Significant Treatment Effect of Bupropion in Patients With Bipolar Disorder but Similar Phase-Shifting Rate as Other Antidepressants

A Meta-Analysis Following the PRISMA Guidelines

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Abstract: Bupropion is widely used for treating bipolar disorder (BD), and especially those with depressive mood, based on its good treatment effect, safety profile, and lower risk of phase shifting. However, increasing evidence indicates that the safety of bupropion in BD patients may not be as good as previously thought.

The aim of this study was to summarize data on the treatment effect and safety profile of bupropion in the treatment of BD via a meta-analysis.

Electronic search through PubMed and ClinicalTrials.gov was performed.

The inclusion criteria were: (i) studies comparing changes in disease severity before and after bupropion treatment or articles comparing the treatment effect of bupropion in BD patients with those receiving other standard treatments; (ii) articles on clinical trials in humans. The exclusion criteria were (i) case reports/series, and (ii) nonclinical trials.

All effect sizes from 10 clinical trials were pooled using a random effects model. We examined the possible confounding variables using meta-regression and subgroup analysis.

Bupropion significantly improved the severity of disease in BD patients ($P < 0.001$), and the treatment effect was similar to other antidepressants/standard treatments ($P = 0.220$). There were no significant differences in the dropout rate ($P = 0.285$) and rate of phase shifting ($P = 0.952$) between BD patients who received bupropion and those who received other antidepressants.

We could not perform a detailed meta-analysis of every category of antidepressant, nor could we rule out the possible confounding effect of concurrent psychotropics or include all drug side effects. Furthermore, the number of studies recruited in the meta-analysis was relatively small.

Our findings reconfirm the benefits of bupropion for the treatment of bipolar depression, which are similar to those of other antidepressants. However, the rate of phase shifting with bupropion usage was not as low compared to other antidepressants as previously thought, which should serve to remind clinicians of the risk of phase shifting when prescribing bupropion to BD patients regardless of the suggestions of current clinical practice guidelines.

INTRODUCTION

Bipolar disorder (BD) is one of the most complicated psychiatric illnesses worldwide. In patients with BD, bipolar depression is one of the most problematic mood states, resulting in a higher risk of suicide, more frequent episodes, and longer duration of illness than manic/hypomanic episodes. The management of bipolar depression is complicated by the risk of phase shifting. Although several risk factors for phase shifting such as a history of previous mood swings, earlier age at onset, and poorer response to antidepressants are known, phase shifting in patients with bipolar depression still remains unpredictable.

Even though the prescription of antidepressants for patients with BD is known to be effective, their use is currently
under debate because of the possible risk of phase shifting. In previous studies, treatment with antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) has been reported to increase the risk of phase shifting in BD patients. Current case-controlled and randomized-controlled trials have revealed inconsistent findings on the benefit/harm of antidepressant treatment in BD patients. The results of a recent meta-analysis suggested that antidepressants are not statistically superior to a placebo or other current standard treatments for bipolar depression.

Bupropion has unique pharmacokinetics as a norepinephrine-dopamine reuptake inhibitor (NDRI), and it is has been approved by the Food and Drug Administration (FDA) for the treatment of major depression since 1989. In addition, increasing evidence suggests that bupropion has unique benefits in the treatment of BD because of its ability to ameliorate depressive symptoms with a lower risk of phase shifting than other antidepressants. Furthermore, it has been recommended as first-line treatment, either as monotherapy or combination therapy, in recent clinical guidelines based on its safety for BD patients and lower risk of phase shifting. However, with increasing clinical experience of the usage of bupropion, an increasing number of clinical studies have reported phase shifting in BD patients related to the use of bupropion. The safety of bupropion as monotherapy or combination therapy in the treatment of BD patients has thus attracted the attention of clinicians and prompted further research to evaluate the role of bupropion in the treatment of BD. Therefore, the aim of the present study was to summarize the current data about the role of bupropion, including the treatment effect and safety profile, in the treatment of BD via a thorough meta-analysis.

