Relapse Prevention and Residual Symptoms: A Closer Analysis of Placebo-Controlled Continuation Studies With Escitalopram in Major Depressive Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, and Obsessive-Compulsive Disorder

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Objective: Analyses of data from 4 relapse-prevention studies with escitalopram were conducted in order to compare patients with and without residual symptoms with regard to relapse rates and global illness during double-blind, 24-week continuation periods.

Method: Clinical Global Impressions-Severity of Illness scores and relapse status in 4 studies published from 2005 to 2007, 1 each in major depressive disorder (MDD), generalized anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder (OCD), were analyzed using mixed-effects model repeated measures as a function of Montgomery-Asberg Depression Rating Scale (MADRS) scores on items 1, 3, and 7 at randomization.

Results: All studies showed a statistically significant ($P < .0001$) standardized effect size of about 0.7 for escitalopram versus placebo, with a number needed to treat ~ 4. Patients with residual symptoms (MADRS score > 0) and without residual symptoms (MADRS score = 0) at the start of continuation treatment were defined by how patients scored on 3 core items of the MADRS: depressed mood (observed), inner or psychic tension, and lassitude. At randomization, patients with a residual symptom were globally more ill than patients without such a symptom. Patients who did not continue active treatment worsened, even if they were initially free of a residual symptom. In contrast, patients who continued receiving escitalopram remained stable or further improved, regardless of residual symptoms or diagnosis. No clear picture emerged regarding whether patients with residual symptoms had a higher relapse rate.

Conclusions: The presence of residual symptoms is associated with significantly worse overall illness severity in all 4 diagnostic groups and with a higher (although not significantly) risk of relapse for patients with MDD or OCD. The greatest difference in all of the studies was between patients treated with escitalopram (relapse rates ~ 20%) and placebo (relapse rates of about 50%).

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The prevalence of depression and anxiety disorders is increasing, and the World Health Organization predicts that over the next decade, depression will be the second most common cause of disability.[1] Furthermore, these disorders are frequently comorbid. In patients with lifetime depression,[2] the prevalence of a lifetime anxiety disorder has been estimated at around 50%. Anxiety disorders have been reported to be as common with depression as alone.[3]

Effective pharmacologic treatments for major depressive disorder (MDD) have been available for the past 5 decades.[4] Tricyclic antidepressants were recommended as first-line treatment of depression until the introduction of the selective serotonin reuptake inhibitors (SSRIs) 2 decades ago. More recently, the serotonin-norepinephrine reuptake inhibitors (SNRIs) have been introduced.

Several weeks of treatment are required for full amelioration of symptoms and recovery from the acute MDD episode. It has long been recognized,[5,6] and is reflected in clinical treatment guidelines, that continued treatment for another 4 to 6 months beyond acute remission is essential to prevent relapse or recurrence of a depressive episode. In a systematic review of evidence from 31 randomized trials, Geddes et al[7] concluded that continuing treatment with an antidepressant reduced the odds of depression relapse by 70% compared with placebo. The average relapse rates in the groups were 18% (continued on antidepressant) and 41% (continued on placebo). They also noted that the risk of relapse seemed similar across heterogeneous groups of patients.

Frank et al[5] noted that neither demographic nor baseline clinical characteristics were associated with time to relapse. While the number of previous episodes is an obvious risk factor for relapse, there is also evidence of increased risk in patients with residual depressive symptoms following acute treatment.[8,9] Judd et al[8] states that ongoing residual

Table 1. Summary of Relapse-Prevention Trials Using Escitalopram Versus Placebo for Treatment of MDD, GAD, SAD, and OCD

Study	Indication	Patients Randomly Assigned, n	Age, Mean (range), y	Responders[a] During Open-Label Escitalopram Treatment, %	Relapse in Placebo Group, %	Relapse in Escitalopram Group, %	Placebo Versus Escitalopram, Hazard Ratio (95% CI)	Number Needed to Treat
Gorwood et al (2007)[13]	MDD	305	73 (64–91)	75	33	9	4.4 (2.4–8.2)	4
Allgulander et al (2006)[14]	GAD	373	41 (18–65)	76	52	18	3.8 (2.5–5.6)[b]	3[b]
Montgomery et al (2005)[15]	SAD	371	37 (18–78)	72	50	22	2.8 (2.0–4.1)	4
Fineberg et al (2007)[16]	OCD	320	36 (18–65)	68	52	23	2.7 (1.9–4.0)	4

[a]Patients randomly assigned (%) were required to have a Montgomery-Asberg Depression Rating Scale score ≤ 12 in the MDD study, Hamilton Anxiety Rating Scale score ≤ 10 in the GAD study, Clinical Global Impressions-Improvement scale score ≤ 2 in the SAD study, and ≥ 25% decrease in Yale-Brown Obsessive Compulsive Scale score in the OCD study.
[b]After first 24 weeks.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, SAD = social anxiety disorder.

subthreshold depressive symptoms following resolution of a major depressive episode are a stronger predictor of early relapse than the number of previous episodes.

