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Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Amitifadine (EB-1010, formerly DOV 21,947) is a serotonin-preferring triple reuptake inhibitor with a relative potency to inhibit serotonin, norepinephrine, and dopamine uptake of ~1:2:8, respectively. This 6-week, multicenter, randomized, double-blind, parallel, placebo-controlled study evaluated the efficacy and tolerability of amitifadine in 63 patients with major depressive disorder. Eligible patients (17-item Hamilton Depression Rating Scale [HAMD-17] $\geq$ 22 at baseline) were randomized to amitifadine 25 mg twice daily (BID) for 2 weeks, then 50 mg BID for 4 weeks or placebo. Mean baseline scores in the modified intent-to-treat population ($n = 56$) were 31.4 for the Montgomery-Åsberg Depression Rating Scale (MADRS), 29.6 for the HAMD-17, and 25.4 for the Derogatis Interview for Sexual Functioning – Self Report (DISF-SR). At the end of the 6-week double-blind treatment, estimated least squares mean change from baseline (mixed-model repeated measures [MMRM]) in MADRS total score was statistically significantly superior for amitifadine compared to placebo (18.2 vs. 22.0; $p = 0.028$), with an overall statistical effect size of −0.601 (Cohen's d). Amitifadine also was statistically significantly superior to placebo ($p = 0.03$) for the Clinical Global Impression of Change – Improvement. An anhedonia factor score grouping of MADRS Items 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel) demonstrated a statistically significant difference in favor of amitifadine compared to placebo ($p = 0.049$). No differences were observed between treatments in DISF-SR scores. Amitifadine was well-tolerated. Two patients on each treatment discontinued the study early due to adverse events; however, no serious adverse events were reported. This initial clinical trial in patients with severe major depression demonstrated significant antidepressant activity with amitifadine, including attenuating symptoms of anhedonia, and a tolerability profile that was comparable to placebo. The efficacy and tolerability of amitifadine for major depressive disorder are being investigated in additional clinical trials.

1. Introduction

The introduction of fluoxetine in the late 1980s marked the debut of a new class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs) (Wong et al., 1995). SSRIs increase the synaptic availability of serotonin by inhibiting the serotonin transporter (5-HTT). The serotonin transporter is one member of a family of 12 trans-membrane spanning neurotransmitter transporters (Kuzelova et al., 2010). Uptake by the 5-HTT is the principal means of removing serotonin from the synapse, thereby terminating its action as a neurotransmitter (Kuzelova et al., 2010). As a class, SSRIs are generally better tolerated, safer, and easier to use than the first generation agents, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). In double-blind placebo-controlled studies, however, only about 50% of patients respond to a given SSRI (Walsh et al., 2002), and approximately one-third of patients achieve clinical remission (Thase, 2003). Moreover, the typical onset of action is slow. For those patients who respond, 2–4

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weeks of treatment are required to achieve a clinically meaningful effect. SSRI administration is associated with troublesome weight gain with some agents and sexual dysfunction (Fava, 2000; Rosen et al., 1999). These side effects can contribute to a significant degree of non-compliance to treatment regimens. Moreover, about 30% of patients treated successfully with SSRIs continue to report significant cognitive impairment, such as an inability to stay focused and difficulty with recall, word-finding, and mental acuity (Fava et al., 2006).

The role of norepinephrine in mood disorders has been recognized for almost 50 years (Schildkraut and Kety, 1967). Preclinical studies indicate a pivotal role for the prefrontal cortex, which requires noradrenergic stimulation to function optimally, in modulating high level learning, memory, attention, and emotions (Blier, 2001; El Mansari et al., 2010; Gamo and Arnsten, 2011). Many TCAs inhibit the reuptake of both NE and 5-HT with varying potencies, but possess off-target actions that limit safety and tolerability (Anderson, 2000). Dual uptake inhibitors such as venlafaxine, milnacipran, and duloxetine lack the safety liabilities of TCAs, but are only marginally superior to SSRIs for antidepressant efficacy (Cipriani et al., 2009; Nemeroff et al., 2008).

Dopamine plays a central role in reward, motivation, mood regulatory functions, working memory, attention, and executive functions (Schultz, 2007). Converging lines of evidence indicate that enhancing dopaminergic neurotransmission can diminish anhedonia (a core symptom of major depression) as well as improve cognition and motivation (Skolnick, 2005; Skolnick and Basile, 2007; Dunlop and Nemeroff, 2007), and symptoms of anhedonia respond poorly to SSRIs (Shelton and Tomarken, 2001; McCabe et al., 2010). Bupropion, a dopamine and norepinephrine reuptake inhibitor, and dopamine agonists such as pramipexole have demonstrated antidepressant activities (Tremblay and Blier, 2006).

