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**Title:** A randomized, single-blind, comparison of duloxetine with bupropion in the treatment of SSRI-resistant major depression

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## **Abstract**

*Introduction:* For patients who continue to experience depressive symptoms despite an adequate antidepressant SSRI trial, across-class switch is considered one of the best treatment options. The goal of the present work was to compare in terms of efficacy two different dual-action compounds, duloxetine and bupropion, in patients who failed to respond in two consecutive antidepressant trials with SSRIs.

*Methods:* The patients were allocated randomly to duloxetine (120 mg daily) or bupropion extended release (300mg daily). The intended medication period was 6 weeks. The primary measure of efficacy was depressive symptoms severity.

*Results:* A total of 49 participants were randomly assigned to duloxetine 120 mg (n=27) or bupropion 300 mg (n=22). The ITT efficacy patient sample consisted of 46 patients. Relatively high response and remission rates in treatment groups were found: from 60 to 70% of patients responded to treatment, and approximately 30 to 40% were in remission by the endpoint (week 6). No statistically significant difference emerged between the two groups at any postbaseline assessment, neither on mean scores of rating scales nor on qualitative efficacy measures.

*Limits:* Limitations of the study are the lack of a placebo arm, difficult to include owing to ethical reasons, and the relatively small size of the sample.

*Conclusions:* These preliminary results seem to support the hypothesis that in patients unresponsive to SSRIs the administration of antidepressants with different mechanisms of action is an effective switching strategy. Further studies are needed in light of the challenge posed by resistant depression.

**Key Words:** Antidepressant, Resistant, Depression, Switch

## 1. Introduction

Treatment-resistant depression continues to represent a major challenge for clinicians: only 50 to 60% of patients respond to the first antidepressant given ([Kroenke et al., 2001](#)). Switching to a different monotherapy antidepressant medication is the preferred option for many patients and clinicians. The possible advantages of switching to a different monotherapy, as compared with adding a second agent (i.e., augmenting or combining), include reduced medication costs, fewer drug interactions, better adherence, and less patient burden over time ([Marangell, 2001](#)).

In addition, switching to a different antidepressant may be quite appealing to patients, especially when the alternative drug has a more acceptable side effect profile ([Fava, 2000](#); [Fava and Rush, 2006](#)). There are two major types of switching strategies studied in literature: within-class switch and across-class switch. Recently, level 2 of the STAR\*D trial compared switching patients with no remission of symptoms from citalopram to bupropion, sertraline or venlafaxine: no differences in efficacy or tolerability emerged between the three treatment groups, with remission rates across treatments of approximately 25% ([Rush et al., 2006](#)). The results of a recent meta-analysis conducted by Papakostas et al. suggest a modest yet statistically significant advantage in remission rates when switching patients with SSRI-resistant depression to a non-SSRI rather than an SSRI antidepressant ([Papakostas et al., 2008](#)): it is, however, a limitation that only three non-SSRIs (venlafaxine, mirtazapine, and bupropion) were included in the meta-analysis and that most of the studies involved venlafaxine, with the advantage noted being evident regardless of whether or not the two comparisons that utilized mirtazapine and bupropion were included.

Respect to switching strategies from SSRIs to duloxetine, data are limited: an open-label trial conducted on a sample of 40 elderly subjects who have not responded to escitalopram, suggest that duloxetine at doses up to 120 mg/day is a potentially effective and well-tolerated treatment ([Karp et al., 2008](#)). In addition, the results of a multicentre trial comparing two different switching strategies

from SSRIs to duloxetine (direct switch or start-taper switch) in patients with major depression suggest significant improvements in both emotional and painful physical symptoms of depression regardless of which of the switch methods was used (Perahia et al., 2006).

On the basis of these findings, we hypothesize that, in patients unresponsive to SSRIs, the administration of an antidepressant with a different mechanism of action may be an effective switching strategy. The aim of this study is to compare the efficacy of two different dual-action compounds, duloxetine and bupropione, in patients with major depression unresponsive to SSRIs.