It has also been stressed[10] that pharmacologic interventions within affective disorders are effective for several different disorders rather than specific to an individual diagnostic category. A merging of MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD) into a single category of a general neurotic-affective syndrome has thus been suggested.[11,12] However, in the present study, these disorders were analyzed separately, in accordance with *DSM-IV*.[11] Nevertheless, depressed mood is generally considered as the essential symptom of MDD and must be absent in the truly remitted state. Excessive worrying or psychic anxiety is the essential symptom of the 3 anxiety disorders, whether accompanied by avoidance behavior in social situations (SAD) or attempts at down-regulation by obsessive-compulsive behavior (OCD) or without such mechanisms (GAD), as recommended by the American College of Neuropsychopharmacology Task Force for remission symptoms.[12] Other symptoms, notably lassitude affecting performance of everyday activities, could also be of potential interest.

The objective of this study was to make a reanalysis of 4 very similarly designed placebo-controlled relapse-prevention studies with escitalopram in MDD,[13] GAD,[14] SAD,[15] and OCD,[16] focusing on the predictive validity of the presence of residual symptoms at the start of the randomized continuation therapy.

METHOD

Studies Analyzed

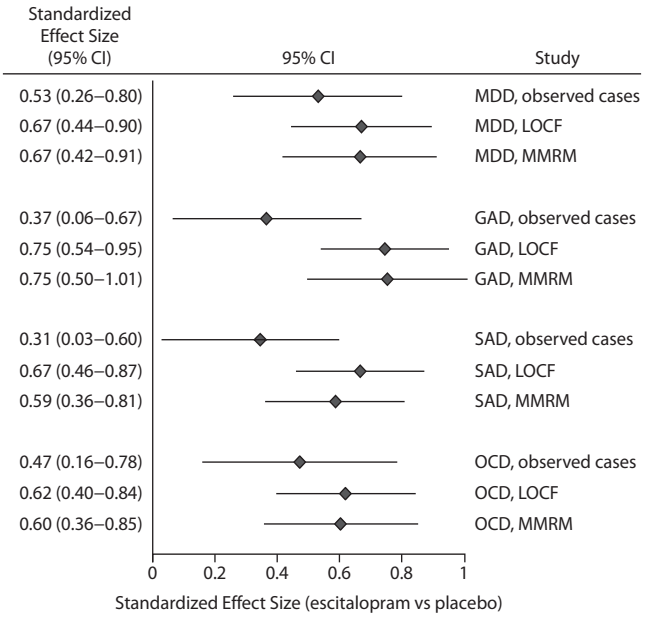
Additional analyses were made of 4 similarly designed relapse-prevention studies with escitalopram in MDD,[13] GAD,[14] SAD,[15] and OCD.[16] All studies enrolled 300 to 400 patients (male and female, aged 18–91 years) who were randomly assigned to continuation treatment following response to 3 to 4 months open-label treatment with escitalopram. Patients randomly assigned to escitalopram continued at the same dose that was effective in achieving response during the open-label period. After open-label treatment, patients randomly assigned to continuation treatment were required to have a Montgomery-Asberg Depression Rating Scale (MADRS) score ≤ 12 in the MDD study; in the GAD study, a Hamilton Anxiety Rating Scale (HARS) score ≤ 10; a Clinical Global Impressions-Improvement scale (CGI-I) score ≤ 2 in the SAD study; and ≥ 25% decrease in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score in the OCD study. Patients in the SAD study were included if their baseline MADRS score was < 18, resulting in a baseline mean MADRS score of 7.6; in the GAD study, patients were included if their baseline MADRS score was < 16, resulting in a baseline mean MADRS score of 11.1; in the OCD study, patients were included if their baseline MADRS score was < 22, resulting in a baseline mean MADRS score of 10.2. Response to open-label treatment was achieved by 68% to 76% of patients, and relapse rates ranging from 9% (MDD) to 23% (OCD) were recorded in the escitalopram-treated groups during the first 24 weeks of continuation treatment (Table 1). The placebo-treated groups had relapse rates of 50% in the GAD, SAD, and OCD studies and 33% in the MDD study. The corresponding hazard ratios were 2.7 to 4.4, and number needed to treat (NNT) values were 3 to 4. Relevant study information is summarized in Table 1.

Defining Subgroups With Residual Symptoms

In all 4 studies, the mean MADRS total score at randomization was between 3 and 5. The MADRS score was, therefore, used to define subgroups with and without residual symptoms when entering the double-blind continuation period, using 3 separate definitions based on MADRS single items.

