RESEARCH ARTICLE

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Potential Role of Bupropion Sustained Release for Cancer-Related Fatigue: a Double-Blind, Placebo-Controlled Study

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Abstract

Background: Cancer-related fatigue (CRF) is very common and can be experienced at all stages of disease and in survivors. CRF causes patients more distress than pain or nausea and vomiting. Different pharmacologic interventions have been evaluated for the management of CRF. The purpose of this study was to determine the efficacy of bupropion sustained release (SR) as a treatment for fatigue in patients with cancer. **Methods:** In this randomized, double-blind, placebo-controlled trial, patients with fatigue due to cancer were randomly assigned to either 150mg daily of bupropion SR or matching placebo. The primary endpoint was the changes in average daily fatigue from baseline to week 4 using the Functional Assessment of Chronic Illness-therapy- Fatigue (FACIT-F) questionnaire. **Results:** 40 patients were randomly assigned to treatment with bupropion SR or placebo (20 in each group). Analysis of covariance (ANCOVA) showed a significant improvement in fatigue and quality of life in the bupropion group compared to baseline (P=0.000). Secondary outcome, including depression, severity of fatigue and performance status didn't show significant difference between groups. Generally, bupropion SR was tolerated well. **Conclusion:** Four weeks of 150 mg bupropion SR improve fatigue significantly in cancer patients. Bupropion has potential as an effective and safe pharmaceutical agent for treating CRF.

Keywords: Fatigue- cancer- Bupropion- clinical trial

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Introduction

Cancer-related fatigue (CRF) is one of the most common symptoms experienced by cancer patients. Clinical trials reported a prevalence of 70% to 80% for fatigue, which is varied according to the type of cancer, treatments and method of assessments (Fatigoni et al., 2015; Gerber, 2017). CRF is defined by National Comprehensive Cancer Network (NCCN) as a "distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is proportional to recent activity and interferes with usual functioning" (Berger et al., 2015). As defined, CRF adversely affects a person's emotional, physical, mental well-being and quality of life (QOL) (Bower, 2014).

Although the underlying mechanisms for CRF have not been fully elucidated, some evidence supports underlying metabolic, cytokine, neurophysiologic, and endocrine changes associated with CRF (Saligan et al., 2015). Elevations in levels of proinflammatory cytokines, 5-hydroxytryptophan (5-HT) dysregulation, hypothalamic-pituitary-adrenal axis dysfunction, circulation-rhythm disturbances and increased vagal tone proposed as current hypotheses about the etiology of CRF (Bower and Lamkin, 2013; Filler and Saligan, 2016). Regarding the multifunctional nature of fatigue, the NCCN guideline, recommend that the clinical evaluation of fatigue considers changes in disease status along with pain, emotional distress, anemia, sleep disturbance, nutrition deficits, decreased functional status, medications/side effects, and comorbidities, including alcohol and substance abuse (Berger et al., 2015).

For the management of CRF, initial efforts should be focused to correct potential etiologies, if possible and appropriate. Strong and consistent evidence suggests that non pharmacological interventions such as psychoeducation, cognitive-behavioral therapies, mind fullness-based stress reduction (MBSR), yoga, Wisconsin ginseng, rehabilitation and relaxation are effective for fatigue (Finnegan-John et al., 2013; Pearson et al., 2016; Mustian et al., 2017). More than 40 meta-analyses or systematic reviews of clinical trials have confirmed the effectiveness of physical activity/exercise to improve fatigue outcome. A Cochrane meta-analysis of drug therapy for management of CRF (including 27 trials and 6,746 participants) showed that both methylphenidate (Z=2.4; P: 0.02) and erythropoietin (Z=2.67; P: 0.008)

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had small effect but significant improvement in fatigue over placebo. Paroxetine and progestational steroids demonstrated no superiority over placebo in treating CRF (Minton et al., 2010). The 2015 NCCN guideline recommends psychostimulants (methylphenidate or modafinil) after ruling out other causes of fatigue, as pharmacological intervention for CRF (Berger et al., 2015).