METHODS AND MATERIALS

Literature Search and Screening

We performed a systematic literature search through PubMed and ClinicalTrials.gov using the search term (bipolar disorder) AND (bupropion) for all articles written in English up to January 12th, 2016. The search was conducted by 2 independent authors (P-TT and Y-WC). At the initial stage of screening, both authors screened all articles via the titles and abstracts. Inconsistent selections and disagreements were resolved by consensus. In the subsequent stage of screening for eligibility, we used the following inclusion criteria: (i) studies comparing changes in disease severity before and after bupropion treatment, either as monotherapy or combination therapy, or (b) articles comparing the treatment effect of bupropion in BD patients to other standard treatments; and (ii) articles on clinical trials in humans. The exclusion criteria were: (i) case reports/series; and (ii) nonclinical trials. The selection protocol is illustrated in Figure 1. We also assessed the quality of the clinical trials using Jadad scores (Supplementary Table 1, http://links.lww.com/MD/A834).

Data Extraction

The primary outcome was changes in disease severity rating scale, which included the Hamilton Depression Rating Scale (HAM-D), Inventory of Depressive Symptomatology (IDS), Montgomery-Åsberg Depression Rating Scale (MADRS), Schedule for Affective Disorders and Schizophrenia, version for measuring Changes in symptomology (SADS-C), and the Global Assessment of Functioning (GAF). We extracted all primary outcomes and clinical variables from all of the studies selected in the final stage. When data were not available in the articles, we attempted to contact the authors to ask for the original data. Furthermore, if multiple rating scales were used in one study, we gave preference to the HAM-D, MADRS, or IDS over the SADS-C or GAF because they are more specific to depressive symptoms. In addition, as most of the studies used the HAM-D, we gave the HAM-D first priority.

Meta-Analytic Methods and Data Extraction

In the present study, the meta-analysis consisted of 3 parts, including (a) studies comparing changes in disease severity
The treatment effect of bupropion in these BD patients significantly decreased disease severity (ESs = −0.021, 95% confidence interval [CI]: −0.033 to −0.009, P < 0.001) (Figure 2A). There was significant heterogeneity within these studies (Q = 6429.82, df = 4, F = 99.94%, P < .001). Furthermore, no significant publication bias was detected using Egger’s test (t = 1.58, df = 3, 2-tailed P = 0.211) and visual examination of the funnel plot.

Among these 5 studies, we could find out 1 outlier study by McIntyre et al 2002 57 (Figure 2A), which might influence the results of current meta-analysis. When we excluded the data of this study from the pooled analysis, the result remained significantly decreased disease severity after bupropion treatment (ESs = −0.021, 95% CI: −0.032 to −0.010, P < 0.001) with significant heterogeneity (Q = 6418.89, df = 3, F = 99.95%, P < .001). Hence the results of the study by McIntyre et al (2002) did not influence the pooled ES significantly.

We could only perform meta-regression analysis of clinical variables including mean age, female gender, duration of current treatment, and dosage of bupropion because of the limited available data. Among them, we only found significant associations between changes in disease severity and mean age (slope = 0.004, P = 0.017) but not in female gender, duration of current treatment, and dosage of bupropion (slope = 0.0003, P = 0.505; slope = 0.009, P = 0.097; slope = 0.0009, P = 0.218, respectively).

We could not perform further subgroup analysis for “bupropion monotherapy versus combination therapy,” “drug-free or not,” and “‘first episode or not’” because only a few studies used monotherapy, included subjects who were drug-free, or those with a first episode.

The Main Results of the Meta-Analysis Comparing Different Effects of Bupropion and Other Treatments in BD Patients

We then compared the different effects of bupropion and other treatments through meta-analysis. A total of 141 BD patients who received bupropion and 271 who received other treatments including idoxoan, desipramine, sertraline, venlafaxine, and topiramate, were extracted from 6 articles.3,4,13,55,57,58 We did not find any statistically significant differences in the treatment effect between the BD patients receiving bupropion and those receiving other treatments (ESs = 0.483, 95% CI: −0.288 to 1.253, P = 0.220) (Figure 2B). In addition, there was significant heterogeneity within these studies (Q = 31.98, df = 5, F = 84.37%, P < 0.001), and significant publication bias was detected using Egger’s test (t = 4.01, df = 4, 2-tailed P = 0.016).