Subgroups were defined by how patients scored on 3 core items of the MADRS: apparent sadness or depressed mood, apparent (item 1); inner tension or psychic anxiety (item 3); and lassitude affecting performance of everyday activities (item 7). Depressed mood measures residual depression,

Figure 1. Mean Treatment Difference Between Escitalopram and Placebo in Patients With Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), and Obsessive-Compulsive Disorder (OCD) After 24 Weeks of Continuation Treatment[a,b]



[a]The following approaches were used for analysis: analysis of covariance (observed cases; last observation carried forward [LOCF]) and mixed-effects model repeated measures (MMRM). Analyses were based on the primary efficacy endpoint for each study: Montgomery-Asberg Depression Rating Scale (MDD), Hamilton Anxiety Rating Scale (GAD), Liebowitz Social Anxiety Scale (SAD), and Yale-Brown Obsessive Compulsive Scale (OCD).
[b]$P < .0001$ for all analyses.

while anxiety is of obvious interest in GAD and SAD but also a prominent feature of MDD and OCD, and lassitude reflects the ability of the patient to function in social and work environments, a relevant aspect for decisions of whether or not to continue treatment. Patients scoring 0 represented the subgroup without residual symptoms; patients scoring 1 or more were those with residual symptoms. Patients with and without residual symptoms were compared on the basis of relapse rate and by using a mixed-effects model repeated-measures (MMRM) approach to model Clinical Global Impression-Severity of Illness scale (CGI-S) scores during treatment. The CGI-S was used because of its clinical relevance and broad usefulness across indications.

Observed Cases, Last Observation Carried Forward, and MMRM

Different statistical models have been used to model the effect of various treatments over time. Two statistical models are mainly used: analysis of covariance (ANCOVA) and MMRM. With ANCOVA, there are 2 standard ways to handle missing data: either observed cases or last observation carried forward (LOCF). With MMRM, no imputation of missing data is needed.

Statistical Methodology

The mean treatment difference between placebo and escitalopram during 24 weeks of double-blind treatment was estimated using ANCOVA and MMRM. Analyses of covariance are based on both observed cases and LOCF data. The analyses were initially made on the primary efficacy variable for each study and reported as the standardized effect size,[17] which is defined as the estimated mean drug minus placebo improvement from baseline divided by the standard deviation, which, in this case, is the square root of the residual variance.[18]

In the ANCOVA, the baseline value was included as a covariate and country and treatment, as factors. For MMRM, the primary efficacy variable was considered as a response variable at all time points, and the included fixed effects were country, treatment, visit, and the visit-by-treatment interaction. An unstructured covariance structure was assumed, and the Kenward-Roger approximation was used to estimate the denominator degrees of freedom.

Mixed-effects model repeated measures was considered to be the most suitable method for modeling the change of efficacy assessments over time. This method was used when the mean CGI-S score in the double-blind period was estimated for the different patients subgroups at various time points in order to determine a plausible development for the mean scores of the individual subgroups. The CGI-S was considered as a response variable at all time points, with country, treatment, and the prespecified subgroup as fixed effects. Interactions between treatment, visit, and residual symptom subgroup were added to model the development over time for the various subgroups.

The probability of relapse for each treatment group was reported and compared using hazard ratios estimated by Cox regression. Number needed to treat values were also calculated.[19] For the different residual symptoms subgroups, the time to relapse was compared using a log-rank test. The NNT is the inverse of the difference between the relapse (or response or remission) probabilities of 2 treatments.

RESULTS

Relapse Prevention Across Indications

The standardized effect sizes of treatment with escitalopram versus placebo in the individual indications were estimated using ANCOVA (observed cases, LOCF) and MMRM and were based on the primary measure of MADRS, HARS, Liebowitz Social Anxiety Scale, or Y-BOCS. Standardized effect sizes were similar for LOCF and MMRM (0.59–0.75) and lower for observed cases (0.31–0.53) (Figure 1). Statistical significance was seen with all indications.

The NNT, based on relapse rates for escitalopram versus placebo, was 3 to 4 for these studies. The number needed

Table 2. Relapse Rates Based on Diagnosis, Treatment, and Residual Symptoms in Patients Receiving Escitalopram or Placebo Therapy During Continuation Period

