

## The Role of Bupropion in the Management of Major Depressive Disorder

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**Abstract:** Bupropion is an antidepressant of the aminoketone class that is chemically unrelated to any other known antidepressant agent. In the treatment of major depressive disorder (MDD), bupropion has shown comparable therapeutic efficacy to selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). Bupropion effectiveness in treating co-morbid fatigue, hypersomnia, anhedonia, and mild to moderate anxiety symptoms (contrary to common clinician beliefs) associated with MDD is well documented. It is generally well tolerated with minimal undesirable side effects associated with antidepressants, such as sexual dysfunction and weight gain. Bupropion has shown effectiveness in augmentation as well as in switching strategies of antidepressant medications. Due to its favorable side-effect profile, bupropion has been used in the treatment of geriatric depression with good therapeutic efficacy and health outcome measurements. Bupropion has also shown usefulness as a smoking cessation agent and in treating depression in patients with medical co-morbidities such as asthma and HIV. Limitations of use include individuals at risk for seizures and patients with eating disorders.

**Keywords:** bupropion, major depressive disorder, major depression, fatigue, anhedonia

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## Introduction

Major depressive disorder (MDD) is a common and often overwhelming disorder for the patient as well as for the family. In 2004, the World Health Organization (WHO) estimated that 151.2 million people worldwide suffered from depression.<sup>1</sup> Depression was the leading cause of years of healthy life loss due to disability for both men and women in low-, middle-, and high-income countries. By the WHO estimates of causes of burden of disease as measured by disability-adjusted life years,<sup>1</sup> depression will move from being the third leading cause worldwide in 2004 to being the number one leading cause of disease burden in the world by 2030. When disease burden was broken down by income in 2004, depression was already the leading cause in middle—and high-income countries such as the Americas.<sup>1</sup>

In the US, results from the National Comorbidity Survey Replication showed that MDD had a lifetime prevalence of 16.2% with severity stratification of the 12-month MDD cases showing 10.4% of the cases were mild, 38.6% moderate, 38.0% severe, and 12.9% very severe.<sup>2</sup> Functional impairment was also substantial as measured by the Sheehan Disability Scale which showed 59.3% of the 12-month cases had associated severe or very severe role impairment.<sup>2</sup> Statistical data of various populations demonstrated the wide-ranging effects of MDD particularly in women worldwide, aged 15 to 44 years, who experienced depression as the leading cause of disease burden in both high-income and low- and middle-income countries.<sup>1</sup> In the elderly population in the US, while MDD prevalence has traditionally been lower than in the general population, the increasing rates of depression and projected burden of MDD as well as the strong association with suicidality in the elderly continue to make MDD a significant health concern.<sup>3</sup>

Major depressive disorder, as classified by the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fourth Edition, Text Revision, is characterized by at least one major depressive episode where there is at least two weeks of depressed mood or loss of interest or pleasure plus at least four additional symptoms of depression, such as changes in appetite or weight, sleep, psychomotor activity, energy level, worthlessness/guilt, concentration, or suicidality.<sup>4</sup> There are a number of treatment options available for MDD, including selective serotonin reuptake inhibitors (SSRIs),

serotonin—norepinephrine reuptake inhibitors (SNRIs), norepinephrine—dopamine reuptake inhibitors (NDRIs such as bupropion), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), norepinephrine reuptake inhibitors (NRIs), serotonin receptor antagonists and agonists, and  $\alpha_2$ -adrenergic receptor antagonists.<sup>5</sup>

Bupropion is approved for the treatment of MDD, smoking cessation, and seasonal affective disorder. It is dosed from 100 mg to a maximum of 450 mg per day due to increased risks of seizures, a dose dependent effect. Effectiveness has been demonstrated in patients with MDD characterized by fatigue, hypersomnia, reduced energy and anhedonia.<sup>6</sup> Off-label uses of bupropion include evidence of effectiveness in improving decreased libido and delayed orgasm side effects of SSRIs, weight loss, attention deficit hyperactivity disorder, and severe bipolar depression.<sup>7</sup> Effectiveness was also shown in treating fatigue in cancer patients.<sup>8</sup>

Previous reviews on bupropion have discussed details regarding its pharmacodynamic and pharmacokinetic profiles, therapeutic efficacy, and tolerability.<sup>9,10</sup> The purpose of the current review is to more closely examine the evidence for bupropion's therapeutic efficacy and the most useful role of bupropion in the treatment of MDD from a clinical perspective using research findings. Studies addressing patient preferences and bupropion's effects on health-related quality of life (HRQOL) will also be addressed.