The Main Results of the Meta-Analysis of Comparisons of Safety Profiles

With regard to the safety of bupropion, we focused on 2 specific areas: the drop-out rate and phase-shifting rate, either to a manic or hypomanic state. We did not find any statistically significant differences in the rate of phase shifting in the BD patients treated with bupropion or other treatments, including desipramine, SSRIs, SNRIs, or other antidepressants (ESs = −0.130, 95% CI: −0.367 to 0.108, P = 0.285) (Figure 3A), and there was no significant heterogeneity (Q = 9.69, df = 6, F = 38.08%, P = 0.138) or publication bias (t = 1.14, df = 5, 2-tailed P = 0.306). Furthermore, subgroup meta-analysis of the phase-shifting rate in specific categories of antidepressants revealed the same results, and there were no significant
| Study            | Diagnostic Criteria | Diagnosis Comparison | N  | Dropout Rate | Phase Shift | Gender ( % Female ) | Mean Age (y) | Severity | Primary Outcome | Study Types               | Country   |
|------------------|---------------------|----------------------|----|--------------|-------------|--------------------|--------------|----------|----------------|---------------------------|-----------|
| Sepede G (2014)  | DSM-IV-TR           | Bipolar I depression Bupropion (add-on) | 5  | 0.0          | 0.0         | 40.0               | 38.6 ± 4.4  | 20.0 ± 1.9 | HAM-D          | Prospective cohort study  | Italy     |
| Gao K (2008)     | DSM-IV              | Bipolar I/II Disorder Bupropion | 7  | 0.0          | 0.0         | 14.3               | 38.3 ± 8.4  | 19.9 ± 1.8 |                | Prospective cohort study  | USA       |
| Truman CJ (2007) | DSM-IV              | Bipolar disorder     Bupropion | n/a| n/a          | 29.5        | 62.0               | 42.1 ± 12.9 | n/a      |                | Prospective cohort study  | USA       |
| Leverich GS (2006)| DSM-IV             | Bipolar disorder     Bupropion | 50 | n/a          | 16.8        | 48.0               | 41.6 ± 11.0 | n/a      |                | Prospective cohort study  | USA       |
| Post RM (2006)   | DSM-IV              | Bipolar disorder     Bupropion | 109| 20.3        | 47.7        | 41.5 ± 12.6       |              |          |                | Prospective cohort study  | USA       |
| Wilens TE (2003) | DSM-IV              | Bipolar disorder     Bupropion (pre-post Tx) | 36 | 17.0        | n/a         | 75.0               | 34.0 ± 11.0 | 10.6 ± 7.7 | HAM-D          | Case-controlled study      | USA       |
| McIntyre RS (2002)| DSM-IV             | Bipolar I/II Disorder Bupropion + Mood stabilizer | 18 | n/a          | n/a         | 38.9               | 39.0        | 20.5      | HAM-D          | Single-blind randomized controlled study | Canada     |
| Grossman F (1999)| DSM-IV              | Bipolar I disorder   Bupropion + Mood stabilizer | 18 | 44.4        | 43.0        | 20.0               |              |          |                | Double-blind randomized controlled study | USA       |
| Goodnick PJ (1998)| DSM-III-R          | Bipolar disorder     Idazoxan | 7  | 0.0          | 57.1        | 42.2 ± 9.1        | 21.3 ± 4.0  |          |                | Prospective cohort study  | USA       |
| Sachs GS (1994)  | DSM-III-R           | Bipolar disorder     Bupropion (pre-post Tx) | 11 | 26.8        | n/a         | 61.0               | 44.9 ± 9.6  | 22.4 ± 4.7 | HAM-D          | Double-blind randomized controlled study | USA       |
|                  |                     |                      Bupropion | 8  | 0.0          | 11.0        | 75.0               | 41.6 ± 13.9 | n/a      |                | Double-blind randomized controlled study | USA       |
|                  |                     |                      Desipramine | 7  | 0.0          | 50.0        | 85.7               | 32.3 ± 14.6 |          |                |                           |           |

Data presentation: mean ± SD.

DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revision, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text-Revision, GAF = Global Assessment of Functioning, HAM-D = Hamilton Depression Rating Scales, IDS = Inventory of Depressive Symptomatology, MADRS = Montgomery–Åsberg Depression Rating Scale, n/a = not available, pre-post Tx = comparison of pre-treatment and post-treatment, SADS-C = Schedule for Affective Disorders and Schizophrenia, version for measuring Change in symptomology, SD = standard deviation, USA = United States.
differences in the rates of phase shifting in the BD patients receiving bupropion compared to those receiving SSRIs (ESs = −0.147, 95% CI: −0.538 to 0.243, P = 0.460) or SNRIs (ESs = −0.119, 95% CI: −0.420 to 0.183, P = 0.440).

There were also no significant differences in the drop-out rate between the BD patients treated with bupropion or those treated with other antidepressants (odds ratio ESs = 0.948, 95% CI: 0.168 to 5.347, P = 0.952) (Figure 3B).