Bupropion is the only antidepressant available with a dual effect on norepinephrine (NE) and dopamine (DA) neurotransmitter systems, therefore shares actions with psychostimulants (Stahl et al., 2004). The safety of bupropion in humans has been extensively studied. Bupropion has been used to treat attention-deficit hyperactivity disorder in adults and children and to increase the functional status of patients with depression. It has also been used to treat chronic fatigue syndrome, antidepressant-induced fatigue, and fatigue associated with multiple sclerosis. The psychostimulant profile of bupropion, unique mode of action and the low-risk of abuse, making it suitable for treatment of CRF (Fava et al., 2005; Furukawa et al., 2014; Patel et al., 2016). Based on a case series (Cullum et al., 2004) it was hypothesized that bupropion would improve symptoms of depression and fatigue (Cullum et al., 2004). Moss et al., (2004) in an open-label study reported that bupropion sustained release (SR) in the range of 100-300 mg per day for 4 weeks, improve fatigue and depressive symptoms in cancer patients (N=21).

To further explore these observations and regarding the possible effectiveness of bupropion, we conducted a randomized, double-blind, placebo-controlled trial in patients with cancer and fatigue.

The primary objective of this study was to investigate the effects of bupropion SR on fatigue in a heterogeneous group of cancer patients. Our secondary objectives were to examine the effects of bupropion SR on patient quality of life and depression score.

Materials and Methods

We conducted a randomized, double-blind, placebo-controlled clinical trial to examine the effect of bupropion SR on fatigue in a heterogeneous group of cancer patients. Eligibility criteria including, being at least 18 years old, having a diagnosis of cancer with survival expectancy greater than 6 months, having a cancer-related fatigue as defined by a score 4 or more on brief fatigue inventory (BFI) (Shahid et al., 2011) screening scale that range from zero (none) to 10 (as bad as it can be), and hemoglobin ≥9g/dl taken ≤ 4 weeks before enrollment. The exclusion criteria were karnofsky performance scale of ≤50, history of convulsive seizure, current use (within 6 weeks preceding participation) of erythropoietin, psychostimulants or antidepressants, brain metastasis, unable to refer for clinic visit every two weeks, history of fatigue prior to cancer diagnosis, any medical cause for fatigue identified on screening tests or a review of systems, hypersensitivity to bupropion and illiteracy. The study protocol was approved by the ethic committee of Isfahan University of Medical Sciences (IUMS). The informed consent was obtained from all patients. The trial was registered at IRCT (Iranian registry of clinical trial) with the code number of IRCT201706191497N7.

The subjects were screened for diabetes (fasting blood sugar), thyroid disease (serum thyroid stimulating hormone), anemia (complete blood count), liver function abnormalities, and adrenal dysfunction (24 h urine cortisol). They were excluded if they had a history of seizures and were not taking anticonvulsant medication, medical cases for fatigue (see above), or had a rheumatologic condition, e.g. arthritis, fibromyalgia, or chronic fatigue syndrome.

Random assignment

Eligible patients were randomized into two groups. A research coordinator conducted the randomization and delivered the study drug and placebo. The participants and investigators blinded to the treatment assignment. A list of random numbers generated by a research coordinator. Eligible participants randomly assigned 1:1 to either the treatment group or the control group in accordance with the predefined randomization list with a block size of four.

Treatment protocol

Eligible patients were randomly assigned to receive 150 mg of bupropion SR (Abidi, Tehran, Iran) tablet or placebo once daily for 4 weeks. The tablet shapes and packaging of the placebo were identical to those of bupropion pills. Both tablets were advised to be taken in the morning. Investigator evaluated drug compliance by counting pills and participants with less than 80% compliance removed from the study.

Outcome measures

The primary outcome variable was defined as the improvement in fatigue (measured by the functional assessment of chronic illness therapy-fatigue (FACIT-F) questionnaires) which was assessed at baseline and after 4 weeks of bupropion SR or placebo supplementation. The questionnaires were fulfilled by the investigator at baseline and after 4 weeks. FACIT-F is a 13-items scale where lower scores correspond to worse fatigue (Tennant, 2015). Brief fatigue inventory (BFI) was used for initial screening.