Variable[a]	Item 1 (depressed mood, apparent), % (n/n)	*P* Value	Item 3 (inner or psychic tension), % (n/n)	*P* Value	Item 7 (lassitude affecting performance of everyday activities), % (n/n)	*P* Value
MDD						
Placebo +	42 (23/55)		33 (29/87)		35 (30/85)	
Placebo –	28 (27/98)	.08	32 (21/66)	.69	29 (20/68)	.29
Escitalopram +	13 (7/55)		13 (11/82)		13 (12/96)	
Escitalopram –	6 (6/97)	.15	3 (2/70)	.02	2 (1/56)	.02
GAD						
Placebo +	48 (13/27)		49 (52/107)		54 (32/59)	
Placebo –	53 (85/160)	.54	58 (46/80)	.15	52 (66/128)	.60
Escitalopram +	10 (3/31)		19 (23/122)		17 (10/59)	
Escitalopram –	20 (31/155)	.23	17 (11/64)	.76	19 (24/127)	.71
SAD						
Placebo +	59 (17/29)		53 (51/96)		56 (35/62)	
Placebo –	49 (74/152)	.54	47 (40/85)	.74	47 (56/119)	.19
Escitalopram +	19 (6/32)		18 (19/107)		25 (15/60)	
Escitalopram –	23 (36/158)	.69	28 (23/83)	.16	21 (27/130)	.65
OCD						
Placebo +	60 (24/40)		60 (61/101)		61 (35/57)	
Placebo –	49 (57/116)	.23	36 (20/55)	.009	46 (46/99)	.03
Escitalopram +	29 (15/52)		22 (26/116)		27 (20/74)	
Escitalopram –	21 (23/111)	.28	26 (12/47)	.57	20 (18/89)	.29

[a]Plus sign equals presence of residual symptoms (Montgomery-Asberg Depression Rating Scale [MADRS] score > 0); minus sign equals absence of residual symptoms (MADRS score equals 0).
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, SAD = social anxiety disorder.

to harm is usually based on the withdrawal rate due to adverse events. However, the adverse event withdrawal rate was higher for patients treated with placebo than with escitalopram in all 4 indications. This was still the case after we censored for adverse event withdrawals during the first 2 weeks after randomization in an attempt to adjust for possible discontinuation effects in patients switched from escitalopram to placebo. In the first 2 weeks after randomization, withdrawal due to adverse events occurred with 1 escitalopram patient in the MDD study, 2 escitalopram patients in the SAD study, 1 escitalopram and 2 placebo patients in the GAD study, and none in the OCD study.

Patients With and Without Residual Symptoms

MADRS item 1 (depressed mood, apparent). Table 2 shows a trend ($P = .08$) in MDD patients with a MADRS item 1 score of 1 or more for a higher relapse rate compared to patients with a MADRS item 1 score of 0 in both the placebo arm and the escitalopram arm. This pattern was also seen in the OCD group but not in the GAD or SAD groups. In the MDD and OCD studies, 60% to 70% of patients scored 0 on MADRS item 1, compared to about 80% in the GAD and SAD studies of patients. Slightly fewer patients scored 0 on MADRS item 2 (depressed mood, reported or patient rated) than on MADRS item 1 (depressed mood, apparent or clinician rated), and MADRS item 1 analyses are presented (Table 2).

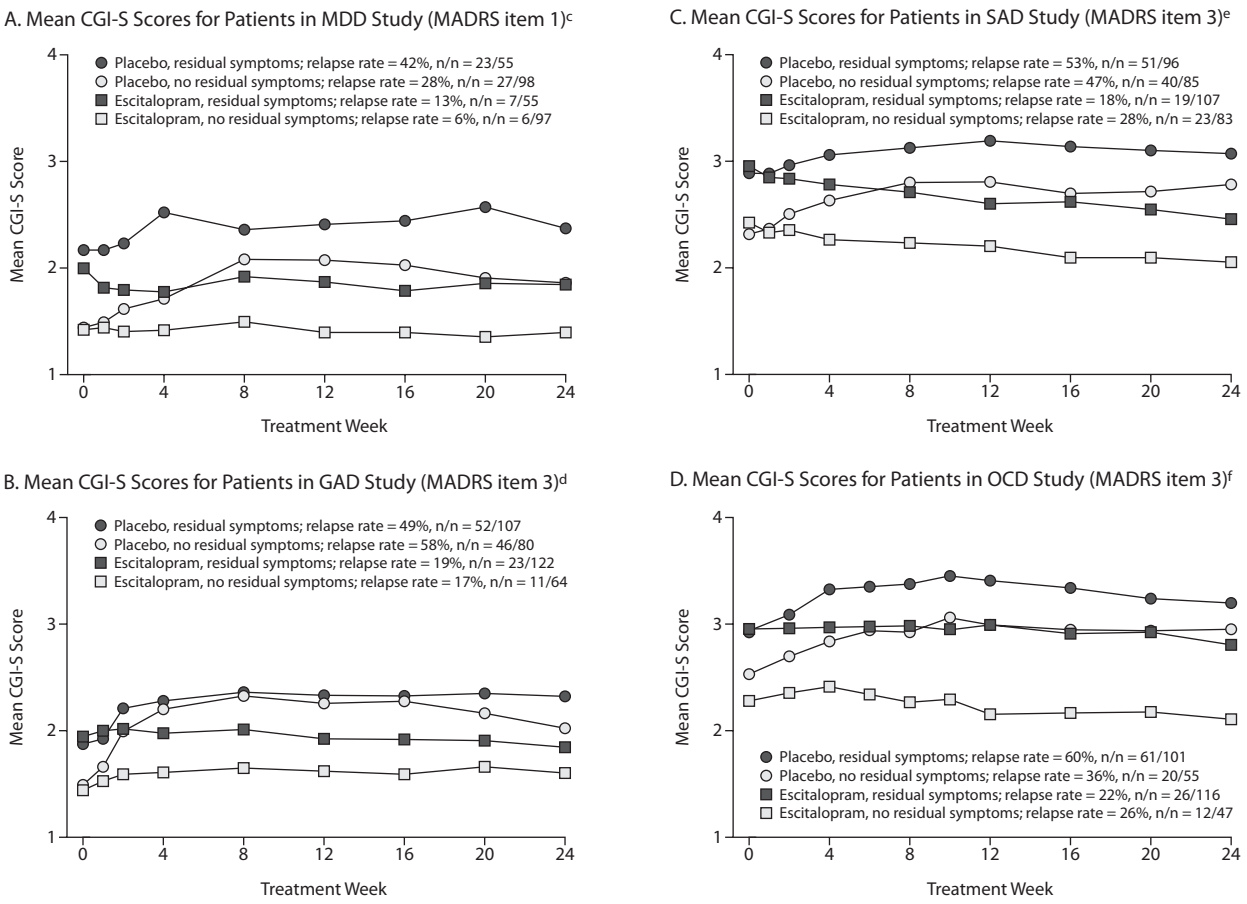
Patients with a MADRS item 1 score of 0 had lower mean CGI-S scores at randomization (1.4–1.7) in the MDD and GAD studies than in the SAD and OCD studies (2.5–2.7). Patients scoring 1 or more (with residual depressed mood) had higher mean CGI-S scores (2.0–2.2 and 3.0–3.3, respectively). Thus, patients with SAD or OCD were globally more ill than those with MDD or GAD, a result that reflects differences in continuation criteria for the different indications.

