Burke *et al.*, 2002; Gorman *et al.*, 2002; Auquier *et al.*, 2003; Lepola *et al.*, 2003; Stahl *et al.*, 2003; Goodman *et al.*, 2005; Kasper *et al.*, 2005; Llorca *et al.*, 2005; Moore *et al.*, 2005; Wade *et al.*, 2005b; Kennedy *et al.*, 2006). The study population consisted of a large, heterogeneous group of patients including 2% elderly patients and patients with psychiatric disorders, for which escitalopram is not officially registered. Still, patients treated with escitalopram showed a highly significant ( $p < 0.001$ ) decrease in illness severity (CGI-S) together with a significant ( $p < 0.001$ ) clinical response (CGI-I).

The apparent correlation between the decrease in severity of illness and the decrease in number of sick leave days indicates that escitalopram was not only able to effectively treat the symptoms of the patients but was also able to restore their ability to work. According to pharmaco-economic analyses, based on data from randomized, double-blind, trials or meta-analyses (Francois *et al.*, 2003; Hemels *et al.*,

2004a; Hemels *et al.*, 2004b; Demyttenaere *et al.*, 2005; Fernandez *et al.*, 2005; Wade *et al.*, 2005a; Wade *et al.*, 2005b), escitalopram offsets the costs of treating depression (including the direct costs of medication and physician visits), and is cost-effective compared to other antidepressants. Furthermore, it is important that studies investigating the costs of mental illness (Berto *et al.*, 2000; Smit *et al.*, 2006; Sobocki *et al.*, 2006) have consistently found that indirect costs (i.e., loss of productivity) are much higher than direct costs (i.e., drug costs, outpatient care, hospitalizations, non-medical costs).

#### Tolerability and compliance

The inclusion criteria allowed the recruitment of a heterogeneous sample of patients, typical of patients seen in everyday clinical practice. Escitalopram was well-tolerated in this study, with 91.6% of patients taking their medication as prescribed. This, together with a relatively low dropout rate of 4.8%, indicates the high satisfaction of the patients resulting in 96.2% of patients completing the study and receiving further treatment with escitalopram after the end of the study. Less than 3% of patients experienced adverse events that either led to a dose reduction or to withdrawal from the study.

#### Limitations

The naturalistic nature of the present study allowed polypharmacy, which needs to be taken into account when evaluating the reported adverse events, since side effects of drugs are more frequent when antidepressants are prescribed together with other psychotropic drugs (Corruble and Puech, 1993). In general, the methodology of observational studies has its own limitations, for example, non-randomization or higher inter-rater variability. Furthermore, our estimation of days on sick leave was based on self-reports of the patients, which encompasses the possibility of a memory bias. Finally, a mirror study design has some inherent limitations like the possibility of spontaneous remissions during the course of illness, or the lack of a parallel group comparator agent to compare, if other antidepressants would be equally effective.

#### CONCLUSION

Escitalopram was efficacious and overall very well-tolerated in this naturalistic, heterogeneous group of employed outpatients. These patients had about 50%

fewer days on sick leave during the 3 months of treatment with escitalopram, when compared to the number of days on sick leave during the 3 months prior to treatment.

Future observational trials should investigate, if escitalopram possesses similar efficacy in the continuation and long-term treatment of affective and anxiety disorders, as has been demonstrated in randomized, controlled studies (Wade *et al.*, 2002; Rapaport *et al.*, 2004; Bielski *et al.*, 2005).

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