Secondary outcome variables were the quality of life (measured by QLQ-C 30 questionnaire) and depression (measured by Hamilton depression rating scale) which was assessed at baseline and after 4 weeks of bupropion SR or placebo supplementation. The EORTC QLQ-C 30 (European organization for research and treatment of cancer quality of life questionnaire) is a 30-item quality of life questionnaire and composed of both multi item scales and single-item measures. The QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / quality of life scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease. All of the scales and single-item measures range in score from 0-100. A high scale score represents a higher

response level (Sprangers and Bonnetain, 2014).

The Hamilton-depression rating scale-17 items (HDRS) (Zimmerman et al., 2013) is a structured interview that assesses the 17 items HDRS, in order to ensure that the items are addressed consistently. Scores above 17 are indicative of at least moderate depression. Internal consistency of the above measures, as indicated by Cronbach alpha coefficients, ranged from alpha=0.85 to 0.96.

Statistical analysis

Analysis of the primary and secondary efficacy measures was performed by an analysis of covariance (ANCOVA) summary statistic approach as suggested by Frison and Pocock (Frison and Pocock, 1992). The method consists in averaging the post-treatment values on each patient and then using this as a dependent variable in an ANCOVA model with baseline fatigue data as covariate. Fisher's exact test was used to assess the relationship between categorical covariates/responses. All reported p-value were two-sided. P value of 0.05 or less was considered to indicate statistical significance. Analysis were performed with SPSS software version 20 (Chicago, USA).

Results

Between January 2016 and March 2017, 40 patients were enrolled in this study. More than 300 cancer patients were visited and 40 of them randomly assigned, with a ratio of 1:1.

Figure 1 reports the trial implementation profile according to the consolidated standard of reporting trials. Of 374 cancer patients who assessed for eligibility, 57 were randomly assigned (35 patients to bupropion and 22 patients to placebo) with a ratio of 1:1. Twenty patients in each group completed the 4 weeks protocol. Reason for interrupting treatment are reported in Figure 1.

Table 1 shows patient demographic and disease characteristics at baseline. There was no difference between groups for any of the factors and characteristics.

Fatigue improved in patients taking bupropion SR than for patients receiving placebo significantly (ANCOVA, P: 0.000, Table 2). Cronbach alpha values for the FACIT-F at each visit was greater than 0.92 and were very similar between treatment arms (data not shown). Thus the FACIT-F seems to be a reliable measure of fatigue in this patient population.

Comparisons of secondary objectives (QOL and depression) are shown in Table 2. Significant improvement was noted in the functional, symptoms and global quality of life domain (P<0.001). No significant improvement was found for level of depression. Only 3 patients of the bupropion group deemed depressed according to HDRS scores (using a cut-off score of ≥17 as an indicator of depression). 15 subjects in each group were severely fatigued according to the proposed cut-off of seven or greater for severe fatigue (BFI).

A post hoc analysis comparing the effect of bupropion on patients with severe fatigue and depression did not show significant difference. By assuming the type of cancer (solid or non-solid) and depression as covariate, there was no significant difference between both arms of the study (P: 0.5). Performance status did not show significant change when the two arms were compared (P: 0.2).

Two patients in the bupropion group and two in the placebo group discontinued treatment due to adverse events (Table 3). The events were not particularly significant in any of the patients. The rate of adverse events didn't differ by treatment arm (P: 0.11).