## **2. Methods**

### *2.1. Patients*

Patients were recruited from referrals to the Mood and Anxiety Disorders Unit, Department of Neuroscience, University of Turin, Italy. This is a tertiary referral center mainly for patients from the Piedmont and Aosta Valley regions of Italy, located in the University General Hospital. Patients are referred by general practitioners, psychiatrists or psychologists due to an anxiety or mood disorder diagnosis (or hypothesized diagnosis), although a few are self-referred (e.g. via information received from other patients).

The participants were male or female outpatients, 18 years of age or older, who met the DSM-IV-TR (APA, 2000) criteria for a primary diagnosis of major depressive episode (MDE). All patients' diagnoses were assessed by means of the criteria of the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997).

Other inclusion criteria were as follows: (1) the major depressive episode had to be resistant to two adequate SSRI treatments (full therapeutic dose for at least 4 consecutive weeks) evaluated through the Antidepressant Treatment History Form — ATHF (Oquendo et al., 2003; Sackeim, 2001); (2) a 17-item Hamilton Depression Rating Scale—HAM-D-17 (Hamilton, 1967) score  $\geq 18$  at baseline

evaluation was required.

Exclusion criteria were: (1) a lifetime diagnosis of bipolar disorder, schizophrenia, other psychotic disorders, severe axis II psychopathology, mental retardation, alcohol and/or drug abuse; (2) an organic brain syndrome or medical illness that would contraindicate the use of antidepressants; (3) pregnant or nursing women and women of childbearing potential not using adequate contraceptive measures; (4) discontinuation of SSRI trials because of side effects; (5) an ongoing psychological treatment.

In addition, patients were excluded if they had previously received unsuccessful treatment with duloxetine or bupropion extended release, or had known hypersensitivity to duloxetine or bupropion.

The study design was reviewed by local ethical committee. Written informed consent was requested for all patients who fulfilled the inclusion/exclusion criteria prior to their study enrollment, after the procedure had been fully explained.

## *2.2. Study design*

The question of the relative efficacy of the duloxetine or bupropion antidepressant therapy was addressed in a 6-week randomized parallel-group design. The patients were allocated randomly to one of the two study drugs depending on the day of inclusion was even (duloxetine) or odd (bupropion).

The trial was preceded by a 2-week period for the drug washout (4 weeks in case of fluoxetine as last treatment). During the washout period, patients were required to discontinue any antidepressant medication: SSRIs were tapered within the first week and then stopped one week before starting the study medications (three weeks before in case of fluoxetine). Benzodiazepines were allowed: lorazepam (or equivalents)  $\leq 1$  mg/day.

### *2.3. Pharmacotherapy*

Duloxetine was given initially at a dose of 60 mg/day with increase in dosage after 3 days to a daily dose of 120 mg. Bupropion extended release was given initially at a dose of 150 mg/day, with increase after 3 days to a daily dose of 300 mg/day. The intended medication period was 6 weeks.

The psychiatrist made 3 appointments of 40 min each with his patient every 2 weeks.

Concomitant benzodiazepines were allowed as needed to ameliorate anxiety or insomnia on weeks 1 and 2: lorazepam (or equivalents)  $\leq 1$  mg/day.

Furthermore, the patients were informed to contact their psychiatrist every time they experienced a worsening of symptoms or side effects/adverse events. The task of the psychiatrist was to provide pharmacotherapy and clinical management. The latter consisted of providing psychoeducation, discussing the effects and side effects of the medication, and motivating the patient to comply with the medication regimen.

### *2.4. Clinical assessment*

The primary efficacy assessments was the HAM-D-17; the secondary efficacy measures included the Clinical Global Impression—Severity (CGI-S) (Guy, 1976) scale, the Clinical Global Impression—Improvement (CGI-I) scale, and the Global Assessment of Functioning (GAF) (Jones et al., 1976). The patients were assessed at the start of the treatment time (baseline: T0) and every two weeks (T1, T2, endpoint). At each evaluation timepoint, all the primary and secondary outcome measures were employed; the CGI-I was rated from T1. In addition, all patients were informed to contact their psychiatrist every time they experienced a worsening of symptoms; in this case, another evaluation was conducted by the same rating scales.

