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Combination antidepressant therapy for major depressive disorder: Speed and probability of remission

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ABSTRACT

Introduction: Only about a third of patients with an episode of major depressive disorder remit with a given treatment and few remissions occur within the first weeks of treatment. This study tested whether combining escitalopram and bupropion as initial treatment would result in quicker remission and a higher remission rate than monotherapy with either drug.
Method: Two hundred forty-five outpatients aged 18–65 having non-psychotic, non-bipolar major depression were randomly assigned to double-blind treatment with bupropion or escitalopram or the combination dosed to a maximum of bupropion 450 mg/d and/or escitalopram 40 mg/d for 12 weeks. A Montgomery–Asberg Depression Rating Scale score of 22 was required for randomization, while a Hamilton Rating Scale for Depression score ≤ 7 defined remission. We hypothesized that bupropion plus escitalopram would outperform both monotherapies in both earlier onset of remission and higher rate of remission.
Results: Primary analyses did not demonstrate that dual therapy outperformed both monotherapies in either timing of remission or remission rate. All three treatments were well tolerated.
Discussion: These results do not support initial use of bupropion plus escitalopram to speed or enhance antidepressant response.
Clinical trials registration: NCT00519428.

1. Introduction

Clinicians face challenges in treating depressed patients. Most importantly, although two thirds improve with initial treatment, only one third remit. Second, even those who remit take weeks to do so, remaining depressed and dysfunctional in the meantime. In addition, there is little guidance as to which patients will more likely benefit from a given treatment, whether antidepressant medication, psychotherapy or brain stimulation device. Methodologies are needed to personalize treatment by providing the tools to match patient with treatment, and to attain remission more quickly in those destined to remit.

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Trivedi et al., 2006) suggested that only 32% of patients remit after up to 14 weeks of vigorous treatment with citalopram. Only half the remitting patients had achieved that status by 6 weeks, in agreement with the concept that for most antidepressants remission, even when achieved, is often delayed (Hordern, 1965; Klerman and Cole, 1965; Quitkin et al., 1987; Thompson, 2002). There is little literature suggesting that single antidepressant agents can improve on the STAR*D result.

The idea that antidepressant medications have delayed onset of efficacy (Hordern, 1965; Klerman and Cole, 1965; Quitkin et al., 1987; Thompson, 2002) has been challenged by re-analyses of data suggesting active drugs may separate from placebo as early as one week (Kasper et al., 2006; Mitchell, 2006; Posternak and

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Zimmerman, 2005; Stassen et al., 1993; Papakostas et al., 2006; Henkel et al., 2009; Derivan et al., 1995; Papakostas et al., 2007). This early separation suggests that at least in some patients, the medications have actions not previously considered. However, even the strongest proponents of the early onset of antidepressant action do not suggest that drug-induced early remissions are likely. For example, a recent meta-analysis demonstrated only remissions obtained with mirtazapine separated from placebo by two weeks, but even these remissions were infrequent (13% on active vs. 7% on placebo, number needed to treat = 17) (Szegedi et al., 2009).

One approach to deal with the twin problems of low remission rates and delay in attaining remission is so-called dual therapy, that is, the combined use of two antidepressants as initial treatment. Dual therapy suggested increased remissions in three open-label (Nelson et al., 1991; Leuchter et al., 2008; Stewart et al., 2009) and two double-blind studies (Blier et al., 2010; Blier et al., 2009), a third randomized trial was equivocal (Nelson et al., 2004) and a fourth randomized but non-blinded study did not differentiate dual therapy from monotherapy (Rush et al., 2011). Nelson et al. (1991) in an open-label study first suggested that combining antidepressants having different putative mechanisms might convey earlier and more robust responses than monotherapy, but the double-blind follow-up study of desipramine plus fluoxetine vs. each as monotherapy showed efficacy on secondary measures but not in the primary analysis (Nelson et al., 2004). Blier et al. (2009, 2010) demonstrated superiority of dual therapy with mirtazapine plus SSRI or SNRI relative to SSRI monotherapy or mirtazapine alone.

An open clinical trial of combined bupropion plus escitalopram as initial therapy for the treatment of depressed patients suggested that dual therapy may increase both early remission and increase ultimate remission rates (Stewart et al., 2009). Among 51 depressed patients receiving open label dual therapy, 32% remitted by two weeks and 62% at six weeks. This compares favorably with a recent analysis of timing of improvement showing the highest two-week rate among the 11 investigated antidepressant medications to be 13%, with end treatment (5–6 weeks) remission rates ranging from 29 to 38% (Szegedi et al., 2009). Leuchter et al. have also reported higher remission rates for patients treated with bupropion plus escitalopram than an historical control of STAR*D Level 1 patients treated with citalopram, but did not report on timing of improvement (Leuchter et al., 2008). CO-MED did not confirm the Leuchter et al. and Stewart et al. findings in a randomized but unblinded comparison of bupropion plus escitalopram with escitalopram alone (Rush et al., 2011).