A growing body of literature suggests that antidepressants with more than one mechanism of action are more effective than a drug with a single mechanism (Blier et al., 2010; Rush et al., 2006; Papakostas et al., 2007). Major depression is a heterogeneous and complex disorder attributed to genetic, developmental, and environmental factors (Millan, 2009; Perović et al., 2010). In addition to treating the core symptoms of depression, a need exists to treat other symptoms including insomnia, fatigue, anxiety, memory and cognitive impairment while avoiding side effects. Because of the diversity of symptoms and co-morbid symptoms, the majority of depressed patients are unlikely to respond to drugs acting at a single receptor (Millan, 2009; Perović et al., 2010). Dopamine, as well as serotonin and norepinephrine, is involved in the pathophysiology and treatment of depression (Skolnick, 2005), which has given rise to a new class of antidepressants that simultaneously inhibit serotonin, norepinephrine, and dopamine (Skolnick et al., 2003a; Guiard et al., 2009; Millan, 2009; Marks et al., 2008;). It has been proposed that activity from all three monoamines may account for an enhanced antidepressant response. The concept of broad spectrum antidepressants, whereby all three monoaminergic systems (serotonin, norepinephrine, and dopamine) are engaged to act in concert to improve symptoms of depression, has been partially validated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study sponsored by the National Institutes of Mental Health (Trivedi et al., 2006; Rush et al., 2006). Patients who did not achieve sufficient symptomatic relief with the SSRI, citalopram, were able to achieve the highest level of remission with bupropion augmentation compared to the other augmentations including buspirone and cognitive therapy. These encouraging results confirmed the conceptual foundation for the development of broad spectrum antidepressants (Skolnick et al., 2003a).

Amitifadine ((1R,5S)-(+)-1-(3,4-dichlorophenyl)-3-azabicyclo [3.1.0]hexane hydrochloride, formerly called DOV 21947) is a "broad spectrum" antidepressant or serotonin-preferring triple reuptake inhibitor (Skolnick et al., 2003b). Amitifadine inhibits the function of the transport proteins responsible for clearing dopamine, serotonin, and norepinephrine from the synaptic cleft. Microdialysis studies show that amitifadine inhibits reuptake of all three neurotransmitters (Bymaster and McKinney, 2010), and inhibition of ex vivo binding of amitifadine that is consistent with in vitro binding has been demonstrated (Lengyel et al., 2008). However, no currently marketed antidepressants inhibit the uptake of all three transmitters at pharmacologically relevant doses. Furthermore, amitifadine exhibits a relative potency to inhibit serotonin, norepinephrine, and dopamine reuptake of ~1:2:8, respectively. The concentration required to inhibit uptake (IC_{50}) in recombinant human transporters was reported as: 12 nM for serotonin, 23 nM for norepinephrine, and 96 nM for dopamine (Skolnick et al., 2003b). It was hypothesized that amitifadine may express unique antidepressant activities in humans, with enhanced efficacy such as improvement of anhedonia. Anhedonia is presumably linked to a deficit in mesocorticolimbic dopaminergic function, and dopaminergic activity is related to a reduced liability to induce sexual dysfunction, weight gain, sleepiness, fatigue, and cognitive dysfunction, adverse effects typically associated with SSRIs (Skolnick, 2005). The present study reports the results of the first proof-of-concept clinical trial of amitifadine in patients with major depressive disorder.

2. Methods

The study was conducted at 11 sites in Romania, 2 sites in Serbia, and 7 sites in the United States. The study was conducted in accordance with the Declaration of Helsinki (Edinburgh, 2000, with paragraph 29 as clarified in Washington, DC, 2002, and note of clarification added on paragraph 30 in Tokyo, 2004). The protocol was approved by an appropriate ethical committee for each site, and written informed consent of all participants was obtained after the nature of the procedures had been fully explained and prior to study participation.