The CGI-S ratings over the 24-week continuation period showed a stable or slightly declining tendency for escitalopram-treated patients without residual depressed mood in all 4 studies. The same pattern was evident, with higher scores, for escitalopram-treated patients with residual depressed mood. In all studies, escitalopram-treated patients with residual depressed mood remained more ill than patients without residual depressed mood throughout the 24-week continuation period.

A different pattern was seen for placebo-treated patients. For patients with and without residual depressed mood at randomization, CGI-S scores increased, ie, increasing severity of illness, over the first 2 to 3 months and then stabilized. In all studies, placebo-treated patients with residual depressed mood had the highest CGI-S scores.

The numbers of relapses in the different patient subgroups in the MDD study are presented in Figure 2A. No significant differences were seen between patients with and without residual depressed mood within a treatment arm; however, relapse rates in the MDD study were higher in escitalopram-treated patients with residual depressed mood than patients without (13% versus 6%) and in placebo-treated patients (42% versus 28%). This trend was also seen in the OCD study (relapse rates of 29% versus 21% and 60%

Figure 2. Relapse Rates of Patients With and Without Residual Symptoms[a] of MDD, GAD, SAD, and OCD After Randomization to Continuation Treatment With Placebo or Escitalopram[b]



[a]Patients in each treatment group were classified as having residual symptoms (MADRS item score ≥ 1) or not (MADRS item score = 0).
[b]Relapse rates for each group are based on the same criteria as those used in the original trials. The CGI-S scores are based on the following: 0 (not at all ill), 1 (borderline ill), 2 (mildly ill), and 4 (moderately ill).
[c]The effect of residual depressed mood on the relapse rate within each treatment was not statistically significant for placebo ($P = .08$) or escitalopram ($P = .15$), although relapse rates were higher in the groups with residual depressed mood.
[d]The effect of residual psychic tension on the relapse rate within each treatment was not statistically significant for placebo ($P = .15$) or escitalopram ($P = .76$).
[e]The effect of residual psychic tension on the relapse rate within each treatment was not statistically significant for placebo ($P = .74$) or escitalopram ($P = .16$).
[f]The effect of residual psychic tension on the relapse rate within each treatment was statistically significant for placebo ($P = .009$) but not for escitalopram ($P = .57$).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAD = generalized anxiety disorder, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, SAD = social anxiety disorder.

versus 49%, respectively) but not in the GAD study (10% versus 20% and 48% versus 53%, respectively) or SAD study (19% versus 23% and 59% versus 49%, respectively).