Table 1. Patient Characteristics and Disease Characteristics at Baseline

Characteristics	Bupropion (N=20)		Placebo (N=20)		P value
	No	%	No	%	
Age (mean ± SD) (range)	46.8±13.7 (25-85)		55.2±17.6 (24-72)		0.09
Sex					
Male	12	60	10	50	0.4
Female	8	40	10	50	
BFI score	7.8±1.1		7.4±0.8		0.3
Karnofsky performance status score					
40	0	-	0	-	
50	2	10	1	5	
60	11	55	9	45	0.7
70	8	40	5	25	
80	2	10	2	10	
90	0	-	0	-	
100	0	-	0	-	
Primary tumor site					
Solid					
Breast	4	20	4	5	
Lung	1	5	0	-	
Colon	2	10	2	10	
Pancreas	2	10	0	-	
Ovarian	0	-	2	10	
Liver	0		1	5	
Hematologic		-			
CML	1	5	0	-	0.3
MM	1	5	2	10	
Hodgkin	1	5	2	10	
Non-Hodgkin	0	-	1	5	
CLL	1	5	2	10	
Mantle	1	5	0	-	
ALL	0	-	2	10	
AML-M3	0	-	1	5	
Lymphoma	0	-	2	10	
other	2	10	0	-	
Diagnosis					
Solid	6	30	4	20	0.2
Non-solid	13	70	1	80	
Hemoglobin (g/dl)	10.9±1.7		10.1±2.2		0.2

AML, Acute myeloid leukemia; ALL, acute lymphoblastic leukemia; BFI, brief fatigue inventory; CML, Chronic Myeloid Leukemia; CLL, Chronic lymphocytic leukemia; MM,multiple myeloma.

Table 2. Effect of Bupropion on the Fatigue and Quality of Life Scores from Baseline to Week 4

Variables	Week 0	Week 4	P value (ANCOVA)
Fatigue (FACIT-F)			
Bupropion	45.6 ± 9.9	52.6 ± 10.9	0.000
Placebo	51.6 ± 10.1	52.6 ± 10.9	
QLQ-F (Function)			
Bupropion	47.9 ± 13.6	54.2 ± 12.4	0.000
Placebo	52.5 ± 11.8	52.5 ± 11.5	
QLQ-S (Symptom)			
Bupropion	45.5 ± 10.5	40.4 ± 11.4	0.004
Placebo	36.5 ± 12.6	36.7 ± 12.5	
QLQ-G (Global)			
Bupropion	30.8 ± 16.1	48.5 ± 16.2	0.001
Placebo	36.7 ± 17.1	39.2 ± 18	
Depression (HRSD)			
Bupropion	12.5 ± 4.2	11.7 ± 3.8	0.07
Placebo	10.1 ± 2.9	10.2 ± 2.8	
Karnofsky performance status score			
Bupropion	63.5 ± 8.1	65.5 ± 7.5	0.22
Placebo	65.5 ± 2.9	66 ± 7.5	
Drug days	28.6 ± 1.8	29 ± 1.6	0.5
Diagnosis (fatigue score)			
Solid	48.3 ± 10.7	52.5 ± 11	0.61
Non-solid	49.8 ± 9.9	53.9 ± 8.8	0.62

ANCOVA, analysis of covariance; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HRSD, Hamilton Rating Scale for Depression; QLQ, quality of life questionnaire

Discussion

In this randomized, double-blind, placebo-controlled study, we observed that bupropion SR 150 mg once daily supplementation for 4 weeks showed significant improvement in fatigue and quality of life score compared with baseline score and placebo arm. Adjustment of scores with fatigue severity, depression and type of cancer showed these variables didn't moderate the effect of treatment on the fatigue score. However, we should consider that the small sample size makes it difficult to establish a strong relationship between use of bupropion and fatigue improvement. Additionally, the course of treatment was only four weeks, which is a short interval to reach to final decision. However, Cullum et al., (2004) reported that response to bupropion SR was frequently seen early in treatment. Improvement of fatigue in our study confirm the finding of their study. Further improvement may have emerged with a longer treatment time and longitudinal follow-up evaluations. Moss et al., (2006) investigated the effect of bupropion SR on fatigue in a case series of 21 cancer patients with moderate to severe fatigue. The duration of follow-up was 4 weeks in their study and the dose of the bupropion range of 100-300 mg/day. Significant improvement was found for symptoms of fatigue and depression. In sub-group analysis, depressed subjects didn't experience any change in quality of life, however, the non-depressed subjects reported improvement. Although the small sample size and lack of placebo effect limits the generalizability of their findings, but our double-blind, randomized and placebo-controlled trial support the potential role of bupropion for treating of cancer related fatigue. This drug is safe and well-tolerated and seizures didn't occur during our study.

