Eur Arch Psychiatry Clin Neurosci (2011) 261:147–156
DOI 10.1007/s00406-010-0149-3

ORIGINAL PAPER

Testing anxious depression as a predictor and moderator of symptom improvement in major depressive disorder during treatment with escitalopram

George I. Papakostas · Klaus Larsen

Received: 3 December 2009 / Accepted: 1 September 2010 / Published online: 22 September 2010

Abstract The purpose of this analysis was to explore the potential role of anxious MDD as a treatment predictor and moderator in major depressive disorder (MDD) using a large escitalopram clinical trial dataset. Individual patient-level data from 13 double-blinded, randomized, controlled trials in patients with MDD were pooled. Both univariate, last observation carried forward (LOCF) analyses and repeated measurements analyses without imputation (MMRM) were carried out for change in symptom scores, response and remission rates. Of 3,919 patients, 48.0% were classified as having anxious MDD depression (HAMD) somatization/anxiety subscale score $\geq$7 at baseline. Patients with anxious MDD were less likely to report symptom improvement on some outcome measures than patients without anxious MDD (predictor analysis). Specifically, the difference in response rates for patients with vs. patients without anxious MDD according to the MADRS (55.6% vs. 57.7%, respectively) was not statistically different. However, the difference in remission rates for patients with versus without anxious MDD according to the MADRS (37.6% vs. 44.1%, respectively) was statistically significant. Escitalopram was more effective than placebo, and as effective as the SSRIs and SNRIs, in the treatment of anxious MDD. The present analysis provides some evidence that the presence of an anxious MDD subtype is a predictor of poor response. There was no difference in the response to treatment of patients with or without anxious MDD to escitalopram, SSRIs, or SNRIs. The present analysis did not support the notion that SNRIs are more effective than escitalopram in the treatment of anxious MDD, nor was there evidence to support treatment moderating effects for anxious MDD.

Keywords Depression · Anxious · Predictor · Moderator · Antidepressant · Unipolar

Introduction

Major depressive disorder (MDD) is a prevalent illness, associated with considerable morbidity, mortality, and impairment in psychosocial functioning. Despite the development and availability of dozens of pharmacologic treatment options for MDD, studies have shown that antidepressant monotherapy yields, at best, modest remission rates. For example, a report from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial demonstrated that monotherapy with citalopram resulted in remission rates between 28 and 33% [1]. In parallel, large meta-analyses of randomized, double-blinded, placebo-controlled trials of antidepressants for MDD suggest a relative advantage of antidepressants versus placebo, in terms of response rates, ranging between 15 and 20% [2–4]. Clearly, there is an urgent need to develop more effective treatment strategies for MDD.

One possible approach toward the development of novel pharmacotherapeutic strategies for MDD involves identifying subpopulations of depressed patients that are more likely to experience the benefits of a given (existing) treatment versus placebo, or more likely to achieve symptomatic remission with one treatment versus another. Attempts have been made to identify such subpopulations, specifically by testing whether a given biological or clinical marker serves

G. I. Papakostas (✉)
Massachusetts General Hospital, Harvard Medical School,
15 Parkman Street, WACC#812, Boston, MA 02114, USA
e-mail: gpapakostas@partners.org

K. Larsen
H Lundbeck A/S, Copenhagen, Denmark

as a moderator (i.e., a risk factor that can be used to divide the population into groups such that within those groups, another risk factor—therapy—for the same outcome operates differently) of clinical improvement following the treatment of MDD with standard, first-line antidepressants [5, 6]. Numerous studies have examined whether the presence of anxious depression can serve as a predictor (defined as a risk factor, either clinical or biologic, that is found to be statistically correlated with clinical outcome at a later time-point) of antidepressant treatment response [1, 7–15]. Definitions of anxious depression vary throughout these studies and can include depression with high levels of anxiety (symptom threshold approach as done in studies [1, 8, 9, 11, 12, 14, 15]), or depression with a co-morbid anxiety disorder (co-morbidity approach as done in studies [1, 7, 10, 13]). Studies employing either of these two definitions have reported anxious depression to adversely impact treatment outcome during the acute-phase of therapy of MDD with standard antidepressants. For example, Fava et al. [9] (employing the symptom-threshold definition of anxious depression) demonstrated dramatically lower remission rates among patients who received "second-level" treatment in STAR*D (switching from citalopram to venlafaxine, bupropion, or sertraline versus augmentation of citalopram with bupropion versus buspirone) who presented with anxious MDD than those who did not (the presence/absence of anxious MDD served as a treatment *predictor*). Similarly, Souery et al. [13] found the presence of co-morbid panic disorder and social phobia to be associated with an increased risk of patients meeting criteria for treatment-resistant depression. In addition, a more recent study conducted by our group [16] revealed that patients with anxious MDD (defined using the symptom threshold approach) may respond differentially to certain treatments (the presence/absence of anxious MDD served as a treatment *moderator*). Specifically, in that analysis, patients with anxious MDD responded better to acute treatment with a selective serotonin reuptake inhibitor (SSRI) than with the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion, while there were no differences in response to the two treatments among patients with low/moderate levels of anxiety.

It has recently been proposed that, perhaps due to their simultaneous, direct action on serotonin as well as norepinephrine, the serotonin-norepinephrine reuptake inhibitors (SNRIs) may be more effective than the SSRIs in the treatment of anxious MDD [17, 18]. The goal of the present work was threefold: (1) to examine the efficacy of escitalopram in treating patients with anxious MDD, (2) to confirm whether anxious MDD status is a predictor of treatment outcome in MDD, and (3) to test whether anxious MDD status is a moderator of treatment response for escitalopram versus the SNRIs, as well as several older SSRIs (fluoxetine, sertraline, paroxetine, citalopram), and placebo. In order to accomplish this, we pooled individual patient data from several randomized, double-blinded, controlled trials of escitalopram for the treatment of MDD.