## Methods

We searched PubMed and PsycINFO from 1984 to 2011. We used the following keywords: “Major Depress\*” and “Bupropion.” Two physicians reviewed the abstracts independently using the following inclusion criteria: articles in English or with an available published English translation, publications in a peer reviewed journal, studies of adult humans, and studies (of any design) that focused on MDD (not merely depressive symptoms). Both reviewers then conducted, independently, a focused literature review using the full text articles of studies that met the above criteria. The reviewers then reached a consensus about the studies to include in this review. The reference lists of identified articles were reviewed manually for additional articles. Additional studies, recommended by expert peer reviewers, were examined and added.



Research methodology and key findings were derived from the full text and tables of the selected studies. A total of 71 studies and reviews on bupropion were included in this review.

## Mechanism of Action, Metabolism and Pharmacokinetic Profile

Bupropion is an aminoketone that is chemically unrelated to TCAs, tetracyclics, SSRIs, or to any other known antidepressant agent. While the exact mechanism of bupropion was relatively unknown when it was first introduced in the United States in 1989, it is now believed that bupropion acts as a dual inhibitor of norepinephrine and dopamine reuptake with slightly greater inhibition at the dopamine transporter.<sup>11</sup> In a review of the neuropharmacology of bupropion,<sup>11</sup> studies have confirmed that the dual reuptake inhibition occurs in humans at clinical doses since the brain concentrations of bupropion and its metabolites consistently remained above the 50% inhibitory concentrations ( $IC_{50}$ ) for brain dopamine and norepinephrine transporters after typical dosing intervals. Bupropion has three pharmacologically active metabolites: hydroxybupropion, erythroxybupropion, and threoxybupropion. Their antidepressant effects are unknown with more evidence supporting antidepressant activity of hydroxybupropion. When studies have examined bupropion's effects on other neurotransmitters and receptors, results have shown that bupropion solely inhibits the reuptake of norepinephrine and dopamine in humans without affecting the release or transport of other neurotransmitters and without binding to other receptors.<sup>11</sup> However, other researchers studying bupropion pharmacodynamic activity have found that sustained bupropion administration may lead to an enhancement of norepinephrine release which could be responsible for a drastic increase in mean firing rate of serotonin neurons.<sup>12</sup> The pharmacodynamic properties of bupropion are summarized in Table 1.

The pharmacokinetic properties of bupropion, which have been studied and reviewed by other researchers and which will be summarized here, consist of bupropion being absorbed unaffected by the presence of food in the gastrointestinal tract with  $T_{max}$  values varying between an average of 1.5 hours (Immediate Release), 3 hours (Sustained Release), and 5 hours (Extended Release).<sup>15</sup> Following absorption,

**Table 1.** Mechanism of action.

1. Inhibitor of norepinephrine and dopamine reuptake<sup>11</sup>
2. Non-competitive inhibitor of nicotinic acetylcholine receptor<sup>13,14</sup>
3. No effects on monoamine oxidase neurotransmission<sup>14</sup>
4. No effects on serotonin neurotransmission<sup>11</sup>
5. No effects on post-synaptic receptors like histamine, dopamine, acetylcholine, serotonin or alpha and beta adrenergic receptors<sup>11</sup>

bupropion is metabolized by the liver into its three active metabolites with the cytochrome P450 (CYP) enzyme CYP2B6 being responsible for forming the primary active metabolite hydroxybupropion. Other isoforms including CYP1A2, 2A6, 2C9, 2D6, 2E1, and 3A4 also play lesser roles in metabolism.<sup>15</sup> A few studies have reported that bupropion inhibits the activity of CYP2D6 which has been shown to interact with other medications, including increasing plasma levels of desipramine, venlafaxine, and dextromethorphan. Additionally, there are other medications such as carbamazepine which induce various cytochrome pathways involved in bupropion metabolism as well as medications which inhibit pathways.<sup>15</sup>

