European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro

Duloxetine-bupropion combination for treatment-resistant atypical depression: A double-blind, randomized, placebo-controlled trial

Michele Fornaro[a,*], Matteo Martino[b], Chiara Mattei[b], Davide Prestia[b], Valentina Vinciguerra[b], Domenico De Berardis[c], Concetta De Pasquale[a], Felice Iasevoli[d], Sergio Mungo[b], Pantaleo Fornaro[b]

[a]*Department of Education Science, University of Catania, Catania, Italy*
[b]*Department of Neurosciences, Ophthalmology and Genetics – Section of Psychiatry, University of Genova, Genoa, Italy*
[c]*Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, "ASL 4", Teramo, Italy*
[d]*Laboratory of Molecular Psychiatry and Psychopharmacotherapeutics, Section of Psychiatry, Department of Neuroscience, Reproductive Sciences and Odontostomatology, University School of Medicine" Federico II" of Naples, Italy*

Received 16 November 2013; received in revised form 26 February 2014; accepted 27 April 2014

KEYWORDS
Duloxetine;
Bupropion;
Treatment-resistant depression;
Atypical depression;
Placebo-controlled;
Randomized trial (RCT)

Abstract
The efficacy, safety, and tolerability of combined bupropion versus placebo using duloxetine as active reference drug, in patients with a DSM-IV diagnosis of major depression with atypical features and a history of treatment resistance, were evaluated in this preliminary six-week study. Patients (n=46) had a baseline Hamilton Depression Scale (HAM-D) $\geq$14 and were randomly assigned to 150/300 mg/day bupropion vs. placebo, which was added to 60 to 120 mg/day duloxetine depending on baseline depression severity. Atypical features of depression were assessed using the additional eight-item module of the Structured Interview Guide for the HAM-D with the Atypical Depression Supplement. By week 6, only five (21.7%) patients receiving duloxetine+placebo vs. six (26.1%) patients on the bupropion combination achieved response. No significant difference in final HAM-D scores between the two groups was

*Correspondance to: Department of Formative Sciences, University of Catania, via Teatro Greco n. 84, ZIP 95125, Catania, Italy. Tel.: +39 10 3537681; fax: +39 10 353 7681.

E-mail addresses: dott.fornaro@gmail.com (M. Fornaro), matteomartino9@gmail.com (M. Martino), chiaramattei@gmail.com (C. Mattei), davideprestia@alice.it (D. Prestia), sailing_boat@libero.it (V. Vinciguerra), dodebera@aliceposta.it (D. De Berardis), depasqua@unict.it (C. De Pasquale), felix_ias@hotmail.com (F. Iasevoli), sergiomungo@libero.it (S. Mungo), prof.fornaro@gmail.com (P. Fornaro).

http://dx.doi.org/10.1016/j.euroneuro.2014.04.004

observed between those patients achieving response. The presence of a higher number of atypical features significantly predicted non-response, with the relevant binary logistic regression model correctly classifying 17 out 22 (77.3%) of non-responders [Exp(B)=0.294; p=0.016] vs. 17 out 23 (73.9%) [Exp(B)=0.353; p=0.028] non-responder cases in the "+placebo" and "+bupropion" groups, respectively. In those patients receiving bupropion, treatment-emergent adverse events leading to withdrawal were more common among those receiving lower doses of the combination drug, and no life-threating dangers were noted. Additional studies, including an adequate course of duloxetine trial, are nonetheless aimed to allow a firm conclusion about the usefulness of the combination of duloxetine and bupropion for treatment-resistant cases of major depression with atypical features.