Methods

Study design

The trial database includes individual patient data from all randomized, controlled trials sponsored by H. Lundbeck or Forest Labs, in MDD patients treated with escitalopram, in which the Hamilton Depression Rating Scale [19] was assessed (see Table 1 for details) [20–32]. Anxious MDD was defined as a score of 7 or greater on the HAMD—anxiety/somatization subscale (HAMD-AS; sum of HAMD items 10, 11, 12, 13, 15, 17) [33]. Since anxious MDD is a subscale of the HAMD, only studies also using the HAMD were included. All of these trials also employed the Montgomery-Åsberg Depression Rating Scale [34]. These trials were conducted in accordance with the principles of *Good Clinical Practice* and the *Declaration of Helsinki*. Local ethics committees approved the study design, and eligible patients gave their written informed consent before participating.

The pre-defined primary efficacy variable in each of the studies was the MADRS total score, and the estimated mean treatment difference in MADRS total score at week 8 was the primary outcome endpoint. Response was defined as $\geq$50% reduction from baseline total score, and remission was defined as a 17-item HAMD ($HAMD_{17}$) score $\leq$7 or a MADRS score $\leq$10 (for all studies employing the MADRS, even those which, when the original protocol was written, defined remission as an endpoint MADRS score of 12 or less). The intent-to-treat dataset (ITT), which included all patients who received at least one dose of study medication, was used to define the study population of interest.

Statistical methods

Since individual studies varied in duration (the shortest of which was 8 weeks), and in order to introduce homogeneity with regard to the duration of the follow-up interval in the present dataset, week 8 was defined as the endpoint of interest for the present analysis (i.e., studies greater than 8 weeks in duration were "truncated" at 8 weeks). In order to define endpoint severity for patients who prematurely discontinue treatment, both univariate last observation carried forward (LOCF) analyses and repeated measurements analyses without imputation (MMRM) were carried out for each of the continuous outcomes (change in MADRS and $HAMD_{17}$ symptom scores), as well as for the

Table 1 Overview of studies pooled

Reference	Duration inclusion	Design	Setting	Treatment (dosage)	Dose (mean/median/mode)[a]	ITT (n)	Completers (%)[a]
Burke et al. [20]	8 weeks	Fixed	Spec	PBO	–	122	74.6
	MADRS ≥22	PBO		ESC (10)	10/10/10	119	79.8
				ESC (20)	20/20/20	125	75.2
				CIT (40)	40/40/40	125	74.4
Rapaport et al. (MD-02) [21]	8 weeks	Flexible	Spec	PBO	–	127	82.7
	MADRS ≥22	PBO		ESC (10–20)	17.6/20/20	125	76.8
				CIT (20–40)	35.3/40/40	123	80.5
Bose et al. (MD-13) [22]	12 weeks	Flexible	Spec	PBO	–	134	89.6
	MADRS ≥22	PBO		ESC (10–20)	17.6/20/20	130	81.3
Forest Labs. (MD-16) [23]	8 weeks	Flexible	Spec	ESC (10–20)	17.3/20/20	98	67.3
	MADRS ≥22			FLU (20–40)	34.1/40/40	99	77.8
Ninan et al. (MD-26) [24]	8 weeks	Flexible	Spec	PBO	–	153	85.6
	$HAMD_{24}$ ≥25			ESC (10–20)	15.5/20/20	147	78.9
Baldwin et al. [25]	27 weeks	Flexible	GP & spec	ESC (10–20)	13.9/10/10	165	92.1
	MADRS ≥22			PAR (20–40)	25.4/20/20	158	93.0
Boulenger et al. [26]	24 weeks	Fixed	GP & spec	ESC (20)	20/20/20	229	93.4
	MADRS ≥30			PAR (40)	40/40/40	225	85.8
Ventura et al. [27]	8 weeks	Flexible	Spec	ESC (10)	10/10/10	104	84.6
	MADRS ≥22			SER (50–200)	153/200/200	108	86.1
Alexopoulos et al. (MD-27) [28]	8 weeks	Flexible	Spec	PBO	–	132	79.5
	MADRS ≥22	PBO		ESC (10–20)	19.2/20/20	134	80.6
				SER (50–200)	155/200/200	137	82.5
Montgomery et al. [29]	8 weeks	Flexible	GP	ESC (10–20)	12.1/10/10	146	85.6
	MADRS ≥18			VLF (75–150)	95.2/75/75	143	86.7
Bielski et al. [30]	8 weeks	Fixed	Spec	ESC (20)	20/20/20	98	73.5
	$HAM\text{-}D_{24}$ ≥20			VLF (225)	225/225/225	100	66.0
Wade et al. [31]	24 weeks	Fixed	GP & spec	ESC (20)	20/20/20	143	87.4
	MADRS ≥26			DUL (60)	60/60/60	151	84.1
Khan et al. [32]	8 weeks	Flexible	Spec	ESC (10–20)	16.1/20/20	137	86.1
	MADRS ≥26			DUL (60)	60/60/60	133	68.4

ESC escitalopram, *CIT* citalopram, *DUL* duloxetine, *FLU* fluoxetine, *VLF* venlafaxine XR, *PAR* paroxetine, *SER* sertraline, *CLO* clomipramine, *BUP* bupropion XL, *PBO* placebo-controlled study, *Spec* specialist settings, *GP* general practice, *ITT* intent-to-treat dataset

[a] values from week 8

binary outcomes, response and remission (defined using the MADRS and $HAMD_{17}$).

