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Brief report

Assessing the effects of bupropion SR on mood dimensions of depression

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Abstract

Background: We assessed the therapeutic effects of bupropion SR and placebo on mood and anxiety symptoms derived from the tripartite model of mood. Based on evidence indicating linkages between dopaminergic activity and the emotional dimension of positive affect/anhedonia, we hypothesized that the dopaminergic effects of bupropion SR would yield particularly pronounced effects on symptoms of anhedonia, relative to anxiety. *Methods:* Nineteen depressed outpatients were randomly assigned to treatment with either bupropion SR 300 mg/day or placebo during a 6-week initial treatment phase. This was followed by a second open-label phase in which patients previously treated with bupropion SR had their dose increased to 400 mg/day, and the placebo group was initiated on bupropion SR 300 mg/day. *Results:* Random regression analyses revealed that during the initial double-blind phase, bupropion SR elicited greater declines than placebo on all measures except those that assessed anxiety. By contrast, the weakest placebo effects were evident on anhedonia. Items assessing the low positive affect pole of the anhedonia dimension were more sensitive to earlier/lower dose bupropion SR treatment, whereas items assessing the high positive affect pole were more sensitive to later/higher dose bupropion SR treatment. *Limitations:* Replication and extension using a larger sample size are mandated. *Conclusions:* This study suggests that the catecholaminergic effects of bupropion SR tended to produce more robust effects on anhedonia/positive affect than placebo.

Keywords: Depression; Bupropion SR; Placebo; Tripartite model; Dopamine; Anhedonia

1. Introduction

Although antidepressants are sometimes viewed as producing relatively broad effects across the component features of depression, a more recent view specifies that a given drug may produce a distinct

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profile of change across symptom dimensions (Bodkin et al., 1997; Shelton and Tomarken, 2001). We adopted this approach by assessing the effects of bupropion SR on symptoms of anhedonia and anxiety derived from the tripartite model of mood disorders (e.g., Clark and Watson, 1991). This model posits that there are symptoms that are common to both depressive and anxiety disorders and symptoms that are relatively specific to each disorder. Three higher-order dimensions have been posited and empirically derived: general distress, anhedonia/positive affect, and somatic anxiety. Symptoms of general distress are common to both affective and anxiety disorders, while symptoms of anhedonia are relatively specific to depression. Alternatively, somatic anxiety seems primarily linked to panic disorder and perhaps other types of anxiety disorders (e.g., Brown et al., 1998). Watson et al. (1995a,b) have developed and validated a self-report measure, the Mood and Anxiety Symptoms Questionnaire (MASQ), that assesses these dimensions of mood.

To our knowledge no prior studies have used the tripartite model as a vehicle for assessing treatment outcome. This omission is notable because evidence concerning the neurobiological effects of antidepressants suggest linkages to dimensions of mood that are relevant to psychopathology (Shelton and Tomarken, 2001). We investigated the effects of bupropion SR on dimensions of mood relevant to the tripartite model.

Bupropion exhibits some degree of inhibition of the norepinephrine (NE) and dopamine (DA) uptake transporters (e.g., Ascher et al., 1995) and also appears to enhance extracellular availability of both NE and DA in brain regions (Li et al., 2002; Nomikos et al., 1989). In turn, there is a variety of evidence linking decreased DA activity to decreased incentive motivation (Salamone, 1996) and anhedonia (Willner, 1983a,b,c; Wise, 1982). Conversely, increased functional DA activity has been linked to positive affect (e.g., Depue et al., 1994). Therefore, enhancement of DA activity in frontal cortex and nucleus accumbens such as that seen with antidepressants like bupropion might be expected to enhance incentive motivation, improve anhedonia, and increase positive affect (Shelton and Tomarken, 2001). As a cautionary note, we should add that evidence from infrahuman studies indicates that the mechanism of action of bupropion is more related to NE than DA (e.g., Cooper et al., 1994; Dong and Blier, 2001). Whatever the mechanism of action, in an initial study Bodkin et al. (1997) found that bupropion appeared to have more robust effects on symptoms linked to anhedonia than anxiety, while the reverse was true of serotonergic agents (for a review see Shelton and Tomarken, 2001). However, the measures used were neither well-validated nor comprehensive. Using the MASQ, we tested the hypothesis that bupropion SR would have more robust effects relative to placebo on measures of anhedonia than anxiety.