## Therapeutic Efficacy and Role of Bupropion in Treatment of MDD

### Overview

The research literature shows that bupropion is more effective than placebo and is generally comparable to other antidepressants. Bupropion Immediate Release (IR) was found to be more effective than placebo and as effective as fluoxetine, nortriptyline, amitriptyline, doxepin, and trazodone in treating symptoms of depression.<sup>9</sup> Bupropion Sustained Release (SR) has also been found to be more effective than placebo on several efficacy measures with no significant differences between the effectiveness of bupropion SR and SSRIs such as sertraline, fluoxetine, or paroxetine.<sup>9</sup> When Bupropion Extended Release (XR) was reviewed, there were no significant differences in efficacy compared to escitalopram or venlafaxine.<sup>9</sup>

When the rapidity of response was compared between bupropion and SSRIs, a pooled survival analysis of seven double-blind, randomized clinical trials showed that there were no significant differences in time to first response (hazard ratio [HR] = 0.955;  $P = 0.43$ ) or time to first remission



(HR = 1.00;  $P = 0.97$ ).<sup>16</sup> In comparing the efficacy of bupropion XR to venlafaxine XR in a recent 8-week, randomized, double-blind trial, researchers reported a significant change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score for both bupropion XR ( $P = 0.006$ ) and venlafaxine XR ( $P < 0.001$ ) compared to placebo.<sup>17</sup>

Bupropion has been extensively compared to other antidepressants (in original studies, reviews, and meta-analyses) with results showing comparable efficacy, tolerability, and safety. One of the goals of the current review is to find the most suitable clinical settings for the most effective use of bupropion. The literature reveals that bupropion has been shown to help improve MDD symptoms of fatigue, hypersomnia, anhedonia, and decreased energy. Evidence shows that it does improve co-morbid mild to moderate anxiety in MDD, contrary to popular beliefs, as detailed later in this article. When augmentation with bupropion was studied, results showed that bupropion was generally effective in helping to further decrease depression severity and lessen antidepressant-associated sexual dysfunction, but the evidence for switching strategies with bupropion was less promising. In terms of undesirable side effects associated with other antidepressants such as sexual dysfunction and weight gain, bupropion has been shown to help improve antidepressant-associated sexual dysfunction as well as avoid weight gain. Due to its favorable side-effect profile, bupropion has also been used in the treatment of geriatric depression with good therapeutic efficacy compared to other antidepressants as well as good health outcome measurements related to quality of life and daily functioning. For patients with co-morbidities such as asthma, HIV, or nicotine dependence, bupropion has also been shown to help with depression severity that correlated significantly with asthma improvement and smoking cessation. Bupropion's place in therapy is summarized in Table 2.

### Effects on depression symptomatology

Studies examining specific MDD symptoms that are most ameliorated by bupropion treatment, have focused mainly on fatigue, hypersomnia, anhedonia, and anxiety. In one principal component (PC) analysis of the Hamilton Rating Scale for Depression (HAM-D),<sup>18</sup> bupropion SR had the most significant

**Table 2.** Summary of bupropion's role in treatment of depression.

1. Treat symptoms of fatigue, hypersomnia, anhedonia, decreased energy, and depression—associated anxiety
2. Improve antidepressant—associated sexual dysfunction
3. Avoid weight gain
4. Useful in augmentation strategies
5. Treat geriatric depression
6. Help improve co-morbidities such as asthma and nicotine dependence

reduction in symptoms compared to placebo in 4 domains: cognitive, retardation, fatigue/interest, and anxiety.