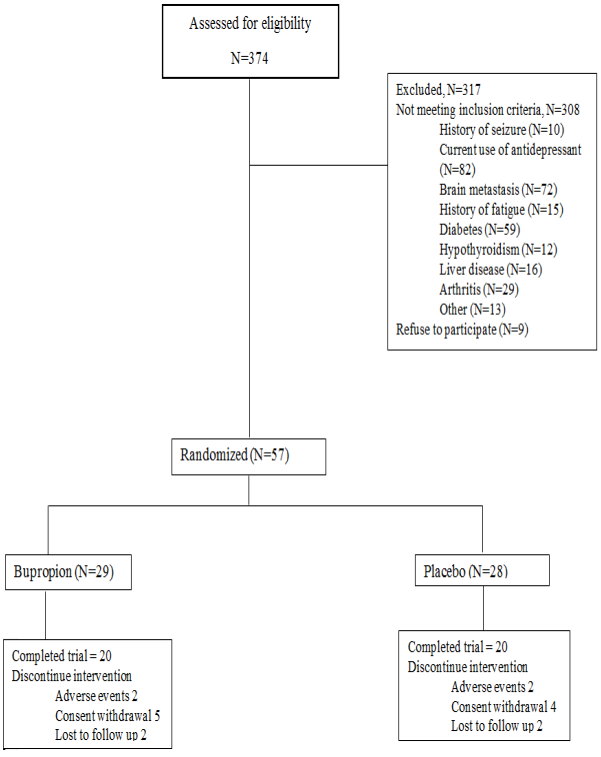

Figure 1. Progress Through the Stage of Trial

Table 3. Reported Adverse Events

Toxicity type	Bupropion (N=20)	Placebo (N=20)	P value*
Anorexia	3	0	
Constipation	1	0	
Nausea/vomiting	5	1	
Abdominal pain	1	2	
Dizziness	0	1	
Insomnia	1	0	0.11
Agitation	1	2	
Delirium	0	1	
Malaise	1	1	
Back pain	1	0	
Total	14	8	

* The p value indicate the difference of frequency of adverse events between treatment arms of the study

In Cullum et al., (2004) study, 15 cancer patients with fatigue were treated with bupropion SR for up to 2 years. All subjects showed improvement within 2 to 4 weeks of treatment and 10 patients were able to continue with bupropion for an extended time. Despite the limitations, this first report of the effect of bupropion SR on CRF, support the efficacy and safety of bupropion in fatigue improvement.

The non-significant difference in both group regarding depression indicated that additional or longer treatment is required in depressed patients and fatigue symptoms improved regardless of initial level of depression. Furthermore, the mechanism of bupropion effect on

cancer-related fatigue might be different from depression.

Overall, all levels of QOL (function, symptoms and global) improved significantly in our patients, which is likely a consequence of fatigue reduction. In Moss et al., (2006) study only the subject's physical quality of life was improved, the other domains (psychological and overall) didn't improve significantly. The long-term antidepressant treatment would not be expected to strongly impact these areas.

The fatigue scores didn't differ between solid and non-solid (hematologic) cancers in our study. After intervention, fatigue improved in both groups of cancer. Therefore, type of cancer is not related to severity of fatigue and didn't affect the final results of our study.

The most reported adverse effects in both groups were gastrointestinal (GI) disturbances and agitation. Three of our patients discontinued treatment because of GI adverse effects. The GI problems (e.g., nausea, vomiting and abdominal pain) have high frequency among cancer patients. We couldn't find the relationship between GI problems and bupropion. As, the GI complaint also observed in placebo group. However, those patients discontinued the treatment. Most of the patients tolerated bupropion very well. Insomnia, restlessness, seizures, or weight loss was not observed in any of the patients who were received bupropion.