2.1. Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of amitifadine in patients with major depressive disorder (MDD). After satisfactory completion of screening, patients underwent a 7-day, single-blind, placebo run-in period to determine study medication compliance and placebo response. All patients took placebo capsules twice daily (BID) during the run-in period. Following completion of baseline assessments, patients were randomized in a 1:1 ratio to amitifadine or placebo, using an interactive voice response system. Study medications were provided as capsules of amitifadine 25 mg and placebo that appeared identical. Patients were instructed to take 2 capsules in the morning and 2 capsules in the evening, each day during the study. For the first 2 weeks of the 6-week double-blind treatment period, patients randomized to amitifadine took 25 mg BID (as 1 amitifadine capsule and 1 placebo capsule), and for the remaining 4 weeks they took 50 mg BID (2 amitifadine capsules). During the treatment period, study visits occurred at days 8, 15, 22, 29, and 43. All patients again took placebo capsules BID for a 7-day single-blind placebo follow-up period, with the final study visit at day 50.

2.2. Patient selection

Adult outpatients or inpatients between ages 18 and 65 years (inclusive) were eligible if they were diagnosed with major

depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Revised (American Psychiatric Association, 2000) and MINI International Neuropsychiatric Interview for major depressive disorder (Sheehan et al., 1998). Patients were required to have a history of recurrent depressive episode of at least 2 months in duration. They also were required to have a previous significant clinical improvement to at least one antidepressant treatment. In addition, they had a 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960) total score ≥ 22 with severity score of ≥ 2 on Item 1 at screening, single-blind placebo run-in, and baseline; HAMD-17 score reduction $\leq 15\%$ between placebo run-in and baseline; Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) total score <17 at screening; body mass index ≤ 35 kg/m^2 and body weight >45 kg at screening; and study medication compliance of 80%–120% during the single-blind, placebo run-in period. In addition, any patient receiving psychotherapy must have been on the same treatment for at least 3 months prior to screening and the therapy must have remained unchanged throughout the study. Women of childbearing potential were required to use adequate contraception and to have a negative serum pregnancy test at screening.

Excluded were patients judged to be a suicide risk, including those with a score of 4 on the HAMD-17 suicide item. Also excluded were patients with $>15\%$ reduction in the HAMD-17 score between screening and the baseline visit, those known to be resistant to antidepressant treatment (failed 2 previous antidepressant treatments from different classes given for at least 4 weeks) or electroconvulsive therapy, or who had electroconvulsive therapy within 1 year before screening. Patients with psychotic depression or those who had taken fluoxetine within 4 weeks prior to screening or other antidepressants within 2 weeks or 5 half-lives of the antidepressant (whichever was longer) before baseline were excluded. Patients with any other psychiatric disorder including substance use disorders were excluded. Study participants were required to be free of major clinically significant medical and/or other psychiatric illnesses. Patients with a history of significant drug or food allergy or hypersensitivity were excluded.

2.3. Outcome measures

The primary efficacy outcome was the change in the total score on the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) from baseline to the end of treatment. Rater training on the MADRS was provided to all raters in this study, and only raters who completed the training and qualification program were allowed to conduct MADRS assessments. Other efficacy outcomes included HAMD-17 total score and individual subscales; the Clinician's Global Impression of Change – Improvement score (CGI-I) and Severity score (CGI-S; Guy, 1976); and an anhedonia factor, based on MADRS items 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel). Response was defined as $\geq 50\%$ reduction (improvement) from baseline on the MADRS or HAMD-17 total score, or a CGI-I score ≤ 2. Remission was defined as MADRS ≤ 12, HAMD-17 ≤ 7, or CGI-S ≤ 2. HAMD-17 assessments were conducted via an Interactive Voice Response System (IVRS) at the study site.

Safety and tolerability assessments included treatment-emergent adverse events based on the classification of the Medical Dictionary for Regulatory Activities (MedDRA), discontinuations due to adverse events, vital signs, laboratory evaluations, and electrocardiograms (ECGs). The Derogatis Interview for Sexual Functioning – Self Report (DISF-SR) was administered at baseline and at weeks 2, 4, and 6 (Derogatis and Melisaratos, 1979).

2.4. Statistical analysis

The modified intent-to-treat (MITT) population was defined as all randomized patients with any confirmed dosing and MADRS data from at least one post-baseline visit. The safety population comprised all randomized patients who received study drug. Comparisons between treatment groups based on MADRS (the primary efficacy parameter), HAMD-17, anhedonia, DISF-SR, CGI-I, and CGI-S scores were analyzed using a mixed-model repeated measures (MMRM) analysis model including factors for patient, visit, treatment arm, and baseline value as a covariate (Mallinckrodt et al., 2003, 2007; Siddiqui et al., 2009). Results from this model are presented as adjusted least-squares means. Comparisons between groups were made at each post-baseline visit using model-based contrasts and adjusted degrees of freedom. For these analyses, no explicit data imputations were made prior to the analysis. Response and remission categorical data were analyzed using chi-square tests. Inferential analyses of safety data were conducted with analysis of covariance (ANOVA) models or chi-square tests. Two-tailed alpha was set to 0.05. All analyses were conducted using SAS version 9.2.