In terms of fatigue, as reported in one extensive pan-European survey of adults who experienced depression within the previous six months, the prevalence of fatigue was 73% which was almost as high as the 76% of adults who experienced low mood.<sup>19</sup> Bupropion has been studied in connection with fatigue in MDD due to the hypothesized role that the neurotransmitters dopamine and norepinephrine play in the pathophysiology of fatigue and somnolence.<sup>20</sup> When researchers pooled the results of six double-blind, randomized clinical trials examining the effects of bupropion versus SSRIs in the resolution of fatigue and hypersomnia as measured by different questions on the Hamilton Depression Rating Scale (HDRS), the data showed that bupropion significantly improved fatigue scores compared to SSRIs ( $P = 0.0078$ ) or placebo ( $P < 0.0001$ ) and that bupropion also significantly improved hypersomnia scores as compared to SSRIs ( $P < 0.0001$ ) or placebo ( $P = 0.0008$ ).<sup>21</sup> Remitters in this pooled analysis also had fewer residual fatigue symptoms ( $P = 0.0020$ ) and residual hypersomnia ( $P = 0.0014$ ) if they were treated with bupropion compared to SSRIs.<sup>21</sup> Despite the statistically significant results, the study did state major limitations that should be kept in mind, including shorter treatment durations, having a primary efficacy measure that had not been validated, and using heterogeneous studies.<sup>21</sup> In an expert review of fatigue in MDD and the role of bupropion,<sup>22</sup> the authors concluded that objective and validated measures of fatigue are still needed since most studies have relied on subscales of broader measurements to assess fatigue. Additionally, more research is needed to determine the true nature



of fatigue as a result of abnormalities with dopamine and norepinephrine in order for definite conclusions to be made regarding the role of bupropion, which currently can only be stated to have the potential to improve fatigue in the treatment of MDD.<sup>22</sup>

Researchers examining the effects of bupropion treatment on anhedonia have also stated promising results. In one small randomized study on outpatients with MDD treated with either bupropion SR 300 mg/day or placebo for six weeks in a blinded initial phase followed by a second open-label phase where those on bupropion SR had their doses increased to 400 mg/day and those on placebo were then placed on bupropion SR 300 mg/day, results showed that the catecholaminergic effects of bupropion SR significantly decreased the Mood and Anxiety Symptoms Questionnaire Anhedonic Depression (MASQ AD) scale during phase one compared to the placebo group ( $P = 0.02$ ).<sup>23</sup> In contrast, when anxiety symptoms were examined in the MASQ generalized distress anxious symptoms (GDA) and the MASQ Anxious Arousal (AA) scale, there were no significant differences between the bupropion and placebo groups during phase one, but individually, both groups experienced significant declines (GDA  $P = 0.003$ , AA  $P = 0.03$ ).<sup>23</sup> These results showed that bupropion SR has greater effects on anhedonic symptoms than placebo and that anhedonia measures may be better at discriminating actual pharmacologic effects of antidepressants than measures of anxiety.<sup>23</sup> When a larger multicenter, double-blind, placebo-controlled, 8-week study was done to evaluate bupropion XL in the treatment of MDD patients with greater symptoms of decreased energy, pleasure, and interest,<sup>24</sup> results showed that bupropion XL significantly decreased scores on the 30-item Inventory of Depressive Symptomatology—Self Report (IDS-IVR-30) total score ( $P = 0.018$ ) and domains of energy, pleasure, and interest ( $P = 0.007$ ) and insomnia ( $P = 0.023$ ) compared to placebo. Secondary measures in the 30-item Inventory of Depressive Symptomatology—Clinician Rated (IDS-C-30) scale also showed significant decline in patients treated with bupropion XL compared to placebo ( $P < 0.001$  for total score;  $P < 0.001$  for the energy, pleasure, and interest domain;  $P = 0.008$  for the insomnia domain).<sup>24</sup> Results of this larger study confirmed bupropion's effects on anhedonia as well as demonstrated the therapeutic efficacy of bupropion use.<sup>24</sup>

