

# Treatment of Comorbid Anxiety and Depression with Escitalopram: Results of a Post-Marketing Surveillance Study

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## Key words

- anxiety
- depression
- escitalopram
- comorbidity

## Abstract



**Introduction:** In this 16-week post-marketing surveillance (PMS) study, antidepressant effects and tolerability of escitalopram was examined in 2911 patients with comorbid depression and anxiety.

**Methods:** Antidepressant effects were assessed using a modified version of the Montgomery-Åsberg depression rating scale (svMADRS), the Hamilton anxiety scale (HAMA) and the hospital anxiety depression scale (HADS-D) and the clinical global impression scale (CGI-S, CGI-I).

**Results:** Treatment was completed by 2718 patients, whose severity of depression decreased from a mean svMADRS total score of 33.0 to 8.9.

At the end of the study, the remission rate (svMADRS ≤ 12) was 72.9% and the response rate (≥ 50% decrease in svMADRS score) was 83.1% (LOCF). Similarly, the severity of anxiety symptoms decreased from a mean HAMA total score of 28.8–8.8; the remission rate (HAMA < 10) was 63.9% and the response rate (decrease ≥ 50%) was 80.2%. The most frequent adverse events were nausea (1.6%), agitation (1.1%) and fatigue (0.7%).

**Discussion:** Antidepressant effects and good tolerability of escitalopram were confirmed in everyday practice in patients with comorbid depression and anxiety. The high response and remission rates were within the range reported in previous RTC's of escitalopram vs. comparators or vs. placebo.

## Introduction



Selective serotonin reuptake inhibitors (SSRI) like escitalopram are mainly used for drug treatment of depression and anxiety disorders. For escitalopram like for many other SSRI's efficacy data for major depression (MDP) and most anxiety disorders are available. Due to their good efficacy and tolerability, they have largely replaced tricyclic antidepressants [1, 2]. Differences between individual SSRIs with regard to effectiveness and adverse effect profile mainly occur due to pharmacokinetic factors and different affinities for the serotonin transporter.

In order to provide scientific evidence of efficacy in controlled randomised clinical studies (RTC's), only patients with one disorder are usually included. However, comorbid anxiety disorders and depression occur frequently in daily practice. Especially generalised anxiety disorder (GAD) rarely occurs alone: 90% of patients with GAD also report other psychiatric disorders in their medical history; in two-thirds of the cases, they also suffer from depression [3]. Inversely, it is

also estimated that 20–30% of the patients with major depression also suffer from GAD [4]. The results of a prospective, longitudinal cohort study in New Zealand [5] even showed somewhat higher values: 48% of the patients with depression also suffered from anxiety disorders at some point in time in their lives and, inversely, 72% of the patients with GAD also had a history of depression. Altogether, 12% of the 1037 persons examined were comorbid with depression and anxiety disorder. The authors concluded that the proportion of the population suffering from comorbid depression and anxiety disorder is larger than usually assumed.

A summary of methodical requirements on controlled, randomised double-blind studies on the treatment of anxiety disorders can be found in Broich [6].

Within the scope of a post-marketing surveillance (PMS) study, the practically relevant, naturalistic use of a drug can be better evaluated than in a typical RTC. Thus, the present study examines the usefulness and tolerability of escitalo-

## Bibliography

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pram under routine conditions in Germany in outpatients with comorbid anxiety and depression.

## Patients and Methods



### Patients

The data in this multicentre study were collected from November 2005 until December 2006 in Germany. A total of 994 registered physicians of different specialties (general physicians, practical physicians, internists and specialists for psychiatry) treated 2911 patients with escitalopram over a period of 16 weeks. The participating patients were outpatients and at least 18 years old. Patients were comorbid and suffered from depression and anxiety. In this context, comorbidity of depression and anxiety was defined as a combination of the diagnosis “depression” on the basis of ICD-10 classification F32 or F33 and a baseline svMADRS > 12 with the diagnosis “anxiety” on the basis of ICD-10 classification F40 or F41 and a baseline HAMA ≥ 10. Patients were not treatment resistant defined as showing no response to 2 previous different antidepressants in sufficient dosing over a period of at least 2 weeks. Patients with known intolerance to escitalopram or citalopram or a contraindication for treatment with escitalopram were not included. Patients were not permitted to simultaneously participate in other studies.

### Study design

Patients were treated (tablets or drops) for 16 weeks. The dose was decided by the attending physician. During this period, 4 examinations were performed within the scope of the study: 1 examination at the time of the inclusion into the study (week 0), 2 follow-up examinations (week 2 and week 8) and 1 final examination (week 16). During the inclusion examination, the following data were collected: demographics, height, weight, diagnosis, psychotropic pre-treatment, concomitant diseases and medication, and medical history.

This study did not influence physicians' individual decision concerning diagnosis, dosing, or course of treatment.