**DISCUSSION**

The main findings of the current meta-analysis are the significant improvements in disease severity after bupropion treatment in BD patients. In addition, bupropion was found to exert a similar treatment effect to other treatments in BD patients. Furthermore, in addition to the safety of bupropion being similar to other antidepressants in terms of drop-out rate, the phase-shifting rate in the patients receiving bupropion was not lower than that in the patients receiving other antidepressants, as previously assumed.

Our results are consistent with previous reports about the significant benefits of bupropion for the treatment of depressive symptoms in patients with BD.10,54 Furthermore, in our meta-regression analysis, the treatment effect of bupropion in BD patients was significantly positively associated, albeit only slightly, with mean age rather than the duration of treatment or dosage of bupropion. We could not rule out the possible confounding effects of concurrently prescribed psychotropics on the treatment effect, which may have had beneficial effects on disease severity, led to unnecessary drug-drug interactions, or prevented phase shifting. In addition, our results may be affected by the small number of studies included and thus the limited amount of data available. Therefore, caution should be taken in applying our results to clinical practice.

Bipolar depression remains a troublesome affective disorder which attracts a large amount of attention due to the high risk of phase shifting to a manic/hypomanic state during the treatment of BD. At present, many review articles and clinical guidelines suggest the usage of bupropion, either as monotherapy or combination therapy, in the treatment of bipolar depression.10,11,38,54,60,61 and evidence suggests the significant benefits of bupropion treatment in such patients. Our results also support that the treatment effect of bupropion is similar to that of other antidepressants/standard treatments.

Furthermore, in order to ameliorate the disease severity of bipolar depression, some clinical guidelines suggest that bupropion be considered as the first-line of treatment in such patients.10,11 In these studies, bupropion has been reported to be safe and to carry the least risk of phase shifting among other antidepressants based on current evidence.11,38 However, an
increasing number of studies have reported their clinical experience of bupropion usage in clinical practice4,12,15,20,43,46,55 in recent years, and thus the safety of bupropion with regard to phase shifting needs to be seriously reconsidered. The present study provides up-to-date key information about the safety of bupropion in BD patients. The rate of phase shifting with bupropion use seems to be similar to other antidepressants such as desipramine, sertraline, venlafaxine, or other categories of antidepressants. This suggests that bupropion may not be as safe as previously presumed with regard to phase shifting, and therefore clinicians should pay special attention to the risk of phase shifting when prescribing bupropion for patients with bipolar disorder.

LIMITATION

There are several limitations to this study. First, we did not perform detailed subgroup meta-analysis for every category of antidepressant used in each study because of the limited available data. Second, significant publication bias was detected in the current meta-analysis. This may implicate the clinical importance of the present study. Third, we could not rule out the possible confounding effect of concurrent psychotropics, which may have benefitted disease severity, prevented phase shifting, or induced drug–drug interactions. Fourth, with regard to drug safety, we could only perform analysis on the drop-out and phase-shifting rates because of the limited available data. However, many side effects related to the usage of bupropion have been reported, including seizures and headache.62 Fifth, the number of studies recruited in the current meta-analysis was relatively small, especially in the meta-analysis of phase-shifting rate, which may limit the applicability of the results. However, the forest plot of meta-analysis of phase-shifting rate showed that the direction of most studies was in the same direction, namely “favor less phase shifting with bupropion usage.” Sixth, in the meta-analysis of treatment effect of bupropion on the disease severity, there was 1 outlier study.57 Although the results of meta-analysis remained similar after removing the outlier, there might be some confounding effects on the results of current meta-analysis. We found that the treatment duration of bupropion was higher in the study by McIntyre et al (2002) than others. In addition, the female proportion in this study was also lower than that in other studies. Although there was insignificantly positive association, the female gender proportion and the treatment duration of bupropion had some positive association with the treatment effect of bupropion. Therefore, this might be, at least partly, the cause of the discrepancy of these studies. Finally, the total duration of current treatment among the studies recruited in the current meta-analysis was relatively short, ranging from 4 to 8 weeks only.

CONCLUSION

The current meta-analysis reconfirms the benefits of bupropion in the treatment of bipolar depression and that the benefits are similar to other antidepressants. However, the phase-shifting rate with bupropion usage was not lower than that with the use of other antidepressants as previously thought despite a similar drop-out rate between the use of bupropion and
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