Co-morbid anxiety, when present to a high degree, contributes to a subtype of MDD termed anxious depression which has been found to have a prevalence of 46% in the outpatient population and be more likely associated with severe depression and suicidal ideation.<sup>25</sup> Clinicians tend to avoid using bupropion in this patient population for fear of worsening the anxiety symptoms. When researchers conducted a meta-analysis of ten double-blind, randomized studies and attempted to compare the efficacy of bupropion versus other SSRIs in the treatment of co-morbid anxiety symptoms, they found that both treatments resulted in similar improvements in anxiety on the Hamilton depression rating scale Anxiety-Somatization factor (HDRS-AS) score ( $P = 0.130$ ) and the Hamilton anxiety scale (HAM-A) score ( $P = 0.177$ ).<sup>26</sup> Additionally, there was no significant difference in the proportion of patients with residual anxiety following remission when this was defined as a HDRS-AS score  $> 0$  ( $P = 0.081$ ) or a HAM-A score  $> 7$  ( $P = 0.284$ ). However, when patients in these studies were stratified according to the level of anxiety, with anxious depression being a HDRS-AS score  $\geq 7$ , the researchers alternatively found that there was a greater response rate of 6-7% with the use of SSRIs than with bupropion in patients with anxious depression on the 17-item Hamilton rating scale for depression (HAM-D-17) (65.4% vs. 59.4%,  $p = .03$ ) and on the HAM-A score (61.5% vs. 54.5%,  $p = .03$ ).<sup>27</sup> The study concluded that there was a modest advantage for the SSRIs compared to bupropion in the treatment of anxious depression and no difference in patients with low to moderate anxiety. Moreover, clinical significance measured using effect size calculation of the number-needed-to-treat (NNT) was equal to 17 (i.e., about 17 patients must receive SSRI over bupropion for 1 patient to benefit). NNTs of 10 or less are considered clinically significant.<sup>27</sup> In patients with moderate or low levels of anxiety, there were no significant differences found in response or remission rates between SSRIs and bupropion on the HAM-D-17 or the HAM-A.

The results of the above meta-analysis raise significant doubt about the widely held dictum by physicians that bupropion worsens anxiety symptoms in MDD patients with co-morbid anxiety.<sup>28</sup> Although patients with prominent anxious depression appear to benefit modestly from treatment with SSRIs than



with bupropion, there were no significant differences between bupropion and SSRIs in the treatment of depression and anxiety symptoms overall.<sup>29</sup> There have also been other studies that have shown comparable anxiolytic effects between bupropion and an SSRI. In a pooled analysis of two identical, 8-week, double-blind, placebo-controlled, parallel-group studies comparing bupropion SR, sertraline, and placebo on outpatients with MDD and anxiety symptoms,<sup>30</sup> the researchers found that bupropion SR and sertraline were both comparable in their antidepressant effects as well as in lowering HAM-A scores. There were also no differences in the median time that it took to reach significant anxiolytic effects.<sup>30</sup> Furthermore, when researchers compared bupropion XL to escitalopram even in the treatment of generalized anxiety disorder in an outpatient setting, results from the randomized, double-blind, controlled pilot study showed that bupropion XL had comparable anxiolytic efficacy to escitalopram.<sup>31</sup> The evidence from these studies would appear to indicate that bupropion is generally comparable to SSRIs in the treatment of anxiety symptoms associated with major depression. However, patients with severe anxious depression may have a modest advantage from treatment with an SSRI.

### Role in treatment resistant depression: augmentation versus switching

Treatments currently available for depression vary in effectiveness depending on specific patient symptomatology and individual responses with even the most optimal situations producing only a 60% to 70% chance of response and 30%–35% chance of remission with the initial medication.<sup>32</sup> Due to medication limitations, clinicians often utilize various strategies to treat antidepressant non-responders, including increasing antidepressant dosages, augmenting treatment with a non-antidepressant agent or a second antidepressant medication, or switching to a different antidepressant.<sup>33</sup> Recently, researchers have also looked into combining antidepressant medications from treatment initiation for MDD. In one double-blind study examining the effects of combining mirtazapine and either fluoxetine, venlafaxine, or bupropion from treatment initiation for six weeks, favorable results showed that all three combination groups had significantly improved HAM-D scores compared to fluoxetine monotherapy.<sup>34</sup> While this

study adds to a growing body of evidence regarding combination treatment, much more research has been done augmentation and switching strategies with regards to the use of bupropion.