There are two LOCF analyses for each of the continuous outcomes. The first analysis is an ANCOVA with center, treatment and anxiety as categorical variables and baseline depression severity score (MADRS or $HAMD_{17}$) as covariate. In this model, the hypothesis of a different treatment effect for anxious versus non-anxious MDD patients was done by testing for a treatment*anxiety interaction. In the second model, only anxious MDD patients are considered. The hypothesis of no treatment effect is tested, including center as a categorical explanatory variable and baseline depression severity score, the treatment effect is estimated. The overall difference in the change from baseline between those with and without anxious MDD was estimated and tested correcting for baseline depression severity score, center and treatment group, and chi-square test for equal proportions of responders/remitters in the anxious and non-anxious groups were performed. The LOCF analyses for each of the binary outcomes are carried out using logistic regression, including the same covariates and testing the same hypotheses as the analysis of the continuous outcomes.

The same hypotheses are tested in repeated measurements models except that the centers were pooled into countries due to convergence problems. For the continuous outcomes, an unstructured covariance matrix was used to capture the correlation between the different time points.

Table 2 Baseline characteristics of patients

	Anxious depression ($n = 1883$)	Non-anxious depression ($n = 2036$)
Age (mean ± SD) in years	43.2 ± 13.7**	43.9 ± 14.5
Female *n* (%)	1,249 (66.3%)###	1,228 (60.3%)
Completed 8 weeks *n* (%)	1554 (82.5%)	1,701 (83.5%)
$HAMD_{17}$ subscale score (mean ± SD)[a]	8.2 ± 1.3	4.8 ± 1.3
$HAMD_{17}$ total score (mean ± SD)	24.0 ± 3.8	18.5 ± 3.6
MADRS total score (mean ± SD)	32.0 ± 4.7***	29.1 ± 4.5
MADRS ≥30 *n* (%)	1,328 (70.5%)###	895 (44.0%)

SD standard deviation, *MADRS* Montgomery Åsberg depression rating scale

** $P < 0.01$; *** $P < 0.001$ (Wilcoxon); ### $P < 0.001$ (chi-square)

[a] Somatization/anxiety subscale score (sum of items 10–13, 15, 17)

For binary outcomes, Generalized Estimation Equations (GEE) are used with an unstructured working covariance matrix. The analyses are performed in the SAS procedures MIXED (continuous outcomes) and GENMOD (binary outcomes). All statistical tests were two-sided.

Results

Patient baseline characteristics

Individual, patient-level data from 13 randomized trials were pooled in the present analysis (see Table 1 for individual trial information). Baseline demographic and clinical data of patients pooled in the present analysis are listed in Table 2. Briefly, of the 3,919 patients included in these 13 randomized controlled trials, 48.0% were classified as having anxious MDD. Of these 1,883 patients with anxious MDD, 858 were treated with escitalopram, 714 with an active comparator (citalopram, sertraline, paroxetine, venlafaxine, or duloxetine), and 311 with placebo. Of 2,036 patients with non-anxious MDD included in the present analysis, 908 were treated with escitalopram, 778 with an active comparator, and 350 with placebo.

Treatment outcome: Adherence

A total of 329 patients with anxious MDD (17.5%), compared to 335 patients with non-anxious MDD (16.4%) withdrew during the first 8 weeks. There were no statistically significant differences in withdrawals due to adverse events (AEs) between anxious (5.2%) and non-anxious MDD patients (5.7%), withdrawals due to lack of efficacy (anxious: 1.5%, non-anxious: 1.3%), lost to follow-up (anxious: 5.0%, non-anxious: 4.9%), or due to other reasons (anxious: 5.8%, non-anxious: 4.5%) ($P > 0.05$ for all analyses).

Treatment outcome: Tolerability

There were no statistically significant differences between anxious and non-anxious MDD patients in the number of patients that had at least 1 AE, or in the incidence of the most frequent AEs, except for insomnia (Table 3).

Treatment outcome: efficacy, predictor, and moderator analyses

Response rates, remission rates, and depression score resolution during treatment for patients with and without anxious MDD are presented in Table 4. Patients with anxious MDD were less likely to report symptom

Table 3 Adverse events (AE) with an incidence ≥5% for patients with versus without anxious MDD

Preferred term	Anxious depression	Non-anxious depression
Total patients, *n*	1,883	2,036
Patient with ≥1 AE (%)	1,527 (81.1%)	1,672 (82.1%)
Headache	412 (21.9%)	467 (22.9%)
Nausea	402 (21.3%)	392 (19.3%)
Diarrhea	219 (11.6%)	215 (10.6%)
Dry mouth	199 (10.6%)	240 (11.8%)
Insomnia	189 (10.0%)	247 (12.1%)*
Dizziness	177 (9.4%)	158 (7.8%)
Upper respiratory tract infection	128 (6.8%)	152 (7.5%)
Fatigue	107 (5.7%)	140 (6.9%)
Ejaculation delayed[a]	40 (6.3%)	43 (5.3%)
Hyperhidrosis	101 (5.4%)	119 (5.8%)
Somnolence	95 (5.0%)	117 (5.7%)
Nasopharyngitis	87 (4.6%)	112 (5.5%)
Constipation	86 (4.6%)	111 (5.5%)

* $P < 0.05$

[a] For men (anxious depression = 653, non-anxious depression $n = 769$)

improvement on some outcome measures than patients without anxious MDD (predictor analysis). The estimated difference between the two groups was 0.65 MADRS points ($P = 0.06$, LOCF, ANCOVA) in favor of the non-anxious group and 2.16 HAMD points ($P < 0.0001$, LOCF, ANCOVA) in favor of the non-anxious group. The difference in response rates for patients with versus patients without anxious MDD according to the MADRS (55.6% vs. 57.7%, respectively; $P = 0.17$, LOCF, ANCOVA) and HAMD (55.4% vs. 54.5%, respectively; $P = 0.56$, LOCF, ANCOVA) was not statistically different. However, the difference in remission rates for patients with versus without anxious MDD according to the MADRS (37.6% vs. 44.1%, respectively, $P < 0.0001$, LOCF, ANCOVA) and HAMD (34.3% vs. 45.3%, respectively, $P < 0.0001$, LOCF, ANCOVA) was statistically significant.

