HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2011; **26**: 63–71.
Published online 9 February 2011 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.1172

An open, non-randomised comparison of escitalopram and duloxetine for the treatment of subjects with Generalized Anxiety Disorder

Andrea Pierò* and Enrica Locati

Mental Health Department ASL TO 4, Mental Health Centre, Chivasso, Italy

Objectives This study compares the effectiveness of a 6-months treatment with escitalopram (ESC), a selective serotonin reuptake inhibitor, or duloxetine (DUL), a balanced serotonin and nor-adrenaline reuptake inhibitor, in 43 subjects with Generalized Anxiety Disorder (GAD).
Methods Assessment was made with the Hamilton Anxiety and Depression scales (HAM-A; HAM-D), with the CGI, and with the GAF at T0 (intake), T1, T3, T6 (1, 3, and 6 months later). The comparison among the two treatment groups (ESC = 20; DUL = 23) at the four endpoints was made through a GLM-ANOVA for repeated measures. Rates of remission (HAM-A < 7), response (HAM-A reduction of 50% or above) and dropout were evaluated.
Results At 1, 3, and 6 months after treatment inception both treatment groups showed a significant improvement in the scores of CGI, HAM-A, HAM-D, and GAF, and an equivalent rate of dropout. The DUL group registered a greater amount of remission and response rates at T1 against the ESC group in all the scales except in the HAM-D scale. Duloxetine was more effective than escitalopram after the first month of treatment only in the somatic subscale of HAM-A. The presence of a cluster C personality disorder was associated in both groups to greater difficulties in attaining remission and to dropout.
Conclusions Implications for clinical practice are discussed. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS — anxiety; anxiety disorders; depression; remission; medication

INTRODUCTION

Generalized Anxiety Disorder (GAD) is a highly prevalent condition in many communities, resulting in considerable individual and social costs (Wang *et al*., 2005; Marciniak *et al*., 2005) and a marked level of impairment (Pierò, 2010), equivalent in magnitude to that reported in patients with major depressive disorder (Katzman, 2009). Moreover, a high rate of comorbidity with unipolar depression is quite frequent in GAD and other anxiety disorders (de Berardis *et al*., 2008); according to the results of the National Co-morbidity Survey (Kessler *et al*., 2005) it might be stated that psychiatric co-morbidity is the rule rather than the exception.

Recent guidelines on GAD treatment (NICE, 2004) highlighted the effectiveness of, in descending order, psychological therapies, medication, and self-help. Although psychotherapy (Davidson, 2009) could be considered among the first-line interventions for several patients, both individually and combined with drug therapy (Ferrero *et al*., 2007), this kind of treatment is often not available in an useful timeframe for professionals who refer to community Mental Health Services (MHS).

Improving the evidence about the effectiveness and safety of medications for GAD in ''real world'' settings seems therefore an important issue for psychiatrists working in community MHS: all treatments of psychiatric disorders offered by these services should in fact be effective but also efficient (Baldwin and Polkinghorn, 2005) and accepted (Ferrero *et al*., 2007). The settings and procedures of many randomized controlled trials are not comparable with community outpatient psychiatric services (Westen *et al*., 2004), because subjects referring to specialized centers are usually more motivated and more influenced by the treatment setting. Naturalistic studies seem to provide important evidence for determining the effectiveness of a therapy in practice, even if their limitations should be extensively addressed (Leichsenring and Ruger, 2004).

Due the involvement of multiple neurobiological systems, several classes of medications have been

* Correspondence to: P. Andrea, Dipartimento di Salute Mentale, ASL TO 4 Chivasso, Centro di Salute Mentale di Chivasso, Via Blatta 10, 10034, Chivasso, Italy. Tel: 011-9176620; Fax: 011-9176619.
E-mail: andrea.piero@unito.it

Received 1 April 2010
Accepted 29 December 2010

widely used for the treatment of GAD (Allgulander, 2009; Baldwin and Polkinghorn, 2005). The most commonly used drugs are benzodiazepines (BDZ) (Allgulander, 2009; Sihvo *et al*., 2006), which are helpful in terms of immediate alleviation of anxiety symptoms; nevertheless, their effectiveness in long-term illness management has been questioned because of concerns about tolerance, dependency, and remission rates. Such concerns have recently resulted in a wider use of new-generation antidepressant such as selective serotonin reuptake inhibitors (SSRI) and serotonin and nor-adrenaline reuptake inhibitors (SNRI) (Baldwin and Tiwari, 2009; de Berardis *et al*., 2008; Carter and McCormack, 2009; Kahn and Macaluso, 2009). Among other classes of drugs, one of the most promising seems to be pregabalin (Lydiard *et al*., 2009).