The MASQ Anhedonic Depression (AD) scales consists of items reflect both the low pole of anhedonia (e.g., low interest) and the high pole of positive affect (e.g., energetic), the latter of which is reverse-keyed. Because this bipolar scale assesses both end-points of the anhedonia/positive affect continuum, a secondary goal of the present study was to assess which poles were most sensitive to treatment effects. A final goal of this study was to assess the effects of placebo on the affective dimensions assessed by the MASQ. In a previous study, we found that placebo produced robust declines on measures of negative affect during the initial stages of treatment but no significant effects on positive affect (Tomarken et al., 1997). In the present study, we hypothesized that placebo would have more pronounced effects on generalized distress, and somatic anxiety, than on anhedonia/positive affect.

2. Method

Written informed consent was obtained from all participants. Patients were adult outpatients who met DSM-IV (American Psychiatric Association, 1994) criteria for recurrent major depression as determined by the Structured Clinical Interview for DSM-IV (First et al., 1996). Participants were recruited by advertisements placed in local newspapers. Participants (1) had scores on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D-17, Hamilton, 1960) that were greater than 17, (2) were free of psychotropic medications for at least 1 week, and (3) did not have atypical depression, psychotic disorders, bipolar disorder, a history of drug or

alcohol abuse in the previous 6 months, a history of central nervous system (CNS) disorders, antisocial, borderline, or schizotypal personality disorders. The final sample included 19 outpatients who were randomly assigned to receive either bupropion SR [$n = 10$; age range: 26.0–61.1 years, mean (S.D.) = 39.4 (9.8), six women] or matched placebo [$n = 9$; age range: 23.0–46.7 years, mean (S.D.) = 37.5 (7.8), six women] for 6 weeks (phase one; double blind). During this phase, bupropion SR was initiated at 100 mg twice per day and increased to 150 mg twice per day after 1 week. During a second 6-week period (phase two; open label), dosages were increased to 400 mg/day for patients treated with bupropion SR in phase one, while patients in the placebo group were titrated to a 300 mg/day of bupropion SR. Patient groups did not differ with respect to age, $t\ (17) = 0.46$, $P > 0.50$, or gender, $\chi^2\ (1) = 0.09$, $P > 0.75$. Below, the two groups of patients will be denoted BUP-BUP and PLA-BUP.

All measures were completed the day before onset of medication and at the completion of weeks 1, 2, 4, and 6 (phase one assessments) and of weeks 7, 8, 10 and 12 (phase two). The primary dependent measures were the 62-item version of the MASQ (Watson et al., 1995a,b), the HAM-D-17, and the Hamilton Anxiety Scale (HAM-A, Hamilton, 1959). The 62-item version of the MASQ contains four scales. Two load on the higher-order dimension of generalized distress (GD): GD depressive symptoms (GDD) and GD anxious symptoms (GDA). The Anhedonic Depression (AD) scale consists of positively keyed items indicative of the anhedonia/low positive affect pole and negatively keyed items indicative of the high positive affect pole. In addition, we assessed the Anxious Arousal (AA) scale of the MASQ.

Random regression analyses were conducted to compare the two groups on all measures (Gibbons et al., 1993). Because of the procedural differences between phases one and two (e.g., changes in medications and dosages, double-blind vs. open-label) and our interest in assessing different patterns of change during the two phases, we specified piecewise models (Bryk and Raudenbush, 1992) that allowed for different patterns of change in the two phases. For each of the two phases, we specified models that included fixed effect predictors coded to represent both linear and quadratic trends. Our models specified linear and quadratic main effects for each phase and group × linear and group × quadratic interactions for each phase. A hierarchical structure was used, in which linear coefficients were entered as a first set and quadratic coefficients were entered at a second step. SAS PROC MIXED was used for all analyses (e.g., Littell et al., 1996).