Compared to switching strategies, augmentation has the added benefits of minimizing any therapeutic loss from removing the initial agent, avoiding withdrawal symptoms, and targeting side effects of the first medication.<sup>33</sup> When bupropion was examined in a review of its use in combination with SSRIs or serotonin–norepinephrine reuptake inhibitors (SNRIs), open trials included in the review showed that combination treatment was effective in the treatment of MDD patients who were non-responders to SSRIs, SNRIs, or bupropion alone.<sup>35</sup> Additionally, controlled and open-label studies in the review reported that bupropion was effective in targeting antidepressant-associated sexual dysfunction.<sup>35</sup> In a randomized, controlled trial comparing bupropion SR and bupropion XL as augmentation medications for adult outpatients with MDD who were non-responders to treatment with citalopram in the STAR\*D trial, bupropion SR resulted in a greater reduction in the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) scores ( $P < 0.04$ ), a lower QIDS-SR-16 score by the end of the study ( $P < 0.02$ ), and a lower dropout rate due to intolerance ( $P < 0.009$ ).<sup>36</sup> Similarly, when bupropion SR was used to augment SSRIs in a six-week open-label trial of patients refractory to SSRI treatment, 54% of patients responded to the augmentation with a decrease in the HDRS or the Beck Depression Inventory (BDI) scores of 50% or more.<sup>37</sup> Patients in a different study who did not respond to 8 weeks of escitalopram monotherapy and who had a greater prevalence of melancholic type of depression also responded to bupropion augmentation (61%) with 53.7% achieving remission and 31.7% who showed insufficient or partial response.<sup>38</sup> The combination of escitalopram and bupropion SR also showed effectiveness in an open pilot study of chronic or recurrent MDD patients where researchers reported a 62% rate of response and a 50% rate of remission with minimal side effects.<sup>39</sup>

Switching strategies have primarily been utilized for the advantages of lowering the risk of drug interactions, better patient compliance, and avoiding intolerable side effects from the initial medication.<sup>33</sup>



In one early open-trial of patients resistant to fluoxetine treatment, switching to bupropion SR resulted in 60% of the patients experiencing a full or partial response.<sup>40</sup> When citalopram-resistant patients were randomized in the STAR\*D study to be switched over to bupropion SR, sertraline, or venlafaxine extended-release (XR) for up to 14 weeks, results showed that about one in four patients experienced remission after switching to another antidepressant with no significant differences between the three medications.<sup>41</sup> Despite some favorable results with switching strategies and bupropion use, alternative findings have been shown in one open-label study where patients were either switched to bupropion SR or citalopram after monotherapy nonresponse versus treated with a combination of bupropion SR and citalopram.<sup>42</sup> The researchers found that the combination treatment group had a significantly greater change in the 29-item version of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD) ( $P < 0.04$ ) with a greater proportion of patients in remission than the monotherapy switch group ( $P < 0.05$ ), suggesting augmentation therapy to be more effective than switching strategies.<sup>42</sup>

### Role in concurrent treatment with electroconvulsive therapy

Electroconvulsive therapy (ECT) is often discussed in the treatment of severe, chronic, or resistant depression, or in those patients who are intolerant of antidepressant medications or who have contraindicated medical illnesses.<sup>43</sup> The data on concurrent use of ECT with bupropion treatment is very limited since the recommended course of treatment is often maintenance antidepressant therapy following ECT for relapse prevention.<sup>43</sup> There are, however, two earlier case reports that showed that longer dosing of bupropion with documented adequate to high levels in serum, when concurrently administered with ECT, did not result in major effects on seizure duration.<sup>44</sup> However, the doses of bupropion used were lower than what would usually be needed to lower the threshold for spontaneous seizures. Alternatively, a later case report of a Bipolar I (Depressed) patient who was simultaneously taking bupropion, lithium, and venlafaxine while he received ECT showed that the patient had a sustained, prolonged seizure as

measured by EEG which could have been due to one or a combination of the medications he was taking.<sup>45</sup> Much more research is needed to determine the exact role of bupropion treatment in relation to ECT.

### Role in geriatric depression

In the geriatric population, bupropion SR, when compared to an SSRI such as paroxetine in a 6-week multicenter, randomized, double-blind study, was found to be comparably efficacious in the improvement of depression rating scores.<sup>46</sup> Due to its favorable side-effect profile, which includes fewer cardiovascular side effects than nortriptyline<sup>47</sup> and few gastrointestinal and sexual side effects,<sup>48</sup> bupropion has often been used to treat geriatric depression. In one naturalistic 12-week study of elderly patients with MDD treated with bupropion IR or SR, 67% of patients were responders with Montgomery-Asberg depression rating scale (MADRS) scores less than 15% and 50% were in full or partial remission with response rates not differing between those with high compared to low medical comorbidities.<sup>49</sup> When bupropion XR was studied in elderly patients in a 10-week multicenter, randomized, double-blind, placebo-controlled study, bupropion XR resulted in significantly greater improvements in depressive symptoms based on MADRS total scores compared to placebo ( $P < 0.001$ ).<sup>50</sup> The number of responders according to the MADRS scores was also significantly greater in the bupropion XR group ( $P = 0.014$ ) but remission rates were not significantly different compared to placebo ( $P = 0.167$ ).<sup>50</sup>