### Assessments

In order to determine the therapeutic effect of escitalopram, validated and established scales were used in this study. Quality of the recorded data was assured by double data entry and analysis by a clinical research organisation (CRO). Physicians were familiar with the used scales or they had the possibility to train the use of the rating scales to assure a good data quality.

Severity of disease was assessed using the Clinical Global Impression of Severity Scale (CGI-S), change in condition was assessed using the Clinical Global Impression of Improvement Scale (CGI-I) [7]. The CGI-I is a 7 point-scale ranging from “condition is much worse” (7 points) to “condition is much better” (CGI-I=2) and “condition is very much better” (CGI-I=1). Patients who described their condition to be “much better” or “very much better” after treatment were considered to be responders.

Severity of anxiety or depression was measured using the German versions of established third-party (clinician) rating scales, the Hamilton Anxiety Scale (HAMA) [7] and the Montgomery-Åsberg Depression Rating Scale (MADRS) [8], which comprises 10 items assessed by the physician from 0 to 6, giving a maximum of 60 points. The svMADRS (sv=short version) is a modified version in which anchor points are not used and the

symptoms are not defined but only mentioned. For the original version of the MADRS, a score ≥ 30 points usually corresponds to severe depression, a score between 13 and 21 to mild depression in individual cases, and a score ≤ 12 to remission.

The maximum HAMA total score is 56; patients with a mild anxiety disorder have a score of 10 or less, and patients with generalised anxiety disorder (GAD) have a score of 20 or more [9]. The German version of the Hospital Anxiety Depression Scale (HADS-D) [7] was used for self-assessment of anxiety and depression symptoms by the patients. This questionnaire consists of 14 items including 7 items referring to depression (HADS-D “depression”) and 7 items referring to anxiety (HADS-D “anxiety”). Both HADS-D scales have a score range of 0–21.

The dosage of escitalopram was individually determined by the attending physician after the initial visit. Escitalopram could be used as coated tablets 10 mg and 20 mg and escitalopram 10 mg/mL solution. Depending on the patient response to treatment, the dosage adaptation was allowed at any time during the study. The primary endpoints included remission using the svMADRS (total score ≤ 12) and HAMA scale (HAMA ≤ 10). Secondary endpoints included the time course of changes in symptom severity and responder rates (≥ 50% decrease from baseline in svMADRS and HAMA scores; CGI-I of 1 or 2 = “very much better” or “much better”). At the end of the observation period, patients and physicians separately evaluated efficiency and tolerability ranging from “insufficient”, to “moderate”, “good”, and “very good”.

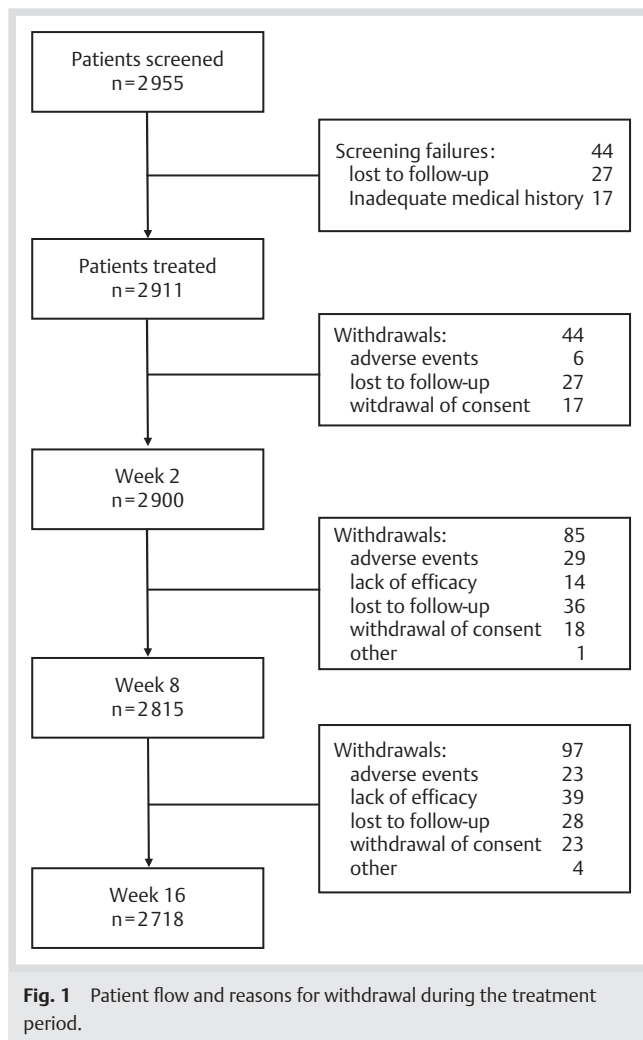
All unexpected events were considered “adverse events”, even if they did not have any apparent causal relationship with treatment. This included the deterioration of an existing condition, but not lack of therapeutic effect. Serious adverse events were defined as symptoms that led to death or permanent disability, were life-threatening, required or extended a hospital stay, and to congenital anomalies or birth defects. Events which required medical intervention in order to prevent one of the above mentioned criteria were classified as severe and adverse.