The SSRIs are usually preferred as first-line (Baldwin *et al*., 2005) treatment of anxiety disorders (AD) because of their safety and tolerability, and they are licensed for the treatment of several AD (de Berardis *et al*., 2008). Escitalopram, a very selective SSRI, was shown by several studies to be an effective and safe medication (Allgulander *et al*., 2006; Davidson *et al*., 2005; Lenze *et al*., 2009). However, despite favorable reports in terms of side effects, SSRIs may cause some adverse effects such as sexual dysfunction, risk of bleeding, discontinuation symptoms, and increased bodyweight (Westenberg and Sandner, 2006; Williams *et al*., 2006); moreover, a high percentage of subjects with GAD did not achieve clinical remission (Baldwin and Tiwari, 2009; Fava *et al*., 2005). For these reasons, greater interest has arisen in recent years for the so-called ''dual acting'' antidepressants or SNRIs (venlafaxine, duloxetine, milnacipran) and mirtazapine (Gambi *et al*., 2005). According to recent non-inferiority trials the effectiveness of duloxetine is equivalent to that of venlafaxine (Allgulander *et al*., 2008; Davidson, 2009; Hartford *et al*., 2007) in the treatment of GAD.

Studies comparing SSRI and SNRI in the treatment of depression demonstrated the non-inferiority of duloxetine with respect to escitalopram, but escitalopram seems better tolerated than duloxetine (Cipriani *et al*., 2009). Comparative studies on the effectiveness of duloxetine and escitalopram in the treatment of subjects with GAD are somewhat scarce. Available data on duloxetine treatment derived by 10–12 week clinical trials have produced incomplete evidences about extended response and durability of effect; moreover, these trials excluded comorbidity, therefore reducing the generalizability of their results to ''real world'' patients (Norman and Olver, 2008).

This study is not born as a clinical trial, but as an evaluation of effectiveness of the two most used treatments for GAD, escitalopram and duloxetine, in our clinical practice. Therefore, the aim was to compare the effectiveness of selective SSRI (escitalopram) therapy versus balanced serotonin and nor adrenaline SNRI (duloxetine) therapy in subjects with Generalized Anxiety Disorder (GAD) during a 6-months treatment period in a community Mental Health outpatient Service (MHS).

METHODS

Subjects and procedures

A total of 115 selected subjects with Generalized Anxiety Disorder with or without Axis I comorbidity (DSM-IV-TR, APA, 2000) referring to the community MHS of Chivasso from 1 October 2007 to 1 March 2009 were evaluated for treatment. These subjects had been referred to the MHS by primary care physicians not employing a standardized shared clinical praxis (in terms of primary care screening and intervention procedures for this specific disorder).

A total of 72 patients with GAD referred to the Services were evaluated at intake, but were excluded from subsequent evaluations for the following reasons: (a) comorbidity of a severe depressive episode which needed inpatient treatment ($n = 6$); (b) comorbidity with a bipolar ($n = 4$) or psychotic ($n = 2$) disorder; (c) actual ($n = 3$) or past ($n = 4$) substance (comprising benzodiazepines and alcohol) dependence disorders (DSM-IV-TR, APA, 2000); (d) subjects receiving evidence-based psychological or pharmacological (excluding benzodiazepines) treatments at the moment of the first visit ($n = 19$); (e) patients aged over 65 ($n = 4$), (f) presence of anxiety disorders secondary to a medical condition ($n = 1$); (g) presence of a Cluster B ($n = 7$) or A ($n = 1$) personality disorder; (h) refusal to complete the questionnaires ($n = 5$). The (g) criterion was adopted because comorbidity with axis II cluster C disorder could be related to the severity of GAD disorder and clinical response to treatment. Other 16 subjects were evaluated at T0, but based on previous history and clinical features for these subjects were recommended different medications than escitalopram or duloxetine and they were excluded from subsequent evaluation.

To maintain a naturalistic setting the subjects ($N = 43$) were assigned to Escitalopram (ESC, $N = 20$) or Duloxetine (DUL, $N = 23$) treatment groups according to the therapist's clinical impression based on previous history of treatment and overall clinical

DOI: 10.1002/hup

features, taking into account previous treatments with drugs (Norman and Olver, 2008) and individual clinical features (Davidson, 2009).

The clinical ''as usual'' management provided by the same therapist consisted in a first visit (T0), one control visit after 2 weeks and 1 month (T1) for the evaluation of clinical efficacy/side effects of drug treatment. Subsequently, patients were visited once in each of the following months. If the subjects were treated with benzodiazepines (before or after the first visit), the medication was suspended in the first 2 weeks. Only non-benzodiazepine drugs such as sleep inducers or regulators (e.g., zolpidem or melatonin) were used after the first 2 weeks of treatment.

T0, T1, T3, and T6 assessments with rating scales (HAM-A, HAM-D, CGI, GAF) were made by a trained researcher blinded on respect to treatment group.

Subjects who interrupted the drug treatment (drop-out) were inserted in a waiting list for a time-limited psychotherapy (Ferrero *et al*., 2007); according to an intention-to-treat model the therapist continued to follow the subject until the end of the 6-months period and the blinded rater continued the assessment.

Diagnostic assessment for Axis I and Axis II disorders was carried out at intake by two trained psychiatrist with the support of the Structured Clinical Interview for *DSM-IV* (SCID-OP I, and SCID II) (First *et al*., 1996, 1997). All subjects were asked to submit an informed written consent to participate in the assessment, and were guaranteed anonymity. The Internal Ethical Committee approved these procedures because a naturalistic setting was preserved.