The planned sample size of 200 patients (100 per group) was determined based on findings of previous multicenter, placebo-controlled studies of patients with MDD with a similar study design. The power computation indicated that 100 patients per treatment group would yield a power of more than 80% to detect a difference with a 0.38 point overall difference in improvement (effect size) in the MITT population (Cohen's d) between placebo and amitifadine, which was consistent with meta-analytic estimates of the effect size from studies of antidepressants (Bech et al., 2000; Turner et al., 2008).

3. Results

The study was initiated in April 2008 and was halted by the sponsor, DOV Pharmaceuticals, early in December 2008 due to lack of funding. At the time of study termination, 63 patients had been randomized, and 61 had received study drug (Table 1). The Safety population ($n = 61$) included 33 amitifadine-treated patients and 28 placebo-treated patients. The MITT population ($n = 56$) included 30 amitifadine-treated patients and 26 placebo-treated patients. Five patients were excluded from the MITT population because they discontinued the study before having any post-baseline MADRS assessment.

The demographic and baseline characteristics were similar between the groups for the safety populations (Table 2). The majority of patients were female and Caucasian, with an average age of approximately 49 years. At baseline, patients were considered severely depressed as evidenced by a mean MADRS score ≥ 30 and a mean HAMD-17 score ≥ 25.

Table 1
Disposition of patients.

	Number (%) of patients		
	Amitifadine	Placebo	Total
Randomized	34	29	63
Completed	16 (47.1)	17 (58.6)	33 (52.4)
Reason for discontinuation			
Adverse event	3 (8.8)	3 (10.3)	6 (9.5)
Lost to follow-up	1 (2.9)	1 (3.4)	2 (3.2)
Patient request	3 (8.8)	3 (10.3)	6 (9.5)
Protocol deviation	0	1 (3.4)	1 (1.6)
Investigator request	5 (14.7)	5 (17.3)	10 (15.9)
Therapeutic failure	2 (5.9)	0	2 (3.2)

Table 2
Demographic and baseline characteristics (Safety population).

Characteristic	Amitifadine ($n = 33$)	Placebo ($n = 28$)
Mean (SD) age, years	48.2 (9.4)	49.5 (6.9)
Gender, *n* (%)		
Male	8 (24.2)	9 (32.1)
Female	25 (75.8)	19 (67.9)
Ethnic origin, *n* (%)		
Caucasian	31 (93.9)	28 (100)
Black	1 (3.0)	0 (0.0)
Hispanic	1 (3.0)	0 (0.0)
MADRS score, mean (SD)[a]	30.6 (4.5)	32.2 (4.2)
HAMD-17 score, mean (SD)[a]	28.8 (3.8)	30.4 (4.5)
CGI-S score, mean (SD)[a]	4.5 (0.5)	4.8 (0.8)
Anhedonia factor score, mean (SD)[a,b]	12.7 (2.1)	13.7 (1.6)

SD = Standard deviation.
[a] MITT population ($n = 56$).
[b] Anhedonia factor score = MADRS items 1, 2, 6, 7 and 8.

3.1. Efficacy

For the primary outcome measure, treatment with amitifadine was associated with a significantly ($p = 0.028$) greater improvement in the MADRS total score at week 6 compared with placebo (Table 3 and Fig. 1). The effect size was −0.63 (Cohen's d).

Significantly greater improvement also was observed with amitifadine compared to placebo for both the CGI-I score ($p = 0.030$) and the anhedonia factor score ($p = 0.049$) at week 6 (Table 3 and Fig. 2). A consistent trend for superiority of amitifadine was observed for the HAMD-17 and CGI-S, but the differences between treatments were not significant.

A significantly ($p = 0.038$) greater remission rate for the CGI-S was observed with amitifadine compared with placebo at week 6 (Table 4). Despite that lack of statistical significance, the proportion of patients experiencing response or remission was 2- to 3-fold greater with amitifadine than with placebo at week 6 on the MADRS. At the 1-week post-treatment assessment, the MADRS response rate was significantly ($p = 0.030$) greater and the CGI-S remission rate was significantly ($p = 0.020$) greater with amitifadine than with placebo.