1. Introduction

Treatment-resistant depression (TRD) represents a common condition, with 50 to 60% of major depressive disorder (MDD) patients receiving antidepressant drugs failing to achieve a clinically meaningful response (Souery et al., 1999). Therefore, "augmentation strategies" (addition of one or more non-antidepressant drugs to an existing antidepressant regimen to enhance mood and overall antidepressant response), "adjunctive therapies" (addition of one or more agents to target specific symptoms of depression) (DeBattista, 2006) or "combination treatments" (augmentations made using two or more drugs from the same class, e.g., two antidepressants) (Papakostas, 2009) represent popular treatment strategies for TRD. While some augmentation strategies for standard antidepressants, including atypical antipsychotics (Nelson and Papakostas, 2009) and lithium or thyroid hormones (DeBattista, 2006), have consistent and/or increasing levels of evidence of support, the actual usefulness of most antidepressant within- or across-class combinations vs. monotherapy remains substantially not supported by existing studies, at least for melancholic cases of TRD or moderately to severe non-psychotic chronic and/or recurrent MDD according to the acute and long-term outcomes reported by the single-blind randomized "Combining Medications to Enhance Depression Outcomes (CO-MED)" study (Rush et al., 2011), despite the popularity of this practice among clinicians (Bares et al., 2013; Gaynes et al., 2012; Souery et al., 2011). This issue could also affect TRD cases with atypical features, which apart from nosological revisions (Fornaro and Giosue, 2010; Perugi et al., 2011; Stewart et al., 2009; Thase, 2009), require further controlled studies on the matter compared with "typical" (melancholic) TRD. Furthermore, atypical TRD itself largely accounts for the variance in TRD outcome, which is actually "very typical" from a prevalence standpoint, as outlined by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Trivedi et al., 2006), with reported rates of 18-19% among depressed outpatients (possibly higher in cases with a history of TRD) and a lower propensity to respond to standard antidepressants, namely the selective serotonin reuptake inhibitors (SSRIs) or their sequenced treatment alternatives (Novick et al., 2005; Stewart et al., 2010). Remarkably, though part of the historical criteria for atypical depression arose from the observation of a fair response to monoamine oxidase inhibitors vs. the tricyclic antidepressants available at the time (Stewart et al., 1993; West and Dally, 1959), because of their poor benefit/risk ratio, modern clinicians tend to use newer antidepressants for all outpatients, regardless of the presence of atypical features, especially upon patient failure to respond to SSRIs (Nierenberg et al., 1998; Schultz, 1999). Such an attitude is exemplified by the spreading use of the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine even for atypical cases of SSRI-TRD, although this drug displays a negligible efficacy advantage vs. the SSRIs, at least for less severe manifestations of depression, as documented by an 8-week, flexible-dose open-label study carried on 20 MDD patients, including a subset of atypical cases (Papakostas et al., 2007; Shelton et al., 2007). A subsequent study failed to demonstrate any difference in therapeutic outcome (50% were responders) compared to non-atypical depressed (Stewart et al., 2008), in contrast to a 12-week, open-label, multi-centric investigation, that had concordant results with the STAR*D wisdom indicating the presence of atypical features as one of the factors associated with the reduced response toward duloxetine in MDD (Howland et al., 2008). In addition, despite the scarce and contradictory evidence, duloxetine is regarded by many clinicians as an "optimal background" for combination with other antidepressants, including the versatile sustained release (Berigan, 2002) form of the Norepinephrine Dopamine Reuptake Inhibitor (NDRI) bupropion (Fava et al., 2005; Papakostas et al., 2006), a polypharmacy, which albeit fostered by pharmacokinetic and pharmacodynamics rationale (Spina et al., 2012), still requires confirmation by additional randomized controlled trials (RCTs), particularly for the treatment of atypical TRD.

Therefore, the aim of this six-week placebo-controlled, parallel-group RCT was to explore the efficacy, safety and tolerability of the "duloxetine plus bupropion" combination vs. "duloxetine plus placebo" association in patients with a history of SSRI-TRD with atypical features.

2. Experimental procedures

2.1. Participants

Outpatients aged 18–65, of both genders, were recruited at the San Martino hospital of Genoa, Italy, from July 2008 to November 2011, upon approval by the local Ethical Committee, in accordance with the principles of the Good Clinical Practices (ICH, 1996), the Declaration of Helsinki (WMA, 2008) and signature of a valid informed consent

Please cite this article as: Fornaro, M., et al., Duloxetine-bupropion combination for treatment-resistant atypical depression: A double-blind, randomized,.... European Neuropsychopharmacology (2014), http://dx.doi.org/10.1016/j.euroneuro.2014.04.004