3. Results

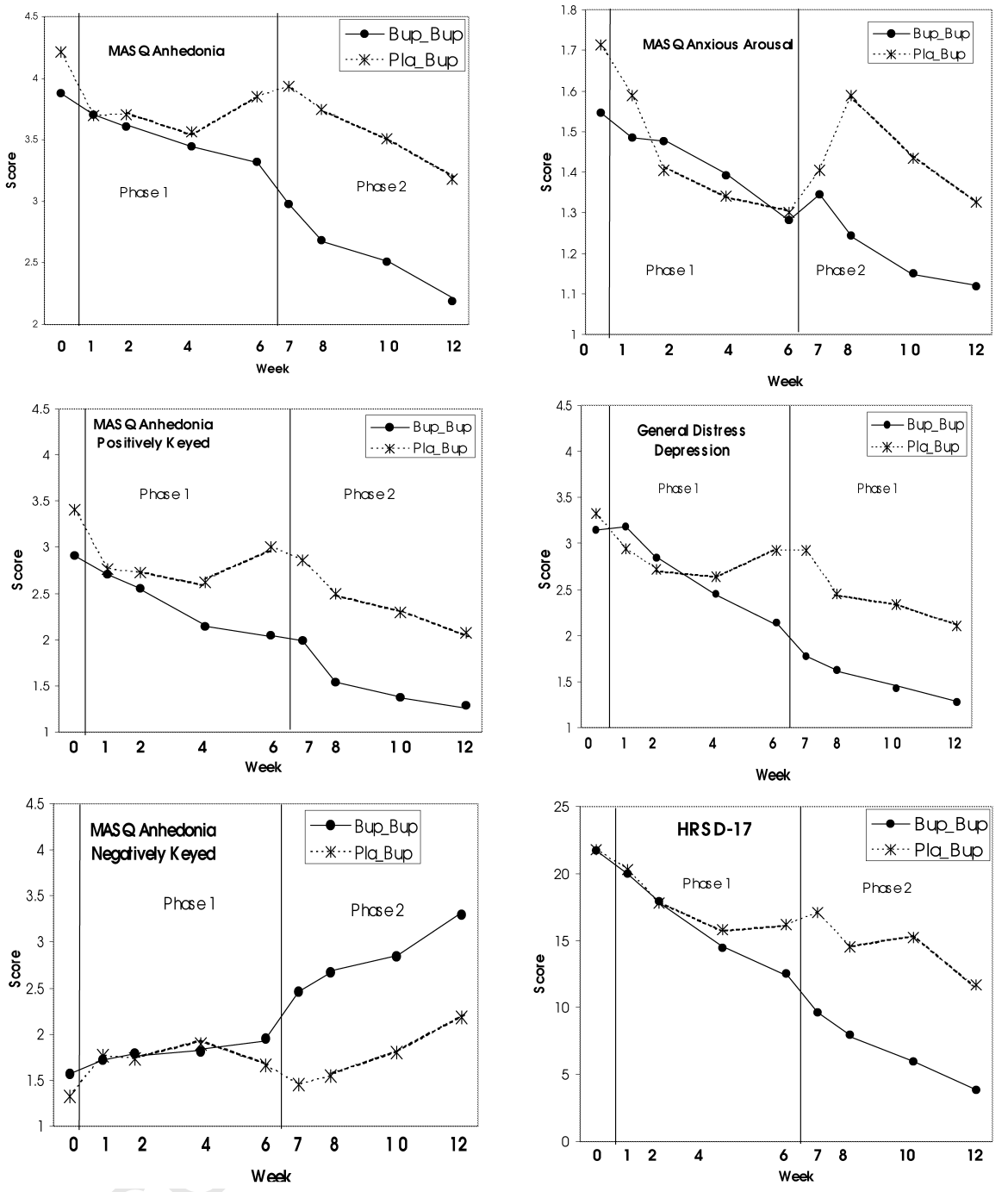
One patient in the BUP-BUP group did not complete phase one. Two additional patients in the BUP-BUP group dropped out during phase two. The random regression analyses estimated effects including all the available datapoints.