3.2. Safety and tolerability

Two (6.1%) patients on amitifadine and two (7.1%) on placebo discontinued treatment due to adverse events. The two patients treated with amitifadine discontinued early due to rash. One patient treated with placebo discontinued early due to rash and another discontinued early due to nausea and palpitations. No serious adverse events or deaths were reported. A total of 43 adverse events were reported in 10 (30.3%) patients with amitifadine and 37 adverse events were reported in 11 (39.3%) patients with placebo. The most common treatment-emergent adverse event was headache occurring in 9.1% of patients with amitifadine and 10.7% with placebo. Various other adverse events occurred with an incidence of 6.1% with amitifadine and at twice the rate of placebo including diarrhea, nausea, rash, and abdominal pain (Table 5). Amitifadine was associated with small mean changes from baseline in vital signs and laboratory analytes that were not clinically significant (Table 6). A statistically significant difference ($p = 0.017$) in change from baseline in standing diastolic blood pressure was observed between amitifadine (−3 mmHg) vs. placebo (2.8 mmHg) that was not considered clinically relevant. Mean heart rate increased by 1.55 bpm with amitifadine and decreased by 1.68 bpm with placebo. Mean body weight increased a non-significant 0.078 kg with amitifadine and 0.04 kg with placebo.

DISF-SR scores were stratified by low mean baseline scores (<25, indicating significant rate of sexual dysfunction) versus high mean baseline scores (≥25, indicating satisfying rate of sexual function). In both the low baseline and high baseline groups, no significant differences were observed between amitifadine and placebo (Fig. 3).

4. Discussion

The present study is a proof-of-concept trial that assessed the treatment outcomes of amitifadine, one of a class of "serotonin-preferring" triple reuptake inhibitor" to enter clinical development in patients with major depressive disorder. Despite early termination because of a lack of funding, the results of this placebo-controlled study demonstrated that treatment with amitifadine initiated at 50 mg daily dose and titrated to 100 mg daily dose is efficacious in the treatment of patients with severe major depressive disorder. Amitifadine was superior to placebo for the primary endpoint and several secondary endpoints as measured by standard validated instruments. In this trial, the difference between amitifadine and placebo for mean change from baseline in MADRS score was 3.8, which was higher than mean changes of 3.0–3.25 reported in meta-analyses of randomized clinical trials with SSRIs (Kennedy et al., 2006; Taylor et al., 2006). Another approach to comparing results between studies is the effect size. An extensive review and meta-analysis of data from antidepressant clinical trials submitted to the FDA reported an overall effect size of 0.32 for active drug vs. placebo, which varied from 0.37 for published studies to 0.15 for unpublished studies (Turner et al., 2008). The treatment difference on the primary endpoint, MADRS total score, demonstrated a much more robust effect size of −0.601 (Cohen's d), which is about double that of the average −0.32 effect size achieved with standard antidepressant drugs (Turner and Rosenthal, 2008; Bech et al., 2000). An analysis of depression by baseline severity reported an effect size of 0.47 among patients with very severe depression (HAMD-17 ≥ 23) compared with effect sizes of 0.11 and 0.17 for less severe depression (Fournier et al., 2010). Both the effect size and NNT estimates support a strong antidepressant signal with

Table 3
Least square adjusted means with differences in primary and secondary efficacy measures at week 6 (MITT population).

Measure	Least squares adjusted mean (Standard error)					
	Amitifadine ($n = 30$)	Placebo ($n = 26$)	Difference (95% CI)	*P*-value	Effect Size	Number needed to treat
MADRS	18.2 (1.21)	22.0 (1.24)	3.8 (0.41, 7.26)	0.028	−0.601	5.42
HAMD-17	14.9 (1.40)	18.0 (1.46)	3.1 (−0.87, 7.12)	0.125	−0.421	6.82
Anhedonia factor	7.9 (0.50)	9.3 (0.50)	1.4 (0.01, 2.82)	0.049	−0.542	NA
CGI-I	2.1 (0.20)	2.8 (0.20)	0.6 (0.06, 1.18)	0.030	−0.593	NA
CGI-S	3.3 (0.15)	3.5 (0.15)	0.2 (−0.21, 0.66)	0.306	−0.280	NA

CI = confidence interval; NA = not available
Statistical analysis using mixed-measure repeated model (MMRM) analysis.