Two raters assessed all patients; they were 2 psychiatrists who did not participate in the clinical management of patients and were kept blind with respect to the treatment assignment. The patients were advised not to talk to the evaluators about the type of pharmacotherapy they were on.



In the early phase of the study, the interrater agreement on the diagnosis and on the primary efficacy measures was ascertained. The interrater reliability of the DSM-IV diagnosis was good ( $\kappa=0.79$ ; 95% CI=0.71–0.87). In 10 depressed subjects, the correlation of the scores obtained by our raters from the HAM-D-17 was above 0.90.

## 2.5. Analysis

All statistical analyses were performed by SPSS software version 15.0. The results of the statistical comparisons of the treatment groups were presented as two-sided p values rounded off to 3 decimal places. The criterion for statistical significance in all comparisons was a p value < 0.050.

Analyses of variance were performed to test the comparability of continuous socio-demographic variables in the 2 groups (index age and educational level) and to test intergroup and intragroup differences in rating scale scores (HAM-D-17, CGI and GAF). Further, a sub-analysis on core depressive symptoms through the comparison of means of the 6-item HAM-D (O'Sullivan et al., 1997) has been conducted.

Pearson's  $\chi^2$  calculations were used to compare sex ratio, marital status and occupational status among the groups and to compare the 3 different outcome measures of the qualitative evaluation: (a) HAM-D-17 response (HAM-D-17 reduction of at least 50% from base rate); (b) HAM-D-17 remission (HAM-D-17 score of 7 points or less), and (c) CGI success (CGI-S score: 1–2).

The data analysis method used for outcome measures was performed on the 'intent-to-treat (ITT) efficacy' patient sample, which consisted of those patients randomized to the trial who took at least 1 capsule of study medication and had at least 1 valid post-baseline efficacy evaluation either on the study medication or within 3 days of drug discontinuation. To define the sample size of the 2 groups, we used the formula for minimum sample size related to the comparison of means (in particular, we considered the HAM-D-17 means) given a significance level of 0.05 and a statistical power of 90% (Kirkwood and Sterne, 2006); thus, the size of each subgroup had to be at least 15

patients.

### 3. Results

A total of 49 participants were randomly assigned to duloxetine 120 mg (n=27) or bupropion 300 mg (n=22). The SSRI treatments taken by randomized patients before the inclusion in the study are showed in [Table 1](#).

The dropout rate was 7.4% (n=2) in the duloxetine group, and 4.5% (n=1) in the bupropion group (difference not statistically significant). In the group of patients treated with duloxetine, the dropouts were due to the fact that patients didn't take any medication (n=1) or stopped medication because of side effects (headache and nausea, n=1); in the group of patients treated with bupropion, one patient stopped medication because of side effects (restlessness and worsening of insomnia).

The ITT efficacy patient sample consisted of 46 patients (25 in duloxetine group and 21 in bupropion group). The characteristics of the ITT sample are given in [Table 1](#). No statistically significant differences were found between the 2 treatment groups in demographic or baseline rates. [Table 1](#) also presents the efficacy results expressed in mean of HAM-D-17 total score, CGI scores (severity and improvement), and GAF scores: no differences between the two treatment groups were found at any point by any assessment method in the ITT sample. From a more detailed analysis of the improvement of specific depressive symptoms between the two subgroups one difference emerged at week 2 (T1): patients treated with bupropion improved more than those treated with duloxetine on item-1, depressed mood (mean=1.10±.625 vs 1.52±.770; F=3.444; d.f.=44; p=0.45). No other statistically significant difference emerged.