To determine whether the two pilot studies or the randomized comparison trial more accurately portrayed an advantage bupropion plus escitalopram might have over monotherapy, we conducted a double-blind study of escitalopram plus bupropion dual therapy as initial treatment for major depressive disorder compared to each drug used alone as monotherapy. We hypothesized that:

1) Onset of remission would be earlier in patients treated with dual therapy compared with monotherapy, and
2) End study remission would be increased in patients treated with dual therapy compared with monotherapy

2. Methods

Patients were evaluated using the Structured Clinical Interview for DSM-IV-TR Diagnoses (First et al., 2002). Enrolled patients had to meet criteria for Major Depressive Disorder but not psychosis or another Axis I disorder considered primary. Also excluded were patients having a history of anorexia, bulimia, bipolar disorder or a seizure disorder. Initial and randomization Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979) (MADRS) score had to be at least 22. They also could not have an unstable medical condition or be taking other psychoactive medications. Patients taking medication for stable medical conditions, such as hypertension or hypothyroidism currently with controlled blood pressure or normal thyroid indices, were accepted. The study was conducted at four sites (two in New York City and two in the Ottawa region) and was approved by the respective research ethics boards. Patients were enrolled between August, 2007 and August, 2011; the last study visit occurred in January, 2012. All subjects gave written informed consent.

After baseline ratings were obtained, general health was assured with physical examination and laboratory testing and it was determined all inclusion and no exclusion criteria were met, patients were randomly assigned to double-blind treatment with bupropion (plus a placebo matching escitalopram), escitalopram (plus a placebo matching bupropion) or escitalopram plus bupropion. There was no single-blind placebo lead-in, although there was always a delay while awaiting laboratory results at which reassessment required continued meeting of entry criteria, including minimal MADRS score. Bupropion was dispensed as the XL formulation in 150 mg pills. Escitalopram was dispensed in 10 mg pills. Bupropion dosing was 150 mg/d for the first week, 300 mg/d for two weeks and 450 mg/d for the remaining weeks of the 12-week study. Escitalopram dosing was 10 mg for the first week with weekly 10 mg/d dose increases to 40 mg/d at week 4 and beyond. All dose increases occurred only if the patient had not remitted (17-item Hamilton Rating Scale for Depression (Hamilton, 1960) [HAM-D_{17}] score $\leq$ 7) and was tolerating the medication.

HAM-D_{17}, HAM-D_{29}, MADRS, Clinical Global Impression Scale (Guy, 1976) (CGI), and the Quick (16-item) Inventory of Depressive Symptoms (Rush et al., 2003) (QIDS-SR_{16}) were obtained at every study visit, which occurred at weeks 1, 2, 3, 4, 6, 8, 10 and 12 after the randomization visit. At every post-randomization visit, a modified Systematic Assessment Form for Treatment Emergent Events (Levine and Schooler, 1986) (SAFTEE) was obtained to record and track adverse events independently of whether the patient or clinician considered these events to be related to the study medication. The modification of the SAFTEE was that instead of the 32 items utilized in the original SAFTEE, the specific inquiry section asked about the 16 adverse events found to have occurred in at least 10% of patients treated with escitalopram plus bupropion in our pilot study (Stewart et al., 2009). A 17th item, "emergent anger/irritability" was added following the initial review of adverse events by the Data Safety Monitoring Board.

To minimize inflation of outcome variable scores at randomization, the MADRS was used as the study entry requirement ($\geq$22) and the HAM-D_{17} was the primary outcome measure.

2.1. Statistical analyses

Percentages, means, and standard deviations describe the patient sample. Pre-treatment variables are compared among treatment groups using ANOVA, baseline variables determined to differ significantly among treatments being included in subsequent outcome analyses.

Hypothesis #1. *Time to remission will be shorter in the dual therapy group compared to the escitalopram group AND time to remission will be shorter in the dual therapy group than time to remission in the bupropion group.*

Hypothesis #1 required two tests, one comparing the outcome of the dual therapy group to the escitalopram group and a second test comparing the dual therapy group to the bupropion