During every follow-up examination and at final examination patients were asked for adverse events. In the case of a serious adverse event it had to be sent within 24 h to the selected CRO responsible for collecting and handling of all adverse events in this post-marketing surveillance study.

### Statistical analyses

This post-marketing surveillance study was evaluated using methods of descriptive statistics using last-observation-carried-forward (LOCF) analysis. Multiple linear regression and covariance analytical models were used to analyse the dose groups (10 mg/day and 20 mg/day) for continuous parameters; logistic regressions were used to compare the dose groups (10 mg/day and 20 mg/day) regarding binary parameters (e.g., remission rates). Categorical data were analysed using the chi-square test. Linear regression, using stepwise backward elimination ( $p > 0.15$ ), was used to model change from baseline to week 16 on the svMADRS, HAMA and HADS-D. The following factors were tested: age, sex, BMI, mono-diagnosis of depression or anxiety, classification by diagnostic group, somatic disorders, other psychiatric disorders, total duration of illness, duration of current episode, pre-treatment of current episode, marital status, concomitant diseases, baseline scores on the svMADRS, HAMA and CGI-S, and escitalopram dose.

The Statistical Software Package SAS<sup>®</sup> was used for the formal statistical analyses.



## Results

### Demographic data

Altogether, 2911 patients treated with escitalopram were included in the study, comprising the all-patient-treated set (APTS) or safety population. Two-thirds (68.0%) of the patients were women, with a mean weight of  $69.8 \pm 12.4$  kg and a mean height of  $167 \pm 6$  cm. Male patients had a mean weight of  $82.1 \pm 11.6$  kg and a mean height of  $178 \pm 6$  cm. There were 193 patients who prematurely withdrew from the study; thus 2718 patients (93.4%) of the APTS completed 16-weeks treatment (Fig. 1).

There were 2185 patients who met the inclusion criteria: comorbidity in the sense of an ICD-10 diagnostic classification of F32/F33 plus F41/F40, a baseline svMADRS  $> 12$  and a baseline HAMA  $\geq 10$ , as well as documented assessments during the study. This group of patients was designated as the "full-analysis set" (FAS) and was evaluated separately. Early study withdrawal occurred for 109 patients, resulting in a completion rate of 95.0%.

The APTS ( $n=2911$ ) could be divided into 4 diagnostic groups: comorbid depression and anxiety disorder ( $n=2371$ : 81.4%), exclusively depression ( $n=284$ : 9.8%), exclusively anxiety ( $n=188$ : 6.5%) and other diagnoses ( $n=68$ : 2.3%). Table 1 provides an overview of the demographic data of the patients at baseline. The median age at the first depressive episode was 35

**Table 1** Demographic and clinical data (FAS,  $n=2185$ ).

| Parameter                                       | Mean                             |
|---|----------------------------------|
| <b>age <math>\pm</math> SD</b>                  | $47.3 \pm 14.1$ years            |
| – $\leq 30$ years                               | 12.9 %                           |
| – 31–40 years                                   | 20.5 %                           |
| – 41–50 years                                   | 25.6 %                           |
| – 51–65 years                                   | 31.4 %                           |
| – $> 65$ years                                  | 9.7 %                            |
| <b>BMI <math>\pm</math> SD*</b>                 | $25.3 \pm 4.1$ kg/m <sup>2</sup> |
| single*   | 30.2 %                           |
| <b>clinical assessments <math>\pm</math> SD</b> |                                  |
| – svMADRS                                       | $33.8 \pm 8.9$                   |
| – HAMA  | $29.5 \pm 8.5$                   |
| – HADS-D  | $30.1 \pm 6.1$                   |
| – CGI-S   | $5.02 \pm 0.74$                  |

\*Based on the APTS ( $n=2911$ ); CGI-S: Clinical Global Impression of Severity scale, HADS-D: Hospital Anxiety and Depression Scale – German version, HAMA: Hamilton Anxiety Scale (assessment of the severity of anxiety), svMADRS: Montgomery-Åsberg Depression Rating Scale – short version, FAS: Full-Analysis Set

years, and the median length of the disease was 10 years. The severity of previous episodes was predominantly moderate. The median age at first occurrence of an anxiety disorder was 38 years, with a median length of disease of 6 years. Treatment of previous depression or anxiety conditions was reported by 55.8% of the patients. The median length of the current episode was 6 weeks, for which 35.7% of the patients had received treatment. In addition, 39.5% of the patients of the comorbid group suffered from a somatic syndrome, and 11.1% from an additional mental disorder.

### Medication

Prior to initiation of treatment with escitalopram, 35.7% of patients had been treated with at least one of the following: tri- or tetracyclic antidepressants ( $n=385$ ), SSRIs ( $n=250$ ), noradrenergic and specific serotonergic antidepressants ( $n=183$ ), serotonin and noradrenergic reuptake inhibitors ( $n=90$ ), phytotherapeutic antidepressants ( $n=82$ ), noradrenergic antidepressants ( $n=13$ ), monoamine oxidase inhibitors ( $n=9$ ), or psychotherapy ( $n=6$ ). For 23 patients, the treatment was not recorded, and 259 patients were treated with other medications.