Analyses comparing the efficacy of escitalopram versus placebo, SSRIs, and SNRIs are presented in Table 5 and in Fig. 1. Escitalopram appeared to be consistently more effective than placebo and equally effective as the SNRIs or SSRIs in the treatment of anxious MDD.

Finally, results of the moderator analysis are listed in Table 6 and Fig. 2. Figure 2 shows the difference in treatment effect (in MADRS points) between patients in the anxious group and the non-anxious group. This difference should be added to or subtracted from the treatment effect (escitalopram versus comparator). A positive treatment difference indicates that anxious patients responded better to escitalopram (compared with comparator) than non-anxious patients, while a negative difference indicates that non-anxious patients responded better to escitalopram (compared with comparator) than anxious patients. Overall, there was no consistent difference in the relative efficacy of any of the comparator arms versus escitalopram in their relative efficacy in treating anxious versus non-anxious MDD, suggesting the absence of a moderator effect for anxious versus non-anxious MDD status.

Discussion

The present analysis is the largest conducted to date focusing on the pharmacotherapy of anxious MDD. Patients with anxious MDD were found to be slightly younger, more likely to be women than men, and much more likely to suffer from severe MDD (baseline MADRS $\geq$30) (70.9% vs. 44.8%) than patients without anxious MDD. There was no difference in antidepressant adherence, tolerability, or side-effect profile when comparing patients with versus without anxious MDD. This finding is consistent with previous analysis suggesting that the degree of psychic and somatic anxiety levels in MDD patients does not affect the likelihood of developing adverse events during pharmacotherapy with fluoxetine [35].

Predictor analyses did not consistently show patients with anxious MDD to have poorer acute-phase treatment outcome than those without anxious MDD. Specifically, similar to a study by Fava et al. [9], much (6–10%) lower remission rates for patients with versus without anxious MDD were observed in the present sample. In part, this may be due to the greater severity of patients with anxious depression at baseline, making it more difficulty for them to achieve remission within 8 weeks although all analyses were conducted controlling for depression severity at baseline. However, when examining efficacy outcome as a continuous measure (i.e., change in symptom severity during treatment), a greater resolution of depressive symptoms in favor of patients without anxious MDD was observed with regard to the MADRS but not the HAMD scale. Response rates were no different between the two groups. This would suggest that, while patients with anxious MDD experience a comparable overall reduction of symptoms as those without anxious MDD, individual symptoms may improve more evenly for the latter than the former groups of patients, such that patients with anxious MDD continue to experience a residual cluster of symptoms by the end of the study leaving more of them short of remission. Future studies are needed to test this hypothesis and, potentially, identify any particular "cluster" of residual symptoms that may be particularly prevalent in this specific patient population. This, in turn, could lead to the development of a more specific treatment algorithm for patients with anxious MDD, which may result in enhanced remission rates.

The presence of anxious MDD was not found to serve as a moderator of symptom improvement of escitalopram versus placebo or active treatment. The mean treatment difference of escitalopram to SSRIs was 0.8 [95% CI: −0.4 to 2.0] MADRS points compared to 0.9 [95% CI: 0.3 to 1.5] MADRS points by Kennedy et al. [36]. Because some trials did not use the HAMD, the treatment difference is not statistically significant in the present analysis in contrast to the Kennedy et al. [36] analysis, due to the smaller number of patients in the present study. In addition, the results of the moderator analysis did not suggest that the presence of anxious MDD significantly altered the relative efficacy of escitalopram versus placebo, the SSRIs, or the SNRIs. In other words, escitalopram was as effective relative to placebo, SSRIs, and SNRIs in the treatment of patients with anxious MDD as in patients with non-anxious MDD. These findings do not support the notion that antidepressants that simultaneously act on serotonin and norepinephrine are more effective in treating MDD accompanied by high levels of anxiety than antidepressants that only directly influence serotonin, such as the SSRIs. However, whether