Assessment instruments

Global Assessment Functioning (GAF). The Goldman's Global Assessment of Functioning Scale evaluates individual level of social and occupational functioning (Hilsenroth *et al*., 2000). The validity and reliability of this instrument were verified in several studies. The score ranges from an excellent level (scored as 100) to a level showing a deficit of functioning (scored as 1).

Clinical Global Impression (CGI). This is a well-known assessment tool, usually administered by clinicians in order to evaluate the illness severity (item 1), through the provision of a score between 0 (non-assessed) and 7 (extreme severity). Item 2 assesses the degree of improvement the patient experiences, and item 3 assesses the balance between effectiveness of the treatment provided and importance of side effects.

Hamilton Rating Scale for Anxiety (HAM-A). The HAM-A scale (Hamilton, 1959) as well known and widely used as the HAM-D, shares some features with the latter. The HAM-A consists of 14 items, each with a score ranging from 0 (absence) to 4 (very severe). This rating scale consists of two subscales: psychic anxiety (items 1–6 and 14) and somatic anxiety (items 7–13).

Hamilton Rating Scale for Depression (HAM-D). The HAM-D was used in its 21-item version (Hamilton, 1960); it has been widely adopted, has good validity, internal consistency, and inter-rater reliability.

Response and remission criteria

In accordance with relevant literature (Ballenger, 1999), subjects who showed a reduction of at least the 50% of anxiety symptomatology (HAM-A total score) at the three endpoints following the beginning of treatment (T1, T3, and T6) were defined as responders, whereas the remission threshold was set at a HAM-A score < 7 (at T1, T3, and T6).

A similar criterion was applied in order to evaluate the remission in depressive symptomatology (HAM-D < 7), whereas HAM-D response rates were not calculated because exceeding the aims of the study.

Definition of dropout

According to relevant literature, subjects who decided to stop taking medication before the end of the study were regarded as dropouts, regardless of their motivation. Patients who kept visiting the MHS after interrupting their drug treatment were put in a waiting list for psychotherapy treatment.

Data analysis

All data analyses were performed using the Statistical Package for Social Sciences-13.0 (SPSS, 2000).

Our first task was a description of our sample of GAD subjects (Table 1), who were also evaluated through a *t*-test for independent samples in order to compare the two treatment groups (ESC and DUL) at T0 in several continuous (age, schooling, overall GAD duration, duration from the onset of the last GAD episode, dose of drug, HAM-A and HAM-D total scores at T0, CGI 1 at T0, GAF at T0) and categorical variables (gender, Axis I comorbidity, Axis II comorbidity for cluster C personality disorder). As a result, the ''illness duration'' variable was considered as potentially confounding in the following analysis.

DOI: 10.1002/hup

Table 1. Sample description

	ESC (20)	DUL (23)	t-test d.f. = 41	$p<$
Age	37.2 ± 3.4	35.3 ± 17.4	0.645	0.523
Schooling[a]	9.11 ± 1.79	9.38 ± 2.03	−0.417	0.679
Illness duration[b]	89.8 ± 43.1	60.9 ± 44.2	2.155	0.037
Duration of last episode[c]	8.7 ± 4.2	9.1 ± 3.7	−0.242	0.810
CGI-SI	3.8 ± 0.8	4.3 ± 0.9	−0.418	0.678
GAF T0	63.1 ± 6.1	64.4 ± 5.3	−0.801	0.428
HAM-A T0	17.1 ± 5.1	18.8 ± 3.9	−1.181	0.242
HAM-D T0	19.1 ± 5.1	19.9 ± 3.9	−0.696	0.490
HAM-A Somatic Scale	4.2 ± 3.0	5.7 ± 2.5	−1.771	0.085

	ESC (20)	DUL (23)	χ^2 d.f. = 1	$p<$
Gender—Females	13 (65%)	18 (78%)		
Gender—Males	7 (35%)	5 (22%)	0.935	0.334
Personality Disorder-Yes	6 (30%)	11 (48%)		
Personality Disorder-Not	14 (70%)	12 (52%)	1.422	0.233
Comorbidity				
GAD pure	8 (40%)	7 (30%)		
GAD + Unipolar Depressive Disorders	8 (40%)	6 (28%)		
GAD + Other Anxiety Disorders	3 (15%)	5 (21%)	2.326	0.344
GAD + Eating Disorders	1 (5%)	5 (21%)		
Not Otherwise Specified				
Substance abuse disorder	2 (10%)	3 (13%)	0.096	0.756

CGI-SI, Clinical Global Impression Severity Index; GAF, Global Assessment of Functioning at T0; HAM-A, Hamilton anxiety total score at T0; HAM-D, Hamilton depression total score at T0.
[a]Years.
[b]Illness duration (months) from the onset of the first GAD episode in the life.
[c]Duration (months) from the onset of the last GAD episode in the life.

A General Linear Model (GLM), controlled for illness duration and presence of personality disorder (PD factor), was then developed (Table 2) in order to compare the effectiveness of both treatments (Group factor) at each observation time. Post-hoc comparisons were made with a Bonferroni t-test (including a correction for multiple comparison).

Through a χ^2 analysis, the ESC and DUL groups were compared according to rates of response, remission, dropout and side effects (see Table 3). All statistical tests were two-sided hypothesis tests carried out at the 5% level of significance.