MADRS item 3 (inner or psychic tension). Table 2 shows a statistically significantly higher relapse rate in MDD patients with a score of 1 or more on MADRS item 3 compared to patients scoring 0 on item 3 ($P = .02$), in the escitalopram arm but not in the placebo arm ($P = .69$). Conversely, OCD patients with a score of 1 or more on MADRS item 3 had a statistically significantly higher relapse rate ($P = .009$) in the placebo arm than did patients with a 0 score on item 3. This pattern was not seen in the GAD or SAD groups.

At randomization, more than 50% of the patients in the 4 studies had a MADRS item 3 score greater than 0, a result that reflects the presence of residual inner or psychic tension. Patients with a MADRS item 3 score of 0 had lower mean CGI-S scores at randomization (1.4–1.6) in the MDD and GAD studies than in the SAD and OCD studies (2.3–2.5). Patients with a MADRS item 3 score of 1 or more, defined as *patients with psychic tension*, had higher mean CGI-S scores, ranging from about 1.8–1.9 in the MDD and GAD studies and approximately 2.9 in the SAD and OCD studies.

The CGI-S ratings over the 24-week continuation period were stable or slightly decreasing for the escitalopram-treated

subgroups without psychic tension in all 4 studies (Figure 2B–D). The same pattern was seen for escitalopram-treated patients with psychic tension. In all studies, escitalopram-treated patients with psychic tension remained more ill throughout the 24-week continuation phase than patients without psychic tension. Patients in the placebo-treated groups consistently exhibited increasing CGI-S scores, ie, worsening symptomatology, during the first 2 to 3 months, followed by a fairly stable score.

Relapse rates in the MDD study (Table 2) were higher for escitalopram-treated patients with psychic tension than for patients without (13% versus 3%) but not for placebo-treated patients (33% versus 32%). In the GAD and SAD studies, there was no clear indication of higher relapse rates in the patients with versus those without psychic tension. In the OCD study, patients with psychic tension had higher relapse rates than patients without when treated with placebo (60% versus 36%) but not with escitalopram (22% versus 26%).

MADRS item 7 (lassitude affecting performance of everyday activities). Table 2 shows a statistically significantly higher relapse rate ($P = .02$) for MDD patients with a score of 1 or more on MADRS item 7 compared to patients with a 0 score in the escitalopram arm, whereas this pattern did not reach statistical significance in the placebo arm. For OCD, the relapse rate was statistically significantly higher ($P = .03$) in the placebo arm for patients with a MADRS item 7 score of 1 or more than for patients with a 0 score. In the escitalopram arm, this difference was not statistically significant. In the groups with GAD or SAD, this pattern was not seen.

At randomization, approximately one-third of patients in the MDD study and two-thirds of patients in the GAD, SAD, and OCD studies scored 0 on MADRS item 7. The mean CGI-S scores for these patients, defined as being "without problems with social functioning," ranged from 1.2 to 1.6 in the MDD and GAD studies and 2.4 to 2.6 in the SAD and OCD studies. Patients scoring 1 or more, defined as being "with problems with social functioning," had higher mean CGI-S scores at randomization, ranging from about 1.8 to 2.1 in the MDD and GAD studies and 2.9 to 3.0 in the SAD and OCD studies.

Over the 24 weeks of continued escitalopram treatment, patients with problems with social functioning remained more ill than those without. Both subgroups had fairly stable (the MDD, GAD, and OCD studies) or decreasing (OCD study) CGI-S scores. In contrast, the CGI-S scores in placebo-treated patients, with or without problems with social functioning, increased over the first months of continuation treatment and then remained stable.

All placebo-treated patients who had problems with social functioning had slightly higher relapse rates than the subgroups without such problems: 35% versus 29% in the MDD study, 54% versus 52% in the GAD study, 56% versus 47% in the SAD study, and 61% versus 46% in the OCD study (Table 2). The same was found for most of the escitalopram-treated patients: 13% versus 2% in the MDD study, 25% versus 21% in the SAD study, and 27% versus 20% in the OCD study, with 17% versus 19% in the GAD study as the exception.

Subgroups based on MADRS total scores. In the MDD study, 56% of the patients had a MADRS total score ≤ 5 at randomization, indicating complete remission; 80% of patients in the GAD and SAD studies and 62% in the OCD study achieved complete remission. In the MDD study, patients in complete remission had a mean CGI-S score of about 1.3 compared to 2.1 for patients with a MADRS score > 5 at randomization. These values remained virtually unchanged during escitalopram treatment in both of the groups. The relapse rate (after 24 weeks) was 6% (5 of 83 patients) for patients in complete remission versus 12% (8 of 69 patients) for those with a MADRS score > 5 at randomization. In contrast, a gradual increase in CGI-S scores over time was seen in both of the placebo-treated subgroups to about 1.7 and 2.5, respectively. Relapse rates were essentially the same in both subgroups (34% [30 of 89 patients] and 31% [20 of 64 patients], respectively).