Table 4 Treatment effect, response, and remission at 8 weeks

	Change in symptom score		Response % (*n*)		Remission % (*n*)[a]	
	Non-anxious	Anxious	Non-anxious	Anxious	Non-anxious	Anxious
MADRS, LOCF						
ESC	−13.6	−13.1	50.4% (197)	46.1% (136)	40.0% (142)	30.2% (89)
PBO	−10.5	−10.7	34.9% (122)	31.2% (97)	26.3% (92)	22.5% (70)
ESC	−17.1	−16.2	63.9% (326)	62.5% (288)	47.8% (244)	38.8% (179)
SSRIs	−17.0	−15.4	63.3% (329)	60.0% (268)	49.0% (255)	41.4% (185)
ESC	−19.5	−18.1	69.5% (184)	67.4% (174)	53.2% (141)	44.2% (114)
SNRIs	−17.5	−16.9	61.6% (159)	56.6% (151)	46.5% (120)	41.6% (111)
$HAMD_{17}$, LOCF						
ESC	−7.8	−9.7	45.4% (161)	47.1% (139)	36.9% (131)	24.7% (73)
PBO	−6.1	−8.3	37.1% (130)	34.1% (106)	27.4% (96)	19.9% (62)
ESC	−9.6	−12.0	57.8% (295)	61.0% (281)	48.0% (245)	34.7% (160)
SSRIs	−9.6	−11.3	58.5% (304)	57.0% (255)	50.6% (263)	35.3% (158)
ESC	−9.6	−12.0	63.4% (168)	64.0% (165)	52.8% (140)	45.0% (104)
SNRIs	−9.6	−11.3	54.7% (141)	56.9% (152)	46.9% (121)	37.1% (99)
MADRS, MMRM						
ESC	−14.8	−14.2	59.8% (171)	52.7% (125)	47.9% (137)	35.9% (85)
PBO	−10.7	−11.2	37.8% (111)	33.8% (68)	28.9% (85)	25.0% (65)
ESC	−18.5	−19.1	71.8% (313)	68.7% (266)	54.1% (236)	43.4% (168)
SSRIs	−18.0	−18.5	69.1% (311)	66.8% (253)	54.2% (244)	46.4% (176)
ESC	−19.5	−18.9	77.0% (174)	74.3% (165)	59.3% (134)	50.0% (111)
SNRIs	−18.5	−18.8	72.3% (146)	68.8% (148)	53.5% (108)	51.2% (110)
$HAMD_{17}$, MMRM						
ESC	−8.8	−10.6	53.5% (153)	54.0% (128)	43.0% (123)	29.1% (69)
PBO	−6.5	−8.8	40.4% (119)	36.9% (96)	29.9% (88)	21.9% (57)
ESC	−10.2	−13.6	64.9% (283)	67.4% (261)	53.9% (235)	38.2% (148)
SSRIs	−8.8	−10.6	64.7% (291)	64.1% (243)	56.0% (252)	40.1% (152)
ESC	−11.2	−14.2	69.0% (156)	72.1% (160)	57.5% (130)	45.5% (101)
SNRIs	−10.7	−14.0	62.9% (127)	67.4% (145)	53.5% (108)	45.6% (98)

ESC escitalopram, *$HAMD_{17}$* 17-item Hamilton Depression Rating Scale, *LOCF* last observation carried forward, *MADRS* Montgomery-Åsberg Depression rating Scale, *MMRM* mixed model repeated measures, *SNRI* serotonin noradrenalin reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

[a] Remission defined as MADRS ≤10 or $HAMD_{17}$ ≤7

there is a difference in the degree of resolution of specific anxious symptoms (i.e., psychic versus somatic anxious symptoms) or other depressive symptoms between these two broad categories of pharmacologic treatments remains unclear and should be the subject of future analyses.

There are several limitations to our work that should be taken into account when interpreting the findings. One limitation is that by focusing on data from controlled trials, which necessarily employ inclusion and exclusion criteria to reduce sample heterogeneity, it is likely that the participants in these studies represent only a fraction of the patients seeking treatment for depression. Thus, it may be difficult to directly extend the findings of this study to patients treated outside of research settings. Second, our definition of anxious MDD is based on the severity of anxiety symptoms, as measured by the HAMD anxiety/somatization factor. Although the HAMD does include anxiety items, only a limited number of anxiety symptoms are captured by the HAMD, and, therefore, the possibility of a misclassification (i.e., patients with anxious MDD classified as not having anxious MDD) cannot be ruled out. However, the report of a significant correlation between a dimensional definition of anxious MDD and the degree of anxiety disorder co-morbidity suggest that such risk may be relatively low [37]. An additional limitation is that HAMD, used to define anxious MDD, was used as a secondary outcome measure in most studies (the MADRS was used as primary in most). Therefore, it may have been more

Table 5 Escitalopram versus placebo, SSRIs, and SNRIs in anxious MDD

Treatment	Treatment effect[b]		Response		Remission	
	Estimate	95% CI	OR[a]	95% CI	OR[a]	95% CI
MADRS, LOCF						
Placebo	2.43**	0.72 to 4.14	1.90***	1.36 to 2.66	1.48*	1.02 to 2.14
SSRIs	0.78	−0.43 to 1.99	1.11	0.84 to 1.46	0.91	0.69 to 1.20
SNRIs	1.03	−0.66 to 2.73	1.59*	1.11 to 2.29	1.13	0.79 to 1.63
$HAMD_{17}$, LOCF						
Placebo	1.28*	0.06 to 2.50	1.74**	1.25 to 2.41	1.32	0.89 to 1.96
SSRIs	0.76	−0.14 to 1.66	1.18	0.90 to 1.55	0.99	0.75 to 1.32
SNRIs	0.86	−0.40 to 2.12	1.33	0.93 to 1.92	1.16	0.81 to 1.67
MADRS, MMRM						
Placebo	2.98***	1.23 to 4.74	2.09*	1.41 to 2.98	1.58*	1.09 to 2.34
SSRIs	0.55	−0.70 to 1.79	1.10	0.82 to 1.48	0.92	0.69 to 1.22
SNRIs	0.20	−1.38 to 1.78	1.35	0.90 to 2.04	0.97	0.67 to 1.41
$HAMD_{17}$, MMRM						
Placebo	1.55*	0.30 to 2.81	1.92***	1.35 to 2.73	1.45	0.97 to 2.18
SSRIs	0.69	−0.22 to 1.61	1.16	0.87 to 1.56	0.98	0.73 to 1.31
SNRIs	0.14	−1.09 to 1.37	1.22	0.82 to 1.82	1.02	0.70 to 1.49

$HAMD_{17}$ 17-item Hamilton Depression Rating Scale, *LOCF* last observation carried forward, *MADRS* Montgomery-Åsberg Depression rating Scale, *MMRM* mixed model repeated measures, *SNRI* serotonin noradrenalin reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *OR* odds ratio, *CI* confidence interval

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ in favor of escitalopram

[a] OR >1 indicates greater response or remission rates with escitalopram versus the comparator

[b] Difference between treatment groups in change in scale scores during treatment. A positive value indicates greater symptom improvement with escitalopram versus the comparator