The results of our study support bupropion SR treatment as a potentially effective method for treating cancer-related fatigue. Bupropion is well tolerated. It has a low potential for abuse, and it is not a controlled substance. Since, cancer-related fatigue is multifactorial, it would be important to investigate bupropion treatment in combination with non-pharmacologic approaches. Although the reported results are interesting, the present study should be regarded with some caution, due to the limited number of patients.

All in all, bupropion is effective in improving fatigue in cancer patients. Certainly better study design with a large number of patients are needed to establish the role of bupropion treatment in cancer-related fatigue.

Acknowledgments

This study was granted by the research deputy of Isfahan University of Medical Sciences. The study protocol was approved by the ethic committee of Isfahan University of Medical Sciences (IUMS). The trial was registered at IRCT (Iranian registry of clinical trial) with the code number of IRCT201706191497N7.

References

Berger AM, Mooney K, Alvarez-Perez A, et al (2015). Cancer-related fatigue, version 2.2015. *J Natl Compr Canc Netw*, **13**, 1012-39.

Bower JE (2014). Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*, **11**, 597-609.

Bower JE, Lamkin DM (2013). Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications. *Brain Behav Immun*, **30**, 48-57.

Cullum JL, Wojciechowski AE, Pelletier G, et al (2004). Bupropion sustained release treatment reduces fatigue in cancer patients. *Can J Psychiatry*, **49**, 139-44.

Fatigoni S, Fumi G, Roila F (2015). Cancer-related fatigue. *Recenti Prog Med*, **106**, 28-31.

Fava M, Rush AJ, Thase ME, et al (2005). 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry*, **7**, 106.

Filler K, Saligan LN (2016). Defining cancer-related fatigue for biomarker discovery. *Support Care Cancer*, **24**, 5-7.

Finnegan-John J, Molassiotis A, Richardson A, et al (2013). A systematic review of complementary and alternative medicine interventions for the management of cancer-related fatigue. *Integr Cancer Ther*, **12**, 276-90.

Frison L, Pocock SJ (1992). Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. *Stat Med*, **11**, 1685-704.

Furukawa TA, Ogawa Y, Takeshima N, et al (2014). Bupropion versus other antidepressive agents for depression. *The Cochrane Library*, 10.1002/14651858.CD011036.

Gerber LH (2017). Cancer-related fatigue. *Phys Med Rehab Clin*, **28**, 65-88.

Minton O, Richardson A, Sharpe M, et al (2010). Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev*, **7**, CD006704.

Moss EL, Simpson JSA, Pelletier G, et al (2006). An open-label study of the effects of bupropion SR on fatigue, depression and quality of life of mixed-site cancer patients and their partners. *Psychooncology*, **15**, 259-67.

Mustian KM, Alfano CM, Heckler C, et al (2017). Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA Oncol*, **7**, 961-8.

Patel K, Allen S, Haque MN, et al (2016). Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant. *Ther Adv Psychopharmacol*, **6**, 99-144.

Pearson E, Morris M, Stefano M, et al (2018). Interventions for cancer-related fatigue: a scoping review. *Eur J Cancer Care*, **27**, e12516.

Saligan LN, Olson K, Filler K, et al (2015). The biology of cancer-related fatigue: a review of the literature. *Supportive Care Cancer*, **23**, 2461-78.

Shahid A, Wilkinson K, Marcu S, et al (2011). Brief fatigue inventory. In 'Stop, that and one hundred other sleep scales', Eds Springer, pp 75-7

Sprangers MA, Bonnetain F (2014). EORTC QLQ-C30. Encyclopedia of quality of life and well-being research. pp 1933-5.

Stahl SM, Pradko JF, Haight BR, et al (2004). A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry*, **6**, 159.

Tennant KF (2015). Assessment of fatigue in older adults: the FACIT Fatigue Scale (version 4). *Psychosom Med*, **65**, 771-7.

Zimmerman M, Martinez JH, Young D, et al (2013). Severity classification on the Hamilton depression rating scale. *J Affect Disord*, **150**, 384-8.