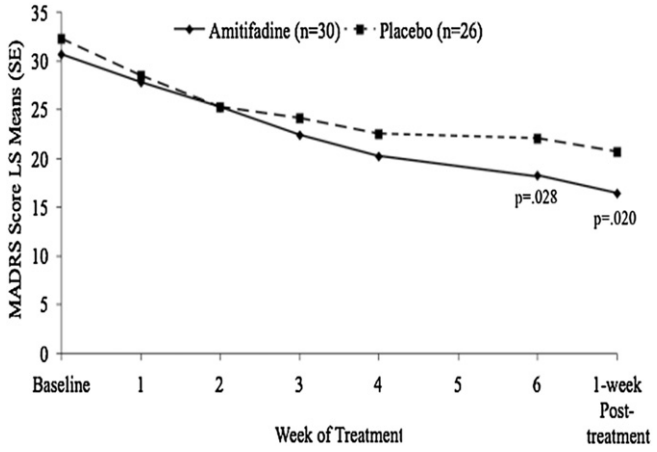

Fig. 1. Weekly MADRS total scores, mixed-model repeated measures, least squares means (MITT population, $n = 56$).

the amitifadine 100 mg daily dose and suggest that it is well within the therapeutic dose range. Therefore, further dosing levels, especially lower doses, should be studied.

In addition to the overall treatment effect, several secondary exploratory hypotheses were evaluated including effects on anhedonia based on a MADRS anhedonia factor score. The design feature of this early clinical study with amitifadine incorporated a forced dose titration during the first two weeks of therapy, which made it difficult to evaluate the effect of a 50 mg daily dose of amitifadine. More importantly, this design prevented a proper evaluation of onset of action of the 100 mg daily dose due to confounding from the low initial dose during the first two weeks of treatment. However, the evaluation of onset of action will become more important in future studies, especially as the optimal therapeutic dosing regimen with amitifadine is elucidated.

Patients with major depressive disorder often suffer from loss of interest in pleasurable activities, commonly described as anhedonia, which has been identified as a core symptom of depression (Dichter, 2010). Researchers have identified a group of symptoms, termed the anhedonia factor, which are extracted from the MADRS and have been shown to be sensitive to change with treatment (Hammond, 1998; Parker et al., 2003). A factor analysis in several cohorts of depressed patients from clinical trials has established the validity of the anhedonia factor in patients with major depression (Hammond, 1998; Parker et al., 2003; Gabryelewicz et al., 2004).

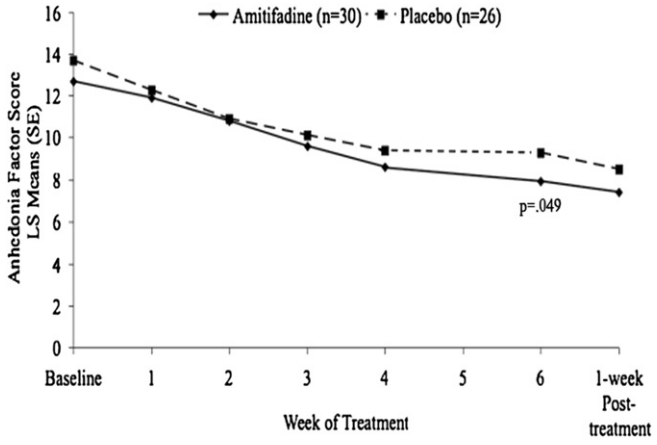

Fig. 2. Weekly anhedonia factor scores, mixed-model repeated measures, least squares means (MITT population, $n = 56$).

Table 4
Response and remission rates LOCF (MITT population).

Outcome	Week 6			1-week post-treatment		
	Amitifadine ($n = 30$)	Placebo ($n = 26$)	P-value[a]	Amitifadine ($n = 30$)	Placebo ($n = 26$)	P-value[a]
Response[b]						
MADRS	9 (30.0)	3 (11.5)	0.093	11 (36.7)	3 (11.5)	0.030
HAMD-17	14 (46.7)	8 (32.0)	0.269	15 (50.0)	8 (32.0)	0.178
CGI-I	16 (53.3)	14 (53.9)	0.969	17 (56.7)	14 (53.9)	0.832
Remission[c]						
MADRS	6 (20.0)	2 (7.7)	0.189	8 (26.7)	2 (7.7)	0.065
HAMD-17	5 (16.7)	4 (16.0)	0.947	7 (23.3)	3 (12.0)	0.278
CGI-S	7 (23.3)	1 (3.9)	0.038	8 (26.7)	1 (3.9)	0.020

LOCF = last observation carried forward.
[a] Chi-square test.
[b] Response was defined as ≥50% reduction (improvement) from baseline on the total score on the MADRS or HAMD-17, or CGI-I score ≤ 2.
[c] Remission was defined as MADRS ≤ 12, HAMD-17 ≤ 7, or CGI-S ≤ 2.