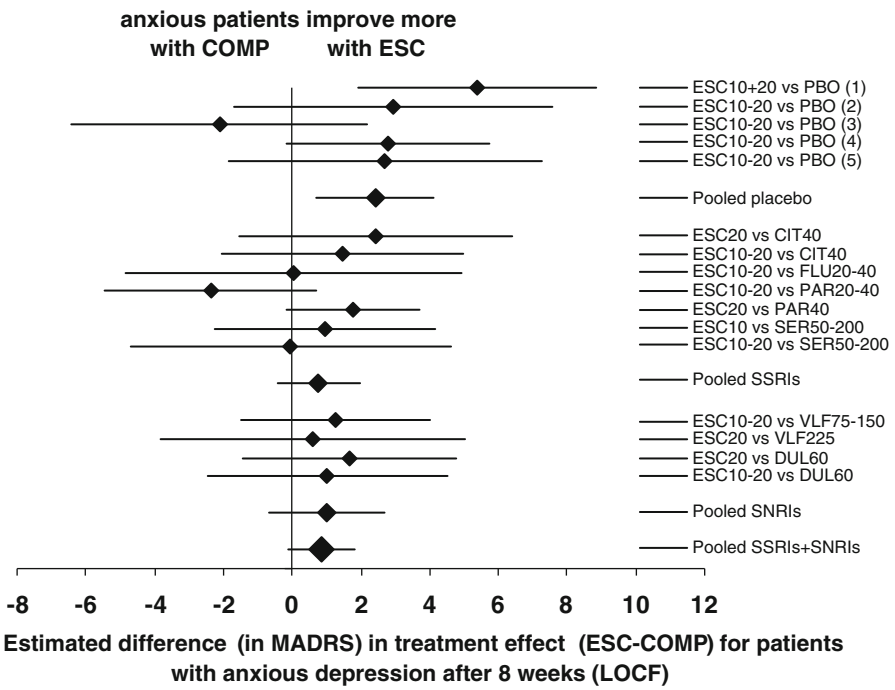

Fig. 1 Difference in change in MADRS score at week 8 (LOCF) for patients with anxious MDD treated with escitalopram (ESC) versus a comparator (COMP) (placebo and active treatments pooled separately), controlling for treatment center and baseline MADRS total score

prone to random measurement error that the primary outcome measure (since rater training in clinical trials focuses, by far, more-so on the primary than secondary outcome measures) and, as a result, have resulted in a greater number of patients without anxious MDD misclassified as having anxious MDD, and vice versa, than if the HAMD

Table 6 Anxious versus non-anxious MDD as a moderator of treatment effect for escitalopram versus placebo, SNRIs, and SSRIs

Treatment	Treatment effect difference[b]		Differential response[a]		Differential remission[a]	
	Estimate	95% CI	OR	95% CI	OR	95% CI
MADRS, LOCF						
Placebo	−0.69	−2.90 to 1.52	0.99	0.63 to 1.56	0.76	0.46 to 1.24
SSRIs	0.78	−0.85 to 2.41	1.08	0.74 to 1.57	0.96	0.66 to 1.39
SNRIs	−0.72	−3.06 to 1.62	1.08	0.64 to 1.81	0.85	0.52 to 1.41
$HAMD_{17}$, LOCF						
Placebo	−0.74	−2.28 to 0.79	1.22	0.78 to 1.93	0.81	0.49 to 1.35
SSRIs	0.61	−0.56 to 1.77	1.22	0.84 to 1.77	1.10	0.76 to 1.60
SNRIs	−0.23	−1.91 to 1.44	0.89	0.54 to 1.48	0.89	0.54 to 1.48
MADRS, MMRM						
Placebo	−1.14	−3.41 to 1.12	0.90	0.56 to 1.46	0.73	0.44 to 1.22
SSRIs	0.76	−1.71 to 3.22	0.99	0.66 to 1.49	0.93	0.63 to 1.37
SNRIs	−0.32	−1.94 to 1.30	1.05	0.58 to 1.90	0.77	0.45 to 1.31
$HAMD_{17}$, MMRM						
Placebo	−0.85	−2.43 to 0.73	1.19	0.74 to 1.92	0.82	0.48 to 1.39
SSRIs	−0.17	−1.53 to 1.87	1.19	0.80 to 1.77	1.08	0.73 to 1.60
SNRIs	1.29*	0.09 to 2.49	0.91	0.52 to 1.60	0.83	0.48 to 1.42

$HAMD_{17}$ 17-item Hamilton Depression Rating Scale, *LOCF* last observation carried forward, *MADRS* Montgomery-Åsberg Depression rating Scale, *MMRM* mixed model repeated measures, *SNRI* serotonin noradrenalin reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *OR* odds ratio, *CI* confidence interval

* $P < 0.05$. All other moderator analyses $P > 0.05$

[a] An odds ratio of differential response and remission greater than 1 indicates a greater difference in favor of Escitalopram versus a comparator for patients with than those without anxious MDD (moderator effect)

[b] The difference in treatment effect between escitalopram and a comparator between patients with and without anxious MDD (moderator effect). A positive value indicates a greater advantage in symptom improvement of escitalopram versus a comparator for anxious versus non-anxious MDD

was considered the primary outcome measure for the study. Furthermore, while our decision to use a threshold of 7 on the anxiety/somatization subscale as the cutoff for defining anxious/non-anxious depression was based on the precedent set by a number of similar studies in the field [1, 8, 9, 11, 14, 15] stemming from a factor analysis by Cleary and Guy [33], we realize that this cutoff point may not be ideal and may result in misclassification of anxious/non-anxious depression. Future factor analysis of datasets involving the use of the HAMD in MDD are clearly warranted to further our understanding of the relationship between HAMD anxiety/somatization subscale scores and the presence of anxiety co-morbidity in depression.