At the beginning of the study, 70.4% of patients ( $n=2049$ ) were treated with 10 mg/day escitalopram, 21.5% ( $n=626$ ) received 20 mg/day, and 7.0% ( $n=203$ ) received 5 mg/day (APTS). Only 3 patients took more than 20 mg/day, 12 patients took 15 mg/day, and the remaining patients ( $n=18$ ) took less than 10 mg/day. By the end of the study, the dose had been changed at least once: for 1355 of the 2270 patients in the 10 mg group (59.7%) and for 171 of the 641 patients in the 20 mg group (26.7%) (APTS). For the FAS, 1687 patients were initially treated with 10 mg/day and 498 received 20 mg/day escitalopram.

For 2546 patients (87.5%, APTS), escitalopram was subsequently used for maintenance treatment, with 48.8% of the patients being treated with 10 mg/day ( $n=1242$ ) and 43.3% with 20 mg/day ( $n=1103$ ). A few patients continued maintenance therapy on 5 mg ( $n=68$ ), 15 mg ( $n=72$ ), 30 mg ( $n=42$ ), or 40 mg escitalopram ( $n=13$ ). At the end of the study, 9.6% of patients ( $n=277$ ) did not continue treatment, 85.8% of patients ( $n=2473$ ) continued with escitalopram alone, 2.5% of patients ( $n=73$ ) combined escitalopram with another antidepressant, and 1.4% of patients ( $n=40$ ) switched to another antidepressant (APTS).

**Table 2** Difference in total scores between inclusion and after 16 weeks, remission and response rates [%] (FAS, LOCF).

|                       | svMADRS      | HAMA        | HADS-D      | CGI-I                     |
|-----------------------|--------------|-------------|-------------|---------------------------|
| change in total score | -25.5 ± 10.8 | -21.2 ± 9.3 | -20.1 ± 8.9 | -1.57 ± 0.75 <sup>‡</sup> |
| response rate         | 86.7%        | 83.8%       | –           | 92.0%                     |
| remission rate        | 76.0%        | 66.3%       | 57.7%       | –                         |

<sup>‡</sup>The CGI-I describes a change in condition compared with the beginning of the study. Negative numbers indicate an improvement. Remission: svMADRS ≤ 12, HAMA < 10, HADS-D ≤ 10. CGI-I: Clinical Global Impression of Improvement scale, HADS-D: FAS: full analysis set, Hospital Anxiety and Depression Scale – German version, HAMA: Hamilton Anxiety Scale (assessment of the severity of anxiety), LOCF: last observation carried forward, svMADRS: Montgomery-Åsberg Depression Rating Scale – short version.

### Severity of depression (svMADRS)

At the beginning of the study, severe depression (svMADRS ≥ 29) was diagnosed in 70.8% of the patients with comorbid depression, moderate depression in 20.0% of patients (svMADRS 22–28), and mild depression (svMADRS ≥ 21) in 9.2% of patients (FAS). During the course of this 16-week surveillance study, the mean baseline svMADRS of 33.8 ± 8.9, decreased to 24.5 ± 10.0 at week 2, 13.5 ± 8.9 at week 8, and 8.2 ± 7.8 at week 16, corresponding to a mean improvement of 25.5 ± 10.8 (◉ **Table 2**, FAS, LOCF). The response rate was 16.9% at week 2, 67.5% at week 8, and 86.7% at week 16; and the remission rate was 11.6% at week 2, 51.4% at week 8, and 76.0% at week 16 (FAS, LOCF). For patients treated with 10 mg escitalopram (n = 1 687), the mean baseline svMADRS was 33.2 ± 8.8, decreasing to 24.5 ± 10.0 at week 2, 13.5 ± 8.8 at week 8, and 8.2 ± 7.8 at week 16, corresponding to a mean improvement of 25.0 ± 10.6 (FAS, LOCF). For patients treated with 20 mg escitalopram (n = 498), the mean baseline svMADRS was 35.5 ± 9.1, decreasing to 24.9 ± 10.1 at week 2, 13.7 ± 9.2 at week 8, and 8.3 ± 7.9 at week 16, corresponding to a mean improvement of 27.1 ± 11.0 (FAS, LOCF).

For the safety population (APTS), the severity of depression decreased from a mean svMADRS total score of 33.0 ± 9.4 to 8.9 ± 8.7, corresponding to a mean difference of -24.0 ± 11.6 (APTS, LOCF). The corresponding response rate (≥ 50% improvement from baseline in the svMADRS score) was 83.1% and the remission rate (svMADRS ≤ 12) was 72.9% (LOCF).