RESULTS

Sample description

Table 1 illustrates some personal, clinical, and psychopathological characteristics of each treatment group (ESC and DUL) before drug treatment.

As showed in Table 1, a flexible dosage approach was adopted. Drug dosage was modulated at the therapist's discretion, but the minimum acceptable dose was escitalopram 10 mg/day and duloxetine 60 mg/die.

Subjects with a PD (PD+ group $N = 17$; PD− group = 26) had a greater HAM-A (PD+ = 19.8 ± 5.5; PD− = 16.8 ± 3.40; t-test −2.209, $p < 0.030$, d.f. = 41) and HAM-D (PD+ = 21.7 ± 5.39; PD− = 18.1 ± 3.08; t-test −2.809, $p < 0.008$, d.f. = 41) score at T0.

Comparison among the four observation times

Table 2 compares our two groups of patients at four different observation times, with regard to a limited number of aspects such as treatment duration (T1, T3, T3, and T6) or factor group (ESC vs. DUL), personality disorder group (yes or not), and controlling for illness duration as covariate. Illness duration seems the only variable not influencing the variations in rating scales scores during the four times of observation. When included as further controls, the HAM-A and HAM-D scores at T0 did not modify the results of GLM ANOVA repeated measures.

Response and remission rates

Table 3 shows the percentages of patients considered as remitted or responders with relation to each treatment group (ESC or DUL) and to comorbidity with a Personality Disorder of Cluster C of DSM-IV-TR (APA, 2000), regardless of their treatment group.

DOI: 10.1002/hup

Table 2. Comparison among the four times of observation

Variable	Times of observation				F^a	$p<$ (effect size)	F^b	$p<$ (effect size)	F^c	$p<$ (effect size)
	T0	T3	T6	T12						
CGI-SI[d]										
ESC	4.50 ± 0.51	3.15 ± 0.81	2.60 ± 1.08	2.35 ± 1.18	50.29	**0.001** (0.57)	4.62	**0.004** (0.11)	11.0	0.001 (0.22)
DUL	4.56 ± 0.50	2.91 ± 0.90	2.13 ± 0.95	1.78 ± 0.95						
GAF[d]										
ESC	63.0 ± 6.10	70.1 ± 7.10	73.1 ± 7.10	75.4 ± 7.36	36.97	**0.001** (0.49)	3.49	**0.018** (0.09)	2.85	**0.040** (0.07)
DUL	64.4 ± 5.28	74.0 ± 5.10	76.9 ± 5.27	78.7 ± 5.36						
HAM-A[d]										
ESC	17.1 ± 5.04	10.2 ± 5.73	6.9 ± 4.42	5.9 ± 4.21	35.70	**0.001** (0.48)	6.15	**0.001** (0.14)	3.14	**0.028** (0.08)
DUL	18.8 ± 3.93	7.4 ± 3.72	5.4 ± 3.61	4.6 ± 3.82						
HAM-D[d]										
ESC	19.0 ± 5.05	9.70 ± 4.81	7.30 ± 4.78	5.75 ± 4.70	49.30	**0.001** (0.56)	2.58	0.060 (0.06)	1.01	0.389 (0.02)
DUL	19.9 ± 3.94	8.21 ± 4.81	5.65 ± 3.65	4.95 ± 3.79						
SoHAM-A[d]										
ESC	4.21 ± 3.01	2.95 ± 2.06	1.95 ± 2.08	2.20 ± 2.01	5.97	**0.002** (0.33)	5.70	**0.003** (0.32)	0.691	0.563 (0.05)
DUL	5.70 ± 2.51	1.39 ± 1.72	1.13 ± 1.94	1.04 ± 1.77						
PhHAM-A[d]										
ESC	12.35 ± 3.3	7.25 ± 4.14	5.05 ± 4.28	4.45 ± 4.46	32.88	**0.001** (0.46)	8.35	**0.001** (0.18)	4.24	**0.007** (0.10)
DUL	12.95 ± 2.5	5.78 ± 3.01	2.91 ± 1.90	2.52 ± 1.90						

CGI-SI, Clinical Global Impression Severity Index; SoHAM-A, the somatic subscale of the HAM-A scale; PhHAM-A, the psychic subscale of HAM-A scale.
[a]Time factor, post hoc: T0 > T1 > T3 > T4 (CGI-SI; HAM-A; HAM-D; PhHAM-A) and T0 > T1,T3,T4 (soHAM-A); T0 < T1 < T3 < T4 (GAF).
[b]Group factor (ESC vs. DUL), post hoc: at T1 DUL group < ESC group (CGI, HAM-A, PhHAM-A) and at T1 DUL group > ESC group (GAF); at T1, T3 and T6 DUL group < ESC group (soHAM-A).
[c]Personality disorder (yes or not) factor.
[d]Illness duration factor (covariate) is not significant in this GLM model.

The association between remission of anxious (HAM-A) and depressive (HAM-D) symptomatology has been assessed through a χ^2 test. In the HAM-A remitted group at T1 ($N = 17/43$) only three subjects were not remitted according to the HAM-D cutoff value ($N = 18/43$). Chi square analysis revealed a significant association between HAM-A T1 remission and HAM-D T1 remission ($\chi^2 = 18.94$; $p < 0.001$; d.f. = 1). A similar association was detected between HAM-A remission at T3 and HAM-D remission at T3 ($\chi^2 = 24.52$; $p < 0.001$; d.f. = 1), and between HAM-A remission at T6 and HAM-D remission at T6 ($\chi^2 = 23.61$; $p < 0.001$; d.f. = 1).