In terms of the effects of bupropion treatment on health outcome assessments in elderly patients with MDD, several studies have addressed this issue and found that bupropion XR significantly improved total ( $P = 0.001$ ), cognitive ( $P = 0.005$ ), and social ( $P = 0.003$ ) subscale scores on the 18-item Motivation and Energy Inventory (MEI).<sup>50</sup> The Sheehan Disability Scale (SDS) total ( $P = 0.003$ ), work ( $P = 0.001$ ), social ( $P = 0.018$ ), and family life ( $P < 0.004$ ) scores have also been shown to significantly improve with bupropion XR treatment.<sup>50</sup> In the same study, the Short Form Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) showed significantly greater scores in life satisfaction and contentment in the bupropion XR-treated group compared to placebo ( $P = 0.01$ ).<sup>50</sup> When quality of



life (QOL) was examined in elderly patients with MDD and medical comorbidities, bupropion SR significantly improved scores on the Medical Outcomes Study Short Form—36 (SF-36), with “mental health” ( $P < 0.01$ ) and “social functioning” ( $P < 0.0006$ ) improving by week 4 and “vitality” ( $P < 0.03$ ) improving by week 12.<sup>51</sup> Additionally, bupropion SR was relatively well-tolerated with significant efficacy findings as shown by reductions in the Clinical Global Impressions—Severity of Illness scale ( $P < 0.0001$ ) and in the HAM-D total score ( $P < 0.0001$ ).<sup>51</sup> When correlations were measured between improvements in depression severity and QOL, another study on bupropion SR found that there were significant correlations between improvements in HAM-D total score and the Quality-of-Life in Depression Scale (QLDS) score ( $r^2 = 0.12$ ;  $P < 0.0004$ ) as well as between HAM-D and the SF-36 Mental Component score ( $r^2 = 0.20$ ;  $P < 0.0001$ ) but not between HAM-D and the SF-36 Physical Component score ( $r^2 = 0.06$ ;  $P < 0.014$ ).<sup>52</sup>

### Effects on medical co-morbidities

Bupropion has been studied in the treatment of depression and several co-morbid conditions, including asthma, HIV, and nicotine dependence. Asthma patients who experienced depression and who were treated with bupropion in a 12-week open-label study had significantly improved HAM-D-17 ( $P = 0.02$ ) and HAM-A ( $P = 0.04$ ) scores.<sup>53</sup> Additionally, significant correlations were found between improvements in the Asthma Control Questionnaire (ACQ) score and HAM-D-17 score ( $r = 0.73$ ,  $P = 0.001$ ), the ACQ score and the Inventory of Depressive Symptomatology—Self-Report (IDS-SR) score ( $r = 0.58$ ,  $P = 0.012$ ), and the FEV<sub>1</sub>% Predicted and HAM-D-17 score ( $r = -0.66$ ,  $P = 0.006$ ).<sup>53</sup> In terms of HIV-seropositive patients with MDD who were treated with bupropion SR in a 6-week, open-label, flexible-dose study, results showed that 60% of patients responded to treatment regardless of their HIV clinical stage.<sup>54</sup>

Patients who are smokers have been found to have higher than average rates of MDD.<sup>55</sup> When treatment options are considered, one review of smoking cessation therapies in depressed patients found that the greatest evidence for smoking cessation was through the use of cognitive behavioral therapy alone or in combination with pharmacotherapy.<sup>56</sup>

One cited study found that treatment with bupropion and intensive behavioral therapy resulted in greater smoking cessation rates compared to using low intensity therapy.<sup>57</sup> When bupropion SR was added to the treatment regimen of patients in another study who were in remission from MDD and maintained on SSRIs, results showed that there was no reemergence of depressive symptoms but that bupropion was only modestly effective in smoking cessation with 32% of subjects being abstinent after 9 weeks of treatment and 44% of subjects who were nonresponders.<sup>58</sup> Despite these results, a Cochrane review of antidepressants used for smoking cessation