The analysis of the anhedonia factor score shows that amitifadine is efficacious in improving a core domain of affective deficit that is presumed to be related to a hypodopaminergia (Dichter, 2010; Perović et al., 2010; Millan, 2009). These results support the hypothesis that broad spectrum antidepressants are useful in treating a wider range of symptom domains in depression than mono- or dual-acting antidepressants, in particular the questionable efficacy of SSRIs in patients with anhedonia (Shelton and Tomarken, 2001; Nutt et al., 2007; McCabe et al., 2010). Other triple reuptake inhibitors have failed to demonstrate antidepressant efficacy in clinical trials. It can be hypothesized that the positive results obtained with amitifadine in this trial are a function of the unbalanced effects on reuptake inhibition with amitifadine, which is in contrast to the balanced effect on all 3 neurotransmitters with earlier failed drugs such as GSK372475.

Despite the modest sample size of this proof-of-concept study, the adverse event profile of amitifadine was similar to that of placebo, suggesting that amitifadine 100 mg daily was well-tolerated. As predicted (Skolnick, 2005), treatment with amitifadine was not associated with changes in sexual function. Of most interest, patients who had preserved sexual functions at baseline did not experience worsening in their sexual function. This is an important feature of amitifadine since sexual dysfunction has been reported with many existing antidepressants and sexual dysfunction is a cause of non-compliance and early treatment failure (Clayton et al., 2002; Montejo et al., 2001; Williams et al., 2006; Serretti and Chiesa, 2011). It is well described that increased dopamine levels in the medial preoptic area are necessary for sexual motivation and facilitate sexual behavior, while dopamine antagonists are associated with erectile dysfunction (Rotenberg, 2010; Serretti and Chiesa, 2009). The mechanism is uncertain, but

Table 5
Treatment-emergent adverse events occurring in ≥5% of EB-1010-treated patients or at least twice the rate of placebo (Safety population).

	Number (%) of patients	
	Amitifadine ($n = 33$)	Placebo ($n = 28$)
Headache	3 (9.1)	3 (10.7)
Abdominal pain	2 (6.1)	1 (3.6)
Anxiety	2 (6.1)	1 (3.6)
Diarrhea	2 (6.1)	1 (3.6)
Irritability	2 (6.1)	1 (3.6)
Nausea	2 (6.1)	1 (3.6)
Rash	2 (6.1)	1 (3.6)
Upper respiratory tract infection	2 (6.1)	1 (3.6)
Emotional disturbance	2 (6.1)	0 (0.0)

Table 6
Changes from baseline in selected vital signs and laboratory values at Week 6 (Safety population).

Assessment, Units	Mean (SD) change		P-value[a]
	Amitifadine ($n = 33$)	Placebo ($n = 28$)	
Supine systolic blood pressure, mm Hg	2.58 (9.19)	2.28 (9.39)	0.904
Supine diastolic blood pressure, mm Hg	−0.38 (7.10)	−0.48 (7.90)	0.961
Standing systolic blood pressure, mm Hg	0.069 (9.75)	2.12 (12.86)	0.509
Standing diastolic blood pressure, mm Hg	−3.00 (8.03)	2.80 (9.23)	0.017
Supine pulse, beats per minute	1.55 (7.94)	−1.68 (8.08)	0.145
Weight, kg	0.078 (2.80)	0.04 (2.5)	0.965
Total cholesterol fasting, mg/dL	−5.86 (24.67)	−11.36 (23.66)	0.412
LDL cholesterol fasting, mg/dL	−4.29 (22.43)	−9.96 (23.65)	0.374
Triglycerides fasting, mg/dL	−12.00 (39.61)	−7.80 (55.41)	0.750

SD = standard deviation.
[a] *P* values were calculated using analysis of variance with treatment group as main effect.

appears to be related to increased activation of 5-HT_2 receptors in response to increased 5-HT signaling (Clayton and Montejo, 2006; Serretti and Chiesa, 2009). Another notable finding is that although this was a short-term study and was not designed specifically to assess the effects of amitifadine on weight, amitifadine was not associated with any weight changes. A trial of longer duration with more subjects will be required to more fully address the issue of weight changes with amitifadine. Weight changes, especially weight gain, are unwanted side effects of many antidepressants and may contribute to co-morbidities and non-adherence to treatment regimens (Fava, 2000; Serretti and Mandelli, 2010). Dopamine activity is known to suppress feeding activity and produce anorexant effects in animal models (Axel et al., 2010).