3.1. MASQ anhedonia

The left-hand column in Fig. 1 displays changes over time on the overall MASQ AD scale (top) and on the scores generated from the positively keyed items that assess the anhedonic pole (middle) and the negatively keyed items that assess the positive affect pole (bottom). Scores were expressed with a potential range of 1 to 5. Below, we report the results of the analyses across both phases but emphasize the phase one results because of the open-label context of phase two.

The overall AD results reveal a significant linear decline for the bupropion SR group in phase one while the placebo group demonstrated an initial decline followed by a return to pre-treatment levels by the end of this phase. Analyses revealed a significant group × linear interaction during phase one ($P = 0.02$) that indicated group differences in linear slopes over time. In addition, re-parameterized models that directly estimated the intercepts and slope coefficients for each group indicated a significant linear trend over the course of phase one for the bupropion SR group ($P = 0.004$) and a significant quadratic trend for the placebo group ($P = 0.021$; Fig. 1). In phase two, the piecewise analyses indicated significant linear declines across both groups ($P < 0.001$).

Analyses of the positively keyed AD items indicated a pattern that was consistent with the overall AD scale (Fig. 1). For example, the re-parameterized



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232 Fig. 1. Weekly scores on the MASQ AD (top left), MASQ AD Positively Keyed (i.e., low positive affect) Items (middle left), MASQ AD
233 Negatively Keyed (i.e., high positive affect) Items (bottom left), MASQ AA (top right), MASQ GDD (middle right), and the HAM-D-17
234 scales (bottom right). Patients in the BUP-BUP group received a moderate dose of bupropion SR (max. 300 mg/day) during phase one and
235 a higher dose (max. 400 mg/day) during phase two. Patients in the PLA-BUP group received placebo during phase one and a moderate dose
236 of bupropion SR (max. 400 mg/day) during phase two.

analyses indicated a significant linear trend for the bupropion SR group ($P = 0.0002$) and a significant quadratic trend for the placebo group ($P < 0.011$) during phase one. During phase two, overall linear declines were observed ($P = 0.03$), with no group differences.

In contrast, analyses of the negatively keyed AD items indicated significant group × linear interactions during phases one ($P = 0.045$) and two ($P = 0.05$). These effects indicate steeper linear increases in positive affective symptoms in the BUP-BUP relative to the PLA-BUP group. The higher dose of bupropion SR administered during phase two significantly increased the rate of change across time, as indicated by a significant difference between the linear coefficients of the two phases for the BUP-BUP group ($P = 0.05$). No differences in the phase one and phase two linear slopes of the BUP-BUP group were reported on any other measures that we report (P values > 0.10).

3.2. MASQ generalized distress and anxious arousal scales

During phase one, the linear decline in GDD scores was greater for the bupropion SR group than placebo (group × linear interaction $P = 0.0005$; see Fig. 1). No significant differences between groups were observed during phase two (interaction P values > 0.05), although there was a significant main effect for the linear slope ($P = 0.006$) that reflects the decline over time evident in both groups. There were no significant between-group differences on either GDA or AA during phase one (group × linear P values > 0.40, group × quadratic P values > 0.50; Fig. 1). Across groups, significant linear declines were evident on both measures during this phase (GDA $P = 0.003$, AA $P = 0.03$). On GDA, the only significant effects yielded for the phase two piecewise coefficients was an overall linear main effect ($P = 0.02$). Analyses of the phase two AA measure indicated a significant group × linear interaction ($P = 0.04$) that appears largely due to an initial increase in AA among patients who were formerly in the placebo condition and administered bupropion SR during phase two (Fig. 1).