### Severity of anxiety (HAMA)

At the beginning of the study, 99.3% of patients had a HAMA > 10. For patients with comorbid depression, the mean baseline HAMA was 29.5 ± 8.5, decreasing to 8.3 ± 7.2, corresponding to a mean difference of 21.2 ± 9.3 (FAS, LOCF). For patients with comorbid depression, the response rate was 15.0% at week 2, 63.5% at week 8, and 83.8% at week 16; the corresponding remission rates were 7.9% at week 2, 38.8% at week 8 and 66.3% at week 16 (◉ **Table 2**, FAS, LOCF).

For the safety population (APTS), the severity of anxiety decreased from a mean HAMA total score of 28.8 ± 8.6 to 8.8 ± 7.9, corresponding to a mean improvement of 20.0 ± 10.0 (LOCF). The response rate (≥ 50% improvement from the baseline HAMA total score) was 80.2%, and the remission rate (HAMA < 10) was 63.9% (LOCF).

### Self-assessment of anxiety and depression (HADS-D)

At the beginning of the study, 99.6% of patients had self-assessment total scores > 10. For patients with comorbid depression, the mean baseline HADS-D score was 30.1 ± 6.1, decreasing to 10.0 ± 7.1, corresponding to a mean improvement of 20.1 ± 8.9 (FAS, LOCF). For patients with comorbid depression, remission was achieved by 3.2% of patients at week 2, 28.2% at week 8, and 57.7% at week 16 (FAS, LOCF). For the safety population (APTS), the total mean HADS-D score decreased from 29.6 ± 6.4 to

**Table 3** Difference in the mean total scores between the beginning and the end of the study in the dose groups 10 mg/day and 20 mg/day (FAS, LOCF).

|         | Escitalopram 10 mg/day<br>(n = 1 687) | Escitalopram 20 mg/day<br>(n = 498) |
|---------|---------------------------------------|-------------------------------------|
| svMADRS | -25.0 ± 10.6                          | -27.1 ± 11.0*                       |
| HAMA    | -20.8 ± 9.2                           | -22.7 ± 9.7**                       |
| HADS-D  | -19.6 ± 8.7                           | -21.8 ± 9.2***                      |
| CGI-S   | -2.50 ± 1.21                          | 2.69 ± 1.25 <sup>‡</sup>            |

\*svMADRS: p = 0.0033

\*\*HAMA: p = 0.0011

\*\*\*HADS-D: p < 0.0001, CGI-S: p = 0.0157, 20 mg vs. 10 mg

CGI-S: Clinical Global Impression of Severity scale, HADS-D: FAS: full analysis set, Hospital Anxiety and Depression Scale – German version, HAMA: Hamilton Anxiety Scale (assessment of the severity of anxiety), LOCF: last observation carried forward, svMADRS: Montgomery-Åsberg Depression Rating Scale – short version

10.7 ± 7.8, corresponding to a mean improvement of 18.9 ± 9.5 (LOCF). The remission rate was 55.2% after 16 weeks (HADS-D ≤ 10) (LOCF).

### Severity and change in condition (CGI-S, CGI-I)

The CGI-S score decreased from 4.97 ± 0.76 to 2.57 ± 1.17, corresponding to a mean difference of 2.41 ± 1.30 (APTS, LOCF). For patients with comorbid depression, the CGI-S score was 5.02 ± 0.74 at the beginning of the study, 4.30 ± 0.97 at 2 weeks, 3.18 ± 1.06 at 8 weeks and 2.48 ± 1.11 at the final examination, corresponding to a mean difference to baseline of 2.54 ± 1.22 (FAS, LOCF). The mean CGI-I scores were 2.84 ± 0.83 at week 2, 1.95 ± 0.75 at week 8 and 1.57 ± 0.75 at the end of the study. At the first follow-up examination (week 2), 31.8% of patients could be classified as responders (CGI-I ≤ 2) (FAS). After 8 weeks, 82.1% of patients were responders, increasing to 92.0% at 16 weeks (FAS, LOCF). The response rates at 16 weeks were not significantly different (p = 0.5234) for patients taking 10 mg/day (92.2%) and 20 mg/day (91.3%).

### Dosage

Patients treated with 20 mg/day (n = 498) had significantly higher mean total scores (svMADRS, HAMA, HADS-D) at baseline than patients treated with 10 mg/day (n = 1 687) – svMADRS: 35.5 ± 9.1 vs. 33.2 ± 8.8, HAMA: 31.0 ± 8.7 vs. 29.1 ± 8.3, HADS-D: 31.5 ± 5.7 vs. 29.7 ± 6.1, respectively (p < 0.0001 for all). For patients whose dosage was fixed at 20 mg/day escitalopram at the beginning of the study, the decrease in the mean total scores was greater than for patients treated with 10 mg/day (◉ **Table 3**), even after adjustment for baseline scores.