Patients with GAD were generally similar to patients with MDD. The placebo-treated groups had an increase in CGI-S scores during the first months. For escitalopram-treated patients, the relapse rate was numerically lower in patients in complete remission versus those with a MADRS score > 5 at randomization (16% [23 of 141 patients] versus 24% [11 of 45 patients], respectively), but, in placebo-treated patients, relapse rates were very similar (52% [81 of 157 patients] and 57% [17 of 30 patients], respectively).

Patients in the SAD and OCD studies had higher mean CGI-S scores at randomization to continued treatment, with about 2.5 in patients in complete remission and about 3.2 in patients with a MADRS score > 5 at randomization. The overall CGI-S pattern during the continuation phase was similar to that in the MDD and GAD studies, characterized by slightly decreasing scores for escitalopram-treated patients versus gradually increasing scores for placebo-treated patients over the first 2 to 3 months. Among the escitalopram-treated patients, relapse rates for patients in complete remission were 21% (33 of 155 patients) and 22% (22 of 100 patients) in the SAD and OCD studies, respectively, and, among placebo-treated patients, relapse rates were 47% (SAD [68 of 144 patients] and OCD [47 of 99 patients]). Also in the SAD and OCD studies, relapse rates in patients with a MADRS score > 5 at randomization were 26% (9 of 35 patients) and 25% (16 of 63 patients), respectively, in escitalopram-treated patients and 62% (23 of 37 patients) and 60% (34 of 57 patients), respectively, in placebo patients.

DISCUSSION

All of the relapse-prevention studies in this analysis demonstrate a large and highly statistically significant

standardized effect size of about 0.7 for escitalopram versus placebo. From a practical point of view, the clinical significance of this finding is confirmed by NNT values of 3 to 4 based on relapse rates,[19] indicating that if one were to continue escitalopram treatment in a group of 3 to 4 patients and continue on placebo in another group of 3 to 4 patients, active treatment would result in 1 less relapsed patient. In real life, the alternative to pharmacologic treatment, of course, is not placebo treatment as performed in randomized clinical trials, which includes the beneficial therapeutic impact of frequent rating sessions.[20] Without the study regimen and the belief in getting active treatment, one would anticipate untreated patients to run an even higher risk of relapse than the placebo-treated patients in these studies.

A major reason for the present analysis was the hope of identifying subgroups of patients that would particularly benefit from continued treatment. Presently, there is little guidance in this respect. The primary publications of the relapse-prevention studies did not identify any significant effect of factors such as sex, age, weight, randomization score, duration, or onset of illness. Although the studies were designed to study the specific disorder and to exclude other disorders, they do have some symptom overlap. Thus, inner or psychic tension is a core item of depressive states in the MADRS, and depressed mood is a core item of the HARS. These symptoms are useful for comparison between disorders, which is meaningful in view of the frequent comorbidity between the disorders and the diagnostic difficulties that face the medical profession. Anxiety is a core element in GADs and SADs and is also a prominent symptom of major depression and OCD. It was of interest to investigate whether residual anxiety or depression after open-label treatment had any impact on the outcome of continuation treatment. This would seem likely in view of reports that the presence of residual depressive symptoms following acute treatment of a major depressive episode is a predictor of early relapse.[8,9]

The MADRS item *lassitude affecting performance of everyday activities* was also included, as this item reflects the patient's ability to function and work and is relevant for decisions on whether or not to continue treatment. This aspect is also reflected in the Sheehan Disability Scale and introduced as an important aspect of anxiety trials.[21] The MADRS total score, because of its composite nature, is obviously less adequate as a potential predictor than individual core items and predictably gave no additional information. The chosen cutoff MADRS score of 5 corresponds to a CGI-S score of 1, ie, "not at all ill,"[22] and seems a reasonable criterion to distinguish between patients with and without residual symptoms used in our approach, although a MADRS score ≤ 12 is conventionally recommended.[23]

At the initiation of continuation treatment, all patients with a residual symptom were globally more ill than patients who did not present with these symptoms. Patients in the SAD and OCD studies were consistently rated as globally more ill than those in the MDD and GAD studies. It should be noted that patients randomly assigned to continuation treatment were required to have a MADRS score ≤ 12 in the MDD study, a HARS score ≤ 10 in the GAD study, a CGI-I score ≤ 2 in the SAD study, and ≥ 25% decrease in Y-BOCS score in the OCD study. The higher CGI-S scores at randomization in the SAD and OCD studies, which had less strict criteria, are therefore not surprising.

Patients who did not continue to receive active treatment worsened, even if they appeared free from residual symptoms (anxiety, depressed mood, or lassitude affecting performance of everyday activities) after at least 12 week's active treatment of MDD, GAD, SAD, or OCD. However, the apparently symptom-free patients remained less ill during continuation treatment than patients who had residual symptoms when starting. Particularly in the SAD and OCD studies, there was a marked separation of CGI-S scores between patients with and without these symptoms.