3.3. Hamilton scales

Although linear declines were evident on the HAM-D-17 during phase one for both groups (both P values < 0.001), the rate of change was greater for the bupropion SR group than the placebo group (group × linear $P = 0.04$). Overall declines were observed across phase two (linear $P = 0.005$), with no significant between-group differences (group × linear $P > 0.30$). Over the full 12 weeks of active treatment, the BUP-BUP group achieved a very low mean HAM-D-17 score (see Fig. 1). During phase one, both groups demonstrated significant linear declines on the HAM-A (both P values < 0.001). However, the changes were not differential across groups, although a trend was evident (group × linear $P > 0.06$). Overall linear declines were observed during phase two ($P = 0.025$).

4. Discussion

In accordance with predictions, we found that, relative to placebo, bupropion SR produced a steeper decline in anhedonic symptoms during phase one. We also found effects of a similar nature on several other measures of depressive symptoms (i.e., MASQ GDD scale and the HAM-D-17). In contrast, during phase one, groups failed to differ on three measures of anxiety (MASQ GDA and AA scales and HAM-A). That both groups demonstrated significant declines in anxiety during phase one indicates that absence of between-group differences on these measure was not due to lack of sensitivity to change.

One question is whether the failure to find effects on anxiety measures during phase one reflects low power due to small sample sizes. One salient index is the proportional reduction in unexplained variability afforded by specific predictors. For each of the MASQ scales, we computed the proportional reduction in the estimated random variability of the phase one linear slopes due to the inclusion of the group × linear interaction terms (Bryk and Raudenbush, 1992). This interaction term models a difference between groups in the slopes of change during phase one. The inclusion of interaction terms produced notable reductions in the random variability of the

per-patient slopes for AD (estimated reduction in error = 38%) but failed to produce such effects for GDA and AA (effectively no reductions in variability). Thus, bupropion SR likely produced larger differences relative to placebo on measures of anhedonia than anxiety. We should note, however, that in prior controlled trials, bupropion SR has demonstrated positive results in treating symptoms of anxiety (e.g., Trivedi et al., 2001). Such effects are comparable to those of serotonergic agents and have been significantly greater than placebo. However, in these studies large sample sizes were used and effects relative to placebo were modest. On balance, the available data suggest that, relative to placebo, bupropion SR produces more robust effects on measures of anhedonia than anxiety.

A further analysis separated the negative and positive ends of the anhedonia vs. positive affect continuum. During the early phase of treatment when the dose was relatively moderate, bupropion SR appeared to produce stronger effects on the affectively negative pole (positively keyed items) than the affectively positive pole (negatively keyed items) Although group × linear interaction effects were significant on both measures during phase one, the interaction on the affectively negative scale accounted for a greater proportion of the random variability of linear slopes (45%) than the affectively positive scale (27%). Later in treatment at higher dosages of bupropion SR, effects were notably larger on the affectively positive items. Whether this effect was a result of the longer time in treatment or the higher dose of bupropion SR cannot be determined.

These findings may reflect the facts that: (a) anhedonia and high positive affect represent opposite poles of a continuum; and, (b) patients are situated at various locations on this continuum at different points in treatment. For example, patients likely enter treatment with significant anhedonia that places them on the negative end of the continuum. During the initial phase of treatment or at moderate doses, they move toward a more affectively ''neutral'' point. If so, it would be expected that treatment effects would be more evident on the negatively toned items that reflect anhedonia. At later points in time and/or higher doses, they begin to move more clearly into the affectively positive range of the continuum. If this scenario is correct, it would suggest that different ranges of the anhedonia/positive affect continuum may be optimally sensitive to treatment effects at different stages of treatment.

Our results also suggest that placebo has more robust effects on anxiety than anhedonia. The MASQ AD scale was the only measure on which he placebo group demonstrated stronger quadratic than linear effects. Such effects indicate a return to pre-treatment levels (Fig. 1) and suggest that measures of anhedonia may discriminate ''true'' pharmacological effects of antidepressants better than measures of anxiety. Overall, our results indicate that bupropion SR is an effective antidepressant with more robust effects on anhedonia than anxiety. Placebo response appears to be more significantly evident on measures of anxiety than anhedonia. These findings would appear to mandate replication in a larger-scale study.

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