### Factors

Higher baseline levels of the svMADRS, HAMA and CGI-S scales and a higher escitalopram dose were significantly correlated with a greater decrease in the mean total scores from baseline. Three factors with a significantly unfavourable influence on the decrease in the mean total scores from baseline were the pres-

**Table 4** Adverse events with at least a possible relationship with escitalopram.

| Preferred term | Escitalopram 10mg/day (n=2270) | Escitalopram 20mg/day (n=641) | APTS (n=2911) |
|----------------|--------------------------------|-------------------------------|---------------|
| nausea         | 43 (1.89%)                     | 3 (0.47%)                     | 46 (1.58%)    |
| agitation      | 31 (1.37%)                     | 1 (0.16%)                     | 32 (1.10%)    |
| diarrhoea      | 15 (0.66%)                     | 2 (0.31%)                     | 17 (0.58%)    |
| hyperhidrosis  | 16 (0.70%)                     | –                             | 16 (0.55%)    |
| dizziness      | 15 (0.66%)                     | –                             | 15 (0.52%)    |
| fatigue        | 12 (0.53%)                     | 1 (0.16%)                     | 13 (0.45%)    |
| weight gain    | 7 (0.31%)                      | 1 (0.16%)                     | 8 (0.27%)     |
| vomiting       | 7 (0.31%)                      | 1 (0.16%)                     | 8 (0.27%)     |
| sleep disorder | 7 (0.31%)                      | –                             | 7 (0.24%)     |
| anxiety        | 7 (0.31%)                      | –                             | 7 (0.24%)     |
| palpitations   | 6 (0.26%)                      | –                             | 6 (0.21%)     |
| loss of libido | 4 (0.18%)                      | 2 (0.31%)                     | 6 (0.21%)     |

ence of other psychiatric disorders or pre-treatment of the current episode. Age, total disease duration, and duration of the current episode also had a negative effect on treatment outcome, but to a lesser degree. Sex, BMI, mono-diagnosis of anxiety or depression, somatic symptoms, and classification by diagnostic group (ICD-10) were without significant influence on outcome.

### Adverse events

In the course of the study, 346 adverse events were reported by 189 patients (6.5%) (APTS). In 157 (5.4%) instances, a causal relationship with escitalopram was at least considered possible. A significantly higher incidence of adverse events was reported in the group of patients who were stabilised on 10 mg/day escitalopram in the beginning. In this group, 171 out of 2270 patients (7.5%) reported adverse events, compared to 18 out of 641 patients (2.8%) in the group that started treatment on 20 mg/day escitalopram in the beginning ( $p < 0.0001$ ). The adverse event was not considered to be severe in 172 of the 189 cases. In 58 cases, escitalopram was stopped due to adverse events. Adverse events with at least a possible relationship with escitalopram are shown in **Table 4**.

### Severe adverse events

17 patients reported 19 severe adverse events. 2 patients attempted suicide, with suicidal thoughts registered in one case, and acute suicidal tendency in another case. A causal relationship with medication was evaluated as “possible” in 2 cases (suicidal thoughts, one attempted suicide). The other severe adverse events were deterioration of condition (3 cases), lack of effect (3 cases), hospitalisation (2 cases), and one case of renal cell carcinoma, myocardial infarction with ST-segment elevation, abnormal gynaecological examination, alcohol abuse, agitation and anxiety, and continuous vaginal bleeding. No deaths were reported in the course of the study. Concerning the cardiac adverse events no cases of QTc-prolongation were reported.

### Therapeutic effect and tolerability of escitalopram

Therapeutic effects and tolerability were described as “good” or “very good” by most physicians and patients. In the APTS ( $n = 2911$ ), 92.2% of physicians and 89.6% of patients assessed the therapeutic effects of escitalopram to be “good” or “very good”, whereas 2.5% of physicians and 3.8% of patients described it “insufficient”.

For the full analysis set ( $n = 2185$ ), 94.8% of physicians and 92.6% of patients described the therapeutic effects as “good” or “very good”, compared to 1.2% of physicians and 1.8% of patients with “insufficient”. Most physicians (97.4%) and patients (96.1%) evaluated tolerability as “good” or “very good”, and 0.9% of physicians and 1.5% of patients considered the tolerability of escitalopram “insufficient”. At the end of the study, 87.5% of the patients continued maintenance treatment with escitalopram.

### Discussion

The therapeutic efficacy of escitalopram in patients with depression or different anxiety disorders was demonstrated in several placebo-controlled, randomised and blind clinical studies [10–14]. Significant improvements of anxiety symptoms in depressive patients could also be shown by means of pooled data from double-blind placebo-controlled studies [15, 16].

The present PMS examined under relevant conditions of daily practice and by means of standardised methods, the use of escitalopram in patients with both indications, i.e., depression and anxiety disorder, a combination which is common in daily clinical practice. In this context, the therapeutic usefulness and good tolerability of escitalopram, which was already known from controlled clinical studies, including patients with comorbid depression and anxiety [17], was confirmed.