Other limitations specifically pertain to the identification of studies to be included in pooled analyses or meta-analyses and include the phenomenon of publication bias as well as the file-drawer phenomenon. Thus, although we included all eligible studies sponsored by H. Lundbeck and Forest labs, regardless of whether they have been published or not, we could not include at least one pertinent study [38], conducted by a different sponsor (since our analysis involves pooling individual patient-level data which would have required us to be able to directly access that database). Including that study may have yielded different results. In addition, our analysis involved pooling studies comparing escitalopram with the SSRIs citalopram, paroxetine, sertraline, and the SNRIs duloxetine and venlafaxine. Since studies involving the SSRI fluoxetine and the SNRIs desvenlafaxine succinate and milnacipran were not included (to the best of our knowledge, no such studies comparing desvenlafaxine succinate or milnacipran with escitalopram have been published to date or presented at major scientific meetings), conclusions drawn from this study cannot be generalized to all SNRIs. Furthermore, due to the reasons of homogeneity and consistency and due to differences in individual trial duration, our dataset was truncated at 8 weeks. Whether the present findings extend beyond 8 weeks is unclear. Finally, pooled analyses and meta-analyses involve combining studies of heterogeneous design (i.e., depression severity, dosing schedules). Whether we would have obtained similar results had studies of different design been pooled is equally unclear.

In conclusion, the present analysis provides some evidence that anxious MDD is difficult to treat, such that

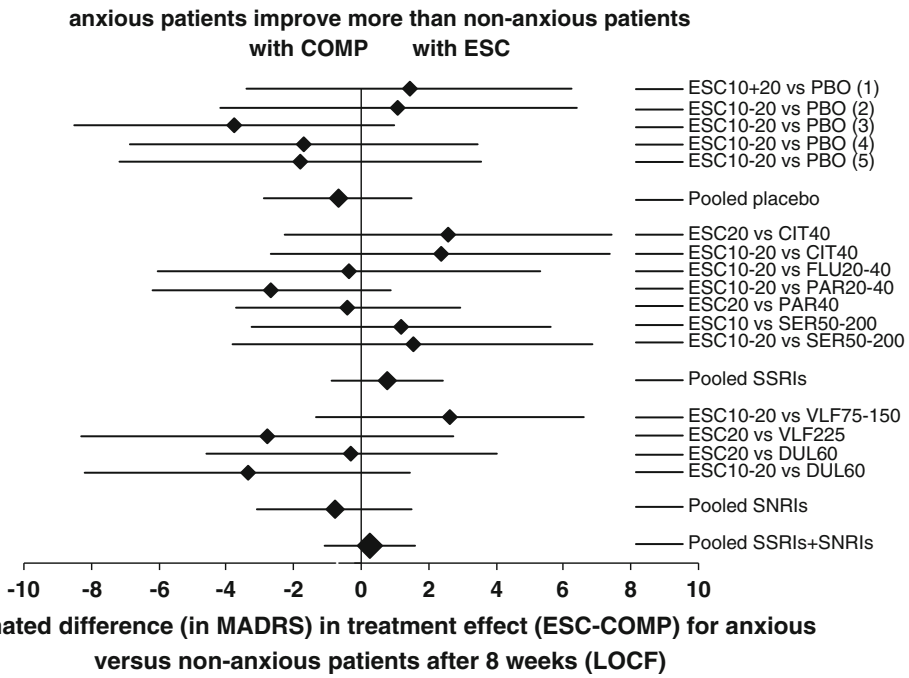

Fig. 2 Estimated treatment difference for patients with anxious *versus* non-anxious depression at week 8 (LOCF), correcting for treatment center and baseline MADRS total score (moderator analysis). A positive treatment difference indicates that anxious patients responded better to escitalopram (compared with comparator) than non-anxious patients, while a negative difference indicates that non-anxious patients responded better to escitalopram (compared with comparator) than anxious patients. The even distribution of the means about a treatment difference of zero indicates that escitalopram was equally effective in treating anxious and non-anxious patients with depression compared to placebo, SSRIs, or SNRIs

patients with anxious MDD continue to experience a residual cluster of symptoms by the end of the study leaving more of them short of remission. There was no difference in the response to treatment for patients with or without anxious MDD to escitalopram, SSRIs, or SNRIs. The present analysis did not support the notion that SNRIs are more effective than escitalopram in the treatment of patients with anxious MDD, nor was there evidence to support treatment moderating effects for anxious MDD. Future studies are needed to examine the presence and type of residual symptoms in patients with anxious depression.

References

1. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M (2006) STAR*D study team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 163(1):28–40
2. Walsh BT, Seidman SN, Sysko R, Gould M (2002) Placebo response in studies of major depression: variable, substantial, and growing. JAMA 287(14):1840–1847
3. Melander H, Salmonson T, Abadie E, van Zwieten-Boot B (2008) A regulatory Apologia—a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. Eur Neuropsychopharmacol 18(9):623–627
4. Papakostas GI, Fava M (2009) Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol 19(1):34–40
5. Papakostas GI, Fava M (2008) Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder. Dialogues Clin Neurosci 10:439–451
6. Kraemer HC, Wilson GT, Fairburn CG, Agras WS (2002) Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry 59(10):877–883
7. Fava M, Uebelacker LA, Alpert JE, Nierenberg AA, Pava JA, Rosenbaum JF (1997) Major depressive subtypes and treatment response. Biol Psychiatry 42(7):568–576
8. Fava M, Martinez JM, Greist J, Marangell LB, Brown E, Chen L, Wohlreich MM (2007) The efficacy and tolerability of duloxetine in the treatment of anxious versus non-anxious depression: a post-hoc analysis of an open label outpatient study. Ann Clin Psychiatry 19(3):187–195
9. Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, Biggs MM, Zisook S, Leuchter A, Howland R, Warden D, Trivedi MH (2008) Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry 165(3):342–351
10. Rush AJ, Wisniewski SR, Warden D, Luther JF, Davis LL, Fava M, Nierenberg AA, Trivedi MH (2008) Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Arch Gen Psychiatry 65(8):870–880
11. Howland RH, Wilson MG, Kornstein SG, Clayton AH, Trivedi MH, Wohlreich MM, Fava M (2008) Factors predicting reduced antidepressant response: experience with the SNRI duloxetine in patients with major depression. Ann Clin Psychiatry 20(4):209–218
12. Papakostas GI, McGrath P, Stewart J, Charles D, Chen Y, Mischoulon D, Dording C, Fava M (2008) Psychic and somatic anxiety symptoms as predictors of response to fluoxetine in major depressive disorder. Psychiatry Res 161(1):116–120
13. Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, Kasper S, Lecrubier Y, Montgomery S, Serretti A, Zohar J, Mendlewicz J, Group for the Study of Resistant Depression (2007) Clinical factors associated with treatment resistance in