Intragroup differences between baseline (T0) and endpoint assessments (T3) were statistically significant in both treatment conditions: a significant reduction in symptomatology emerged from the HAM-D-17 (duloxetine group: t=11.530, d.f.=24, pb.001; bupropion group: t=11.865, d.f.=20, pb.001) and CGI-S (duloxetine group: t=11.616, d.f.=24, pb.001; bupropion group: t=15.031,

d.f.=20, pb.001) total scores. Further, the 6-item-HAM-D mean score decreased significantly already at week 2 in both duloxetine (from 11.84±2.035 to 6.04±2.971: t=10.330; d.f.=24; pb.001) and bupropion subgroup (from 12.05±2.418 to 5.52±2.892: t=10.800; d.f.=20; pb.001).

The statistical analysis of the success rates (HAM-D response, HAM-D remission) showed no difference between the two treatment strategies (Table 1) and the additional information obtained by the CGI-S success rate also confirmed this finding (week 2:  $\chi^2=0.022$ ; d.f.=1; p=1.000; week 4:  $\chi^2=0.124$ ; d.f.=1; p=0.749; endpoint:  $\chi^2=0.000$ , d.f.=1: p=1.000).

#### 4. Discussion

This study addresses the pragmatic question of the clinical utility of switching strategy in case of inadequate response to an antidepressant treatment. The majority of previous studies on this topic have considered patients unresponsive to a single SSRI trial, evaluating the efficacy of within-class and across-class switching (Ruhè et al., 2006; Thase, 2004) and suggesting a modest advantage when switching to a non-SSRI rather than another SSRI antidepressant (Papakostas et al., 2008). Nevertheless, to date it is not yet clear when it is preferable to adopt a strategy rather than another.

In order to increase the information available to the clinicians in case of treating resistant depression, we have selected a small but homogeneous sample of patients with “high” resistance to treatment with SSRIs, defined as the failure of two adequate trials with an SSRI monotherapy.

The results of this randomized, single-blind trial suggest that both switching strategies to duloxetine 120 mg/day or bupropion extended release 300 mg/day are effective in these patients. Relatively high response and remission rates in treatment groups were found: from 60 to 70% of patients responded to treatment, and approximately 30 to 40% were in remission by the endpoint (week 6).

No statistically significant difference emerged between the two groups at any post-baseline assessment, neither on mean scores of rating scales nor on qualitative efficacy measures. Although

response and remission rates are higher than those of the STAR\*D, response rates are similar to the findings of the meta-analysis of Papakostas ([Papakostas et al., 2007](#)). However, the lower rates of response and remission of the STAR\*D can be attributed to the inclusion of patients who were chronically depressed, had lower socioeconomic status and suffered from more comorbid somatic and psychiatric diseases ([Rush et al., 2006](#)).

Further, patients who responded to treatment with duloxetine or bupropion (about two-thirds in each group) improved more quickly than expected: in the majority of cases a reduction of more than 50% on the HAM-D-17 scores appears already at week 2, with a further slight increase of response rates at week 4. The improvement at week 2 might have been influenced by the use of benzodiazepines, which was allowed during the first two weeks of treatment, but has focused on core depressive symptoms, suggesting that in case of switching from SSRIs to dual-action compounds, might be useful to consider the possibility of an early response.

These preliminary results support the hypothesis that in patients unresponsive to SSRI, the administration of antidepressants with different mechanisms of action is an effective switching strategy.

One of the limitations of the study is the lack of a placebo arm which is becoming increasingly difficult to include owing to ethical reasons. A second limitation is represented by the relatively small size of the sample, because the restrictive inclusion and exclusion criteria, including the fact that patients were to be unresponsive to two previous SSRI trials, did not allow the recruitment of a larger number of patients. Finally, a third limitation of the study might be in the selection of the sample, due to the nature of our center (tertiary referral center) and to the not consecutive recruitment of the patients. Conversely, the strengths are represented by the selection of a homogenous study sample (all patients suffered from an unipolar major depressive episode resistant to two adequate SSRI trials) and by the randomized, prospective, single-blind design.

An extension of the study sample is required to find possible differences between duloxetine and bupropion in terms of efficacy and to identify predictors of response.

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