In the group of patients who were stabilised on 20 mg/day escitalopram at the beginning of the study, the decrease in the mean total scores (svMADRS, HAMA, HADS-D) was clearer in the course of the study than in the group treated with 10 mg/day in the beginning. The difference could only be partially explained by the higher level of total scores in the 20 mg group at the beginning of the study. Even after adjustment for baseline severity, a significantly clearer decrease in the total scores on all 3 scales was shown with initial treatment with 20 mg/day.

The adverse events spectrum was similar to that reported in controlled clinical studies with escitalopram and citalopram; however, the incidence was slightly lower. Nausea was the dominant side effect in this study (1.6% of patients), as in controlled studies in which the reported incidence was 6–17% [9–11, 13, 14, 18–20]. A significant higher rate of adverse events was notable in the group of patients who were stabilised on the lower dose of 10 mg/day escitalopram in the beginning. This result, which was surprising, might be attributed to the fact that patients who were treated with 20 mg/day escitalopram perceived a greater improvement in their symptoms at week 2 (a decrease of 11.0 vs. 8.3 svMADRS points for 10 mg) and thus subjectively suffered less from the possible side effects at the beginning of the therapy.

The incidence of severe adverse events was 1.7%. Attempted suicide was reported in 2 cases, and a relationship with escitalopram could not be excluded in one case. As the majority of the study participants suffered from severe depression and/or anxiety disorders, the occurrence of attempted suicide is not surprising [21].

The low incidence of cardiac adverse events (0.2% of patients) confirms the good tolerability of Escitalopram as shown in clinical practice.

Efficiency and tolerability of escitalopram were significantly higher in the group of patients with the higher initial dose of 20 mg/day compared with the lower initial dose of 10 mg/day. These results suggest to start treatment with 20 mg/day for the

**Table 5** Response and remission rates from RCTs with Escitalopram (ESC) and the PMS study.

| Study                                   | Response rate (%) |           |      | Remission rate (%) |           |         |
|---|-------------------|-----------|------|--------------------|-----------|---------|
|   | ESC               | CIT       | PBO  | ESC                | CIT       | PBO     |
| <sup>1</sup> PMS study**                | 67.5/86.7         | –         | –    | 51.4/76.0          | –         | –       |
| <sup>2</sup> Burke WJ et al. 2002       | 51.2°             | 45.6°     | 27.7 | –                  | –         | –       |
| <sup>3</sup> Lepola UM et al. 2003*     | 63.7°'            | 52.6      | 48.2 | 52.1'              | 42.8      | no data |
| <sup>4</sup> Colonna L et al. 2005      | 63.0'/80.0        | 55.0/78.0 | –    | 55.0/76.0          | 45.0/71.0 | –       |
| <sup>5</sup> Moore N et al. 2005        | 76.1"             | 61.5      | –    | 56.1'              | 43.6      | –       |
| <sup>6</sup> Yevtushenko VY et al. 2007 | 95.4""            | 83.3      | –    | 89.8""             | 50.9      | –       |

Response = svMADRS  $\geq$  50% improvement from baseline, Remission = svMADRS  $\leq$  12 (<sup>1</sup> after 8/16 weeks, <sup>2,3,5</sup> after 8 weeks, <sup>4</sup> after 8/24 weeks, <sup>6</sup> after 6 weeks)

ITT, LOCF (\*OC analysis, \*\*FAS), CIT: Citalopram, PMS: Post-Marketing Surveillance

°p < 0.01 vs. PBO, 'p < 0.05 vs. CIT, "p < 0.01 vs. CIT, ""p < 0.001 vs. CIT

acute therapy of patients with comorbid depression and anxiety disorder and to consider reducing the dose in the maintenance phase.

The present data are based on a post-marketing surveillance (PMS) study or non-interventional study (NIS). The methodology of PMS comprises series of intrinsic problems (e.g., inter-rater reliability, handling of missing data, comedication, heterogeneous patient population, inclusion and exclusion criteria). Moreover, PMS do not provide evidence of efficacy, but provide information on adverse events, dosage, medication adherence, and therapeutic effects indifferent group of patients usually not included in RTC's [12, 22–24]. Response and remission rates in this PMS were rather high, which agrees with other PMS using escitalopram. In a naturalistic sample test among employed persons with affective and anxiety disorders, a clear reduction of the conditions was shown with escitalopram, together with an improvement of the severity of the disease according to CGI-S from 4.7 to 2.4 [25]. In another open, multicentric PMS, more than 11 700 outpatients were treated with escitalopram over a period of 8 weeks. The response rate was 70%, the remission rate 57% [26]. 83% of the patients described the efficiency as “good/very good”, and 22% assessed the tolerability as “good/very good”. On the other hand, these remission and response rates are within the range reported for escitalopram in RTC's vs. placebo or comparator in depression or anxiety (◉ Table 5).

Some of the latest controlled, double-blind studies provide response rates (under escitalopram) for depression between 63 and 70% and remission rates between 55 and 62% [27–29]. Pooled results from double-blind placebo-controlled studies on the treatment of generalised anxiety disorders with escitalopram resulted in response rates of almost 48%, and remission rates of 26% [30].