Amitifadine 100 mg daily dose was associated with a small increase in mean heart rate but no change in blood pressure was observed. The mean heart rate increase of 1.5 beats/minute suggests that the 100 mg daily dose is within the physiologic range, and this pharmacodynamic effect is probably related to the known pharmacologic effect of amitifadine on norepinephrine reuptake, which in turn activates noradrenergic receptors in the heart (Thase et al., 2005; Roose and Miyazaki, 2005).

This proof-of-concept trial with amitifadine in patients with severe major depression demonstrated significant antidepressant activity and attenuated symptoms of anhedonia. This robust efficacy with amitifadine was combined with a tolerability profile that was similar to that of placebo. Thus, the efficacy and tolerability of amitifadine warrant additional clinical trials among patients with major depressive disorder to further elucidate its therapeutic profile.

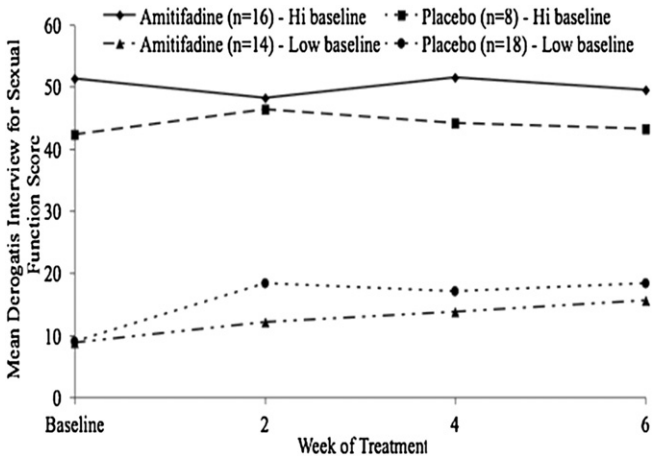

Fig. 3. DISF-SR scores stratified by visit and baseline sexual function, last observation carried forward (MITT population; $n = 56$).

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The original funding for the conduct of this study was provided by DOV Pharmaceuticals, and DOV Pharmaceuticals managed data collection. Euthymics Bioscience Inc. was involved in analysis and interpretation of the data. All authors had full access to the data and were involved in writing and revisions to this paper and in the decision to submit the final paper for publication.

Contributors

Pierre Tran wrote the first draft of the manuscript. Phil Skolnick was involved in the design and review of the analysis. Phil Skolnick, Pal Czobor, and N.Y. Huang were involved with the design of the original study. Mark Bradshaw undertook the statistical analysis. All authors contributed to and approved the final manuscript prior to submission.

Conflict of interest

Mark Bradshaw is compensated as an independent statistical consultant to Euthymics Bioscience Inc. He is neither a shareholder nor an employee of Euthymics Bioscience Inc.

Pál Czobor was a DOV Pharmaceutical, Inc. employee during the conduct of the study. He is neither a shareholder nor an employee of Euthymics Bioscience Inc.

Maurizio Fava is an independent consultant to Euthymics Bioscience Inc. He is neither a shareholder nor an employee of Euthymics Bioscience Inc.

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Equity holdings: Compellis.

Royalty/patent, other income: Patent for Sequential Parallel Comparison Design (SPCD) and patent application for a combination of azapirones and bupropion in Major Depressive Disorder (MDD), copyright royalties for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), and SAFER. Patent for research and licensing of SPCD with RCT Logic; Lippincott, Williams & Wilkins; World Scientific Publishing Co. Pte.Ltd.

Norman Huang was a DOV Pharmaceutical Inc. employee during the conduct of the study. He is neither a shareholder nor an employee of Euthymics Bioscience Inc.

Anthony McKinney is a co-founder and a shareholder and employee of Euthymics Bioscience Inc.

Phil Skolnick was a DOV Pharmaceutical Inc. employee during the conduct of the study. He is neither a shareholder nor an employee of Euthymics Bioscience Inc.

Pierre Tran is a shareholder and employee of Euthymics Bioscience Inc.

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