There is no evidence that the increase in CGI-S score, seen in all placebo-treated patient subgroups, might be the result of discontinuation symptoms appearing following switch from active escitalopram treatment to placebo (cf original study publications). In addition, the increase in CGI-S scores is not limited to the first weeks, but continues over 2 to 3 months.

All of the escitalopram-treated patient subgroups remained stable or further improved, whether or not they had residual psychic tension, depressed mood, or problems with social functioning. The apparently symptom-free patients remained less ill (in the MDD and GAD studies, between "not at all ill" and "borderline ill") than the patients who had residual symptoms.

Different statistical models can be used to model the development of assessment scores over time to compare the effect of treatment. Two different statistical models are mainly used: ANCOVA and MMRM. With ANCOVA, there are 2 standard ways to handle missing data: by using either the observed cases or LOCF approach. With MMRM, no imputation of missing data is needed, as the model handles the data in another way.[24]

In a relapse-prevention study, the patients who relapse are withdrawn from the study, which implies that observed cases and LOCF approaches will result in rather different mean score estimates. With the observed cases approach, it is not possible to obtain a value higher than the relapse criterion score because only nonrelapsed patients are included. However, with a LOCF approach, as a patient relapses, the highest value is carried forward and the estimate can exceed the relapse criterion cutoff. In the current analysis, the main interest is in determining a plausible patient treatment outcome, and MMRM is the most appropriate model. Because the primary efficacy variable differs between the studies, the treatment difference is reported as the standardized effect size; these differences are very similar when determined by LOCF and MMRM. However,

when estimating the change in mean CGI-S score in the double-blind period, only MMRM was used.

No clear picture emerged from the present analysis regarding whether patients with residual symptoms had a higher relapse rate (using the criteria set in each of the original studies) than those without. The markedly higher relapse rates in the MDD study for escitalopram-treated patients with residual depressed mood or psychic tension are in line with previous observations.[8,9] If these residual symptoms were true predictors of relapse, one would expect the difference between the subgroups to be even more pronounced in the placebo-treated patients. This, however, is not reflected in the present set of MDD data. Significantly higher relapse rates were found in placebo-treated patients with residual symptoms of psychic tension and social functioning in the OCD study. The most evident difference in all of the studies was between the escitalopram-treated groups and the placebo-treated groups, which had relapse rates of about 20% and 50%, respectively.

Interestingly, a more consistent pattern emerged with slightly higher relapse rates in all of the studies for patients with residual problems with social functioning. These differences, however, were marginal as compared to the overall difference between active- and placebo-treated patients.

It was not possible, therefore, from the present analysis, to define patients who are in particular need of continuation treatment or patients who can safely manage without continuation treatment of these disorders. Since patients with symptoms of residual psychic tension, depressed mood, or problems with social functioning were consistently assessed as globally more ill, each of the symptoms can be used as indicators that continued treatment is warranted. Even in the absence of these symptoms, however, patients deprived of active treatment become globally more ill, whereas patients in active treatment remain stable or improve further over 24 weeks.

The benefit of continued treatment seems unquestionable. Importantly, there appears to be little downside in terms of side effects or tolerability problems with long-term use of escitalopram. The original study publications of the relapse-prevention studies all report comparable adverse event profiles and incidence in escitalopram- and placebo-treated groups, confirming data from a recent analysis[25] of all double-blind, randomized studies in depression and anxiety disorders. Good tolerability was also evident from the fact that few patients discontinued escitalopram treatment because of adverse events: in fact, the incidence in this group was lower than that seen in the placebo groups.

These results may not be generalizable to patients seen in normal clinical practice due to patient exclusion criteria for the individual trials. In addition, the results are based on post hoc analyses, so the conclusions drawn from them are indicative only. Residual symptoms were based on a depression rating scale in order to compare results between 4 different disorders, only 1 of which was a depressive disorder. However, based on the mean MADRS score of patients randomly assigned to treatment (3–5 in all 4 studies), we believe this is a reasonable measure of residual symptomatology.

Patients randomly assigned to placebo experienced symptoms that worsened, even if they were initially free of these core residual symptoms at the start of continuation treatment. No clear picture emerged from the present analysis regarding whether patients with residual symptoms had a higher relapse rate than those without, but presence of residual symptoms is associated with significantly worse overall illness severity in all 4 diagnostic groups. The greatest difference in all of the studies was between patients treated with escitalopram (relapse rates of about 20%) and placebo (relapse rates of about 50%). In these depression and anxiety studies, escitalopram-treated patients remained stable or further improved during continuation treatment, whether or not they had residual symptoms of psychic anxiety, depressed mood, or problems with social functioning.

Drug name: escitalopram (Lexapro and others).
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