major depressive disorder: results from a European multicenter study. J Clin Psychiatry 68(7):1062–1070
14. Nelson JC, Delucchi K, Schneider LS (2009) Anxiety does not predict response to antidepressant treatment in late life depression: results of a meta-analysis. Int J Geriatr Psychiatry 24(5): 539–544
15. Nelson JC (2010) Anxiety does not predict response to duloxetine in major depression: results of a pooled analysis of individual patient data from 11 placebo-controlled trials. Depress Anxiety 27(1):12–18
16. Papakostas GI, Stahl SM, Krishen A, Seifert CA, Tucker VL, Goodale EP, Fava M (2008) Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of major depressive disorder with high levels of anxiety (anxious depression): a pooled analysis of 10 studies. J Clin Psychiatry 69(8): 1287–1292
17. Thase ME, Entsuah AR, Rudolph RL (2001) Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 178:234–241
18. Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC (2007) Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry 62(11):1217–1227
19. Hamilton MA (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
20. Burke WJ, Gergel I, Bose A (2002) Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry 63:331–336
21. Rapaport MH, Bos, A, Zheng H (2004) Escitalopram continuation treatment prevents relapse of depressive episodes. J Clin Psychiatry 65:44–49. See also: http://www.forestclinicaltrials.com/CTR/CTRController/CTRViewPdf?_file_id=scsr/SCSR_SCT-MD-02_final.pdf
22. Bose A, Li D, Gandhi C (2008) Escitalopram in the acute treatment of depressed patients aged 60 years or older. Am J Geriatr Psychiatry 16:14–20
23. Forest Laboratories (2001) Flexible dose comparison of the safety and efficacy of escitalopram and fluoxetine in the treatment of major depressive disorder. http://www.forestclinicaltrials.com/CTR/CTRController/CTRViewPdf?_file_id=scsr/SCSR_SCT-MD-16_final.pdf. Accessed 21 June 2007
24. Ninan PT, Ventura D, Wang J (2003) Escitalopram is effective and well tolerated in the treatment of severe depression. Poster presented at the Congress of the American Psychiatric Association, May 17–22, San Francisco, CA. See also: http://www.forestclinicaltrials.com/CTR/CTRController/CTRViewPdf?_file_id=scsr/SCSR_SCT-MD-26_final.pdf
25. Baldwin DS, Cooper JA, Huusom AK, Hindmarch I (2006) A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. Int Clin Psychopharmacol 21:159–169
26. Boulenger JP, Huusom AKT, Florea I, Bækdal T, Sarchiapone M (2006) A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. Curr Med Res Opin 22:1331–1341
27. Ventura D, Armstrong EP, Skrepnek GH, Erder MH (2007) Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial. Curr Med Res Opin 23:245–250
28. Alexopoulos GS, Gordon J, Zhang D (2004) A placebo-controlled trial of escitalopram and sertraline in the treatment of major depressive disorder. Neuropsychopharmacology 29(suppl):S87. See also: http://www.forestclinicaltrials.com/CTR/CTRController/CTRViewPdf?_file_id=scsr/SCSR_SCT-MD-27_final.pdf
29. Montgomery SA, Huusom AKT, Bothmer J (2004) A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. Neuropsychobiology 50:57–64
30. Bielski RJ, Ventura D, Chang C-C (2004) A double-blind comparison of escitalopram with venlafaxine XR in the treatment of major depressive disorder. J Clin Psychiatry 65:1190–1196
31. Wade AG, Gembert K, Florea I (2007) A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. Curr Med Res Opin 23:1605–1614
32. Khan A, Bose A, Alexopoulos GS, Gommoll C, Li D, Gandhi C (2007) Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Clin Drug Invest 27:481–492
33. Cleary P, Guy M (1977) Factor analysis of the Hamilton depression rating scale. Drugs Exp Clin Res 1:115–120
34. Montgomery SA, Åsberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389
35. Papakostas GI, Petersen T, Hughes ME, Nierenberg AA, Alpert JE, Fava M (2004) Anxiety and somatic symptoms as predictors of treatment-related adverse events in major depressive disorder. Psychiatry Res 126:287–290
36. Kennedy SH, Andersen HF, Thase ME (2009) Escitalopram in the treatment of major depressive disorder: a meta-analysis. Curr Med Res Opin 25(1):161–175
37. Fava M, Alpert JE, Carmin CN et al (2004) Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med 34(7): 1299–1308
38. Nierenberg AA, Greist JH, Mallinckrodt CH, Prakash A, Sambunaris A, Tollefson GD, Wohlreich MM (2007) Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Curr Med Res Opin 23(2):401–416