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## Conflict of Interests

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## References

- Gorman JM, Kent JM. SSRIs and SNRIs: broad spectrum of efficacy beyond major depression. *J Clin Psychiatry* 1999; 60 (Suppl 4): 33–38
- Isaac M. Where are we going with SSRIs? *Eur Neuropsychopharmacol* 1999; 9 (Suppl 3): 101–106
- Judd LL, Kessler RC, Paulus MP et al. Comorbidity as a fundamental feature of generalized anxiety disorders: results from the National Comorbidity Study (NCS). *Acta Psychiatr Scand* 1998; 393 (Suppl): 6–11
- Pollack MH. Comorbid anxiety and depression. *J Clin Psychiatry* 2005; 66: 22–29
- Moffitt TE, Harrington HL, Caspi A et al. Depression and generalized anxiety disorder. Cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Arch Gen Psychiatry* 2007; 64: 651–660
- Broich K. Anforderungen an klinische Prüfungen mit Arzneimitteln bei Angststörungen. *Psychopharmakotherapie* 2006; 13: 241–247
- CIPS. Internationale Skalen für Psychiatrie. Beltz Test GmbH, 2005
- Möller HJ, Schnitker J. Einsatz einer modifizierten MADRS bei depressiven Patienten in einer prospektiven Kohortenstudie. *Nervenarzt* 2007; 78: 685–690
- Allgulander C, Florea I, Huusom AKT. Prevention of relapse in generalized anxiety disorder by escitalopram treatment. *Int J Neuropsychopharmacol* 2005; 9: 1–11
- Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002; 63: 331–336
- Davidson J, Bose A, Korotzer A et al. Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible dose study. *Depress Anxiety* 2004; 19: 234–240
- Lepola UM, Loft H, Reines EH. Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression on primary care. *Int Clin Psychopharmacol* 2003; 18: 211–217
- Ninan PT, Ventura D, Wang J. Escitalopram is effective and well tolerated in the treatment of severe depression. Poster presented at the 156<sup>th</sup> Annual Meeting of the American Psychiatric Association, San Francisco, USA, May 17–22, 2003
- Wade AG, Lemming O, Hedegaard K. Escitalopram 10 mg/day is effective and well-tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2002; 17: 95–102
- Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. *CNS Spectrums* 2002; 7: 40–44
- Kennedy SH, Andersen HF, Thase ME. Escitalopram in the treatment of major depressive disorder: A meta-analysis. *Curr Med Res Opin* 2009; 25: 161–175
- Boulinger P, Hermes A, Huusom AKT et al. Baseline anxiety effect on outcome of SSRI treatment in patients with severe depression: escitalopram vs paroxetine. *Curr Med Res Opin* 2010; 26: 605–614
- Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. *Ann Clin Psychiatry* 2005; 17: 65–69
- Kasper S, Stein D, Loft H et al. Escitalopram in the treatment of social anxiety disorder. Randomised, placebo-controlled, flexible-dosage study. *Br J Psychiatry* 2005; 186: 222–226

- 20 Rapaport M, Bose A, Zheng H *et al.* Escitalopram prevents relapse of depressive episodes. *Eur Psychiatry* 2002; 17 (i): S97
- 21 Cipriani A, Barbui C, Geddes JR. Suicide, depression, and antidepressants. *BMJ* 2005; 330: 373–374
- 22 Laux G, Schüler P, Bruns S. Reboxetin in Klinik und Facharztpraxis. *Psychopharmakotherapie* 2000; 7: 162–167
- 23 Llorca PM, Azorin JM, Despiegel N *et al.* Efficacy of escitalopram in patients with severe depression: a pooled analysis. *Int J Clin Pract* 2005; 59: 268–275
- 24 Yevtushenko VY, Belous AI, Yevtushenko YG *et al.* Efficacy and tolerability of escitalopram versus citalopram in major depressive disorder: A 6-week, multicenter, prospective, randomized, double-blind, active-controlled study in adult outpatients. *J Clin Ther* 2007; 29: 2319–2332
- 25 Winkler D, Pirek E, Klein N *et al.* Escitalopram bei berufstätigen Menschen. Ergebnisse einer Anwendungsbeobachtung an 2378 Patienten. *Psychopharmakotherapie* 2006; 13: 142–146
- 26 Möller HJ, Friede M, Schmauß M. Behandlung der Depression mit Escitalopram. Ergebnisse einer großen Anwendungsbeobachtung. *Psychopharmakotherapie* 2007; 14: 149–156
- 27 Colonna L, Andersen HF, Reines EH. A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder. *Curr Med Res Opin* 2005; 21: 1659–1668
- 28 Montgomery SA, Huusom AKT, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology* 2004; 50: 57–64
- 29 Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int Clin Psychopharmacol* 2005; 20: 131–137
- 30 Goodman WK, Bose A, Wang Q. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. *J Affect Dis* 2005; 87: 161–167