The statistical analysis (GLM repeated measures) showed an association between changes in anxiety and depression scores after the first month of observation.

Dropout rates and side effects

Table 3 shows the rates of treatment dropout. All treatment discontinuations in the DUL group were due to side effects, whereas in the ESC group one subject gave up his therapy because of side effects, and two on account of perceived ineffectiveness.

The most common treatment-emergent adverse effects in ESC group were nausea (20%), headache (17%), decreased libido (17%), weight gain between 2 and 4 kg (20%), insomnia (7%), and constipation (6%). As for the DUL group, the most common treatment-emergent adverse effects were dizziness (15%), nausea (14%), headache (10%), insomnia (8%), constipation (8%), hyperhidrosis (6%), and decreased libido (5%). No weight gain was detected in the DUL group. Adverse effects emerged in the first 2 weeks of treatment of both treatment groups, and were generally of mild to moderate severity and well tolerated over time.

DISCUSSION

Escitalopram, the S-enantiomer of the racemic citalopram, is a serotonin selective reuptake inhibitor (SSRI), whereas duloxetine is a balanced dual antidepressant, with action on reuptake of the serotonin and the nor-adrenaline (SNRI). Both drugs are approved in many countries for GAD treatment, but pharmacological differences between the two molecules could to lead to different clinical effects. The issue is quite underexplored in available literature.

Three main preliminary evidences emerged from our open and naturalistic comparison between two different class of drugs (SSRI or SNRI) in the treatment of GAD: (1) both escitalopram and duloxetine seem effective in GAD treatment, but the latter seems to have the upper hand in terms of action rapidity, whereas escitalopram

DOI: 10.1002/hup

Table 3. Rates of response and remission at three points of observation (T1, T3, T6)

Variables	ESC (20)	DUL (23)	χ^2	d.f.	$p<$
HAM-A remitted T1	4 (20%)	13 (56%)	5.969	1	**0.015**
HAM-A remitted T3	11 (55%)	16 (70%)	0.971	1	0.324
HAM-A remitted T6	12 (60%)	16 (70%)	0.431	1	0.512
HAM-D remitted T1	5 (25%)	13 (56%)	4.368	1	**0.037**
HAM-D remitted T3	11 (55%)	15 (65%)	0.467	1	0.494
HAM-D remitted T6	14 (70%)	15 (65%)	0.111	1	0.739
HAM-A responders T1	6 (30%)	16 (69%)	6.701	1	**0.010**
HAM-A responders T3	11 (55%)	20 (87%)	5.433	1	**0.020**
HAM-A responders T6	14 (70%)	20 (87%)	1.859	1	0.173
Dropout yes[a]	3 (15%)	3 (13%)		1	
Dropout not	17(85%)	20 (87%)	0.034	1	0.853
Early Dropout[b]	0 (0%)	2 (9%)	1.824	1	0.177
Variables	**DP yes (N = 17)**	**DP not (N = 26)**			
HAM-A remitted T1	2 (12%)	15 (58%)	9.070	1	**0.003**
HAM-A remitted T3	5 (30%)	22 (85%)	13.407	1	**0.001**
HAM-A remitted T6	5 (30%)	23 (88%)	15.779	1	**0.001**
HAM-A responders T1	4 (23%)	18 (69%)	8.592	1	**0.003**
HAM-A responders T3	10 (59%)	21 (81%)	2.461	1	0.168
HAM-A responders T6	11 (65%)	23 (88%)	3.505	1	0.065

Note: HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale.
[a]Any interruption of treatment; no interruptions were registered after the third endpoint (T3).
[b]Interruption before the first endpoint (T1). All the subjects who were dropping out had a personality disorder in comorbidity.

seem better tolerated in the first month of treatment; (2) duloxetine seems to confirm its effectiveness in the treatment of anxious somatic symptomatology, exceeding escitalopram in this specific outcome measure during the course of 6 months treatment; (3) in case of a personality disorder (cluster C) comorbidity with GAD, it is more difficult to obtain remission, and the probability of dropout increase.

Unlike previous trials (de Berardis *et al*., 2008), our clinical open study did not exclude subjects with actual comorbidity with depressive or other Axis I disorders of DSM-IV-TR (APA, 2000) frequently co-occurring with GAD (Kessler *et al*., 2005; Pollack, 2009). Subjects with psychotic disorders, bipolar disorders, substance dependence disorders, cluster A or cluster B personality disorders, and recurrent major depression (DSM-IV-TR; APA, 2000) were excluded since in these patients GAD is often an epiphenomenon or a residual symptomatology of the main disorder (Pollack, 2009).

Our sample included subjects with a CGI-SI range between 4 and 5, almost 35% of pure GAD patients (Table 1), and a relatively low rate of substance abusers (Table 1). Despite an average illness duration of almost 77 months (Table 1), the subjects included in our sample could be defined as having moderately severe disorders. The moderate severity of GAD symptoms in our sample could account for the relatively high rate (Pollack, 2009) of response (ESC = 70%; DUL = 87%) and remission (ESC = 60%; DUL = 70%) in both treatment groups at the end of the study (T6).

As concerns treatment effectiveness, the GLM ANOVA repeated measures showed a significant improvement in all rating scales (HAM-A, HAM-D, CGI-SI, and GAF) after treatment with escitalopram or duloxetine (Table 1). Overall, post hoc comparisons corrected for multiple comparison (Bonferroni) highlighted in significant changes in HAM-A, HAM-D, CGI-SI, and GAF scores in all four times of observation (Table 2). Illness duration does not seem to affect the patients' recovery, whereas the presence of a Cluster C personality disorder apparently reduces the effectiveness of both medication treatments. These data seems to confirm the effectiveness of both medications as first-line treatments in GAD (Davidson, 2009), for the treatment of anxiety and depressive symptomatology (de Berardis *et al*., 2008; Pigott *et al*., 2007), as well as in terms of better psychosocial functioning of GAD patients (Allgulander *et al*., 2008).

Regarding the differences in response between the two medications, the statistical analysis has shown that duloxetine lead to a more rapid clinical response as measured by the CGI severity index (severity of GAD), HAM-A (psychic and somatic anxiety), and GAF (global functioning), whereas no significant differences emerged with reference to depressive symptoms as measured by HAM-D (Table 2). Differences in terms of clinical improvement were confirmed and accounted for by the χ^2 analysis (Table 3): particularly in the first month of treatment, response and remission rates resulted significantly greater in the DUL group than in the ESC group.

DOI: 10.1002/hup

As concerns a possible specific action of the dual antidepressant duloxetine on the somatic component of anxiety (Beesdo *et al*., 2009), the results of our study seem to confirm that duloxetine is effective in this topic. In our sample, duloxetine improves somatic symptoms better that escitalopram in all the three times of observation after T0 (Table 2), whereas about psychic subscale of HAM-A the duloxetine seems superior to escitalopram only in the first month of treatment. Therefore, HAM-A is the only scale which shows a different pattern of change between DUL and ESC groups after T1 endpoint. Off course further investigations are needed, considering that also non-pharmacological approaches can to improve somatic anxiety.

Overall the improvements in anxiety and depression symptoms seem related (see Results section), but duloxetine seem to work faster than escitalopram on global anxiety symptomatology and on functioning, and this effectiveness seem independent from action on depressive symptomatology (no differences in HAM-D at T1 between DUL and ESC groups). On the other hand, absence of remarkable differences between escitalopram and duloxetine in the response to depressive symptomatology (HAM-D) is not surprising and confirms the results of relevant literature (Cipriani *et al*., 2009).

In previous studies the rates of remission and response were largely variable, ranging with escitalopram treatment from near 30% (Bose *et al*., 2008) and 60% (Davidson *et al*., 2005), whereas with duloxetine the rate of remission seems to fall within the 28–31% range (Koponen *et al*., 2007; Rynn *et al*., 2007). In our study these rates are higher, but this could be due to the open trial setting who result in a relatively higher response rate with respect to placebo RCTs (Bose *et al*., 2008; Rutherford *et al*., 2009). In any case the comparison between rates of remission seem quite problematical.

About previous studies, a 12-week double-blind randomized trial involving a sample of 23 subjects with GAD weighed treatment with escitalopram against treatment with Bupropion XL, an antidepressant with a dual action on dopamine and nor-adrenaline neurotransmitters (Bystritsky *et al*., 2008); this study showed a comparable anxiolytic effectiveness and a good tolerability for both these drugs, but no differences in terms of rapidity of action were founded. Similar results were obtained by Bose *et al*. (2008) comparing escitalopram, venlafaxine extended release and placebo: overall efficacy analysis suggested that both drugs were effective treatments for GAD, but escitalopram was better tolerated (Bose *et al*., 2008). Also in this case no differences in rapidity of response were identified.

The apparent superiority of duloxetine versus escitalopram in the first months of treatment of subjects with GAD seems interesting. Hypothetically, the dual action of duloxetine could produce an early response in anxiety symptomatology through a regulation of multiple neurotransmitter pathways (Bose *et al*., 2008). On the other hand, such fast and manifold effects on neurotransmitters could have a high cost in terms of greater side effects during the first weeks of treatment, leading to early dropout (a phenomenon registered only in the DUL group). Off course further studies are needed to confirm this hypothesis.

As concerns safety and tolerability, the dropout rate (15% in the ESC group, 13% in the DUL group) was comparable with data reported in literature (Baldwin and Polkinghorn, 2005; Norman and Olver, 2008). Generally, escitalopram seem better tolerated in the early phases of treatment (first month), whereas in the long term both drugs seem more or less equally manageable. Although preliminary studies suggest an effectiveness of duloxetine in reducing compulsive eating (Leombruni *et al*., 2009), it is doubtful whether the weight gain showed in the escitalopram group of patients might have a clinical significance. The phenomenon could simply be attributed to weight regain. Further studies are needed to confirm or disconfirm the better tolerability of duloxetine with respect to weight and eating-related problems.

Regarding the role of comorbidity in Axis II (DSM-IV-TR, APA, 2000) for a Cluster C personality disorder (PD), the GLM ANOVA and χ^2 analyses clearly showed that non-responders, non-remitted or dropout patients had a PD comorbidity. The presence in Axis II of a Personality Disorder is therefore proved to be a negative prognostic factor for the treatment of anxiety disorders (NICE, 2004; Serretti *et al*., 2009). In our sample, subjects with PD also showed greater severity of GAD at T0. Previous research has highlighted the advisability of combined treatment (Ferrero *et al*., 2007) in subjects with GAD and PD. This study seems to confirm those preliminary evidences, emphasizing the value of psychological treatment in subjects with GAD who failed to respond to medication (Katzman, 2009; Norman and Olver, 2008).

LIMITATIONS

This study presents some limitations due to its naturalistic approach; particularly, the open nature and absence of a control group treated with placebo could have led us to overestimate treatment effective-

DOI: 10.1002/hup

ness (Bose *et al*., 2008). Another possible limitation is the lack of measures accounting for the patient's quality of life (de Berardis *et al*., 2008). Lastly, the limited size of our sample did not allow us to carry out a multivariate analysis of the predictors of response to treatment.

CONCLUSIONS

If the results of this study were confirmed by further trials, duloxetine could be considered as having a specific and uncommon rapidity of action both on psychic and somatic components of anxiety in subjects with GAD. Moreover, a well structured management of early adverse effects of duloxetine could reduce the risk of early dropouts and improve the tolerability of this medication. Escitalopram and duloxetine are confirmed effective first-line treatments for GAD, but closer attention should to be paid to Axis II comorbidity for Cluster C personality disorders.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

REFERENCES

Allgulander C, Florea I, Huusom AK. 2006. Prevention of relapse in generalized anxiety disorder by escitalopram treatment. *Int J Neuropsychopharmacol* **9**(5): 495–505.

Allgulander C, Nutt D, Detke M, *et al*. 2008. A non-inferiority comparison of duloxetine and venlafaxine in the treatment of adult patients with generalized anxiety disorder. *J Psychopharmacol* **22**: 417–425.

Allgulander C. 2009. Generalized anxiety disorder: between now and DSM-V. *Psych Clin North Am* **32**(3): 611–628.

APA American Psychiatric Association. 2000. *DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Text Revision*, 4th edn, American Psychiatric Association: Washington, DC.

Baldwin DS, Polkinghorn C. 2005. Evidence-based pharmacotherapy of generalized anxiety disorder. *Int J Neuropsychopharmacol* **8**: 293–302.

Baldwin DS, Tiwari N. 2009. The pharmacologic treatment of patients with generalized anxiety disorder: where are we now and where are we going? *CNS Spectrum* **14**(S3): 5–12.

Ballenger JC. 1999. Clinical guidelines for establishing remission in patients with depression and anxiety. *J Clin Psychiatr* **60**(S22): 29–34.

Beesdo K, Hartford J, Russell J, Spann M, Ball S, Wittchen HU. 2009. The short- and long-term effect of duloxetine on painful physical symptoms in patients with generalized anxiety disorder: results from three clinical trials. *J Anxiety Disord* **23**(8): 1064–1071.

Bose A, Korotzer A, Gommoll C, Li D. 2008. Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the treatment of Generalized Anxiety Disorder. *Depress Anxiety* **25**(10): 854–861.

Bystritsky A, Kerwin L, Feusner JD, Vapnik T. 2008. A pilot controlled trial of Bupropion XL versus Escitalopram in Generalized Anxiety Disorder. *Psychopharmacol Bull* **41**(1): 46–51.

Carter NJ, McCormack PL. 2009. Duloxetine: a review of its use in the treatment of generalized anxiety disorder. *CNS Drug* **23**(6): 523–541.

Cipriani A, Santilli C, Furukawa TA, *et al*. 2009. Escitalopram versus other antidepressive agents for depression. *Cochr Dat Syst Rev* **2**: CD006532.

Davidson JR, Bose A, Wang Q. 2005. Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. *J Clin Psychiatr* **66**(11): 1441–1446.

Davidson JR. 2009. First line pharmacotherapy approaches for generalized anxiety disorder. *J Clin Psychiatr* **70**: S2.

de Berardis D, Serroni N, Carano A, *et al*. 2008. The role of duloxetine in the treatment of anxiety disorders. *Neuropsychiat Dis Treat* **4**(5): 929–935.

Fava GA, Ruini C, Rafanelli C, *et al*. 2005. Well-being therapy of generalized anxiety disorder. *Psychother Psychosom* **74**(1): 26–30.

Ferrero A, Pierò A, Fassina S, *et al*. 2007. A 12-month comparison of brief psychodynamic psychotherapy and pharmacotherapy treatment in subjects with generalized anxiety disorders in a community setting. *Eur Psychiatr* **22**(8): 530–539.

Baldwin DS, Anderson IM, Nutt DJ, *et al*. British Association for Psychopharmacology. 2005. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* **19**(6): 567–596.

First MB, Spitzer RL, Gibbon M, Williams JBW. 1996. *Structured Clinical Interview for DSM-IV Axis I Disorders Out Patient Edition (SCID-O/P, version 2.0)*. Biometric Research, New York State Psychiatric Institute: New York.

First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. 1997. *SCID II Personality Questionnaire*. American Psychiatric Press: Washington, DC.

Gambi F, de Berardis D, Campanella D, *et al*. 2005. Mirtazapine treatment of generalized anxiety disorder: a fixed dose, open label study. *J Psychopharmacol* **19**(5): 483–487.

Hamilton M. 1959. The assessment of anxiety states by rating. *Br J Med Psychol* **32**: 50–55.

Hamilton M. 1960. A rating scale for depression. *J Neur Neuros Psychiatr* **23**: 56–62.

Hartford J, Kornstein S, Liebowitz M, *et al*. 2007. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol* **22**(3): 167–174.

Hilsenroth MJ, Ackerman SJ, Blagys MD. 2000. Reliability and validity of DSM IV axis V. *Am J Psychiatr* **157**: 1858–1863.

Kahn AY, Macaluso M. 2009. Duloxetine for the treatment of generalized anxiety disorder: a review. *Neuropsychiatr Dis Treat* **5**: 23–31.

Katzman MA. 2009. Current considerations in the treatment of generalized anxiety disorder. *CNS Drugs* **23**(2): 103–120.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatr* **62**(6): 617–627.

Koponen H, Allgulander C, Erickson J, *et al*. 2007. Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. *Prim Care Comp J Clin Psychiatr* **9**(2): 100–107.

Leichsenring F, Ruger U. 2004. Psychotherapy and evidence-based medicine (EBM)–randomized controlled vs. naturalistic studies: is there only one gold standard? *Z Psychosom Med Psychother* **50**(2): 203–217.

Lenze EJ, Rollman BL, Shear MK, *et al*. 2009. Escitalopram for older adults with generalized anxiety disorder: a randomized controlled trial. *J Am Med Assoc* **301**(3): 295–303.

Leombruni P, Lavagnino L, Gastaldi F, Vasile A, Fassino S. 2009. Duloxetine in obese binge eater outpatients: preliminary results from a 12 week open trial. *Hum Psychopharmacol* **24**(6): 483–488.

Lydiard RB, Rickels K, Herman B, Feltner DE. 2009. Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. *Int J Neuropsychopharmacol* **9**: 1–13.

Marciniak MD, Lage MJ, Dunayevich E, *et al*. 2005. The cost of treating anxiety: the medical and demographic correlates that impact total medical costs. *Depress Anxiety* **21**(4): 178–184.

NICE. Clinical Guideline 22. 2004. Anxiety: Management of anxiety (panic disorder, with or without agoraphobia and generalized anxiety disorder) in adults in primary, secondary and community care. URL: www.nice.orh.uk/CG022 NICE guideline.

Norman TR, Olver JS. 2008. Duloxetine in the treatment of generalized anxiety disorder. *Neuropsychiat Dis Treat* **4**(6): 1169–1180.

Pierò A. 2010. Personality correlates of impulsivity in Generalized Anxiety Disorder. *Compr Psychiatr* **51**(5): 538–545.

DOI: 10.1002/hup

Pigott TA, Prakash A, Arnold LM, Aaronson ST, Mallinckrodt CH, Wohlreich MM. 2007. Duloxetine versus escitalopram and placebo: an 8-month, double-blind trial in patients with major depressive disorder. *Curr Med Res Opin* **23**(6): 1303–1318.

Pollack MH. 2009. Refractory generalized anxiety disorder. *J Clin Psychiatr* **70**(S2): 32–38.

Rutherford BR, Rose SA, Sneed JR, Roose SP. 2009. Study design affect participant expectations: a survey. *J Clin Psychopharmacol* **29**(2): 179–181.

Rynn M, Russell J, Erickson J, *et al*. 2007. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible dose, progressive-titration, placebo controlled trial. *Depress Anxiety* **22**: 1–8.

Serretti A, Chiesa A, Calati R, Perna G, Bellodi L, De Ronchi D. 2009. Common genetic, clinical, demographic and psychosocial predictors of response to pharmacotherapy in mood and anxiety disorders. *Int Clin Psychopharmacol* **24**(1): 1–18.

Sihvo S, Hämäläinen J, Kiviruusu O, Pirkola S, Isometsä E. 2006. Treatment of anxiety disorders in the Finnish general population. *J Affect Dis* **96**(1–2): 31–38.

SPSS Base. 2000. *Application Guide*. SPSS: Chicago.

Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. 2005. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatr* **62**(6): 629–640.

Westenberg HG, Sandner C. 2006. Tolerability and safety of fluvoxamine and other antidepressants. *Int J Clin Pract* **60**(4): 482–491.

Westen D, Novotny CM, Thompson-Brenner H. 2004. The empirical status of empirically supported psychotherapies: assumptions, findings, and reporting in controlled clinical trials. *Psychol Bull* **130**(4): 631–663.

Williams VS, Baldwin DS, Hogue SL, Fehnel SE, Hollis KA, Edin HM. 2006. Estimating the prevalence and impact of antidepressant-induced sexual dysfunction in 2 European countries: a cross-sectional patient survey. *J Clin Psychiatr* **67**(2): 204–210.

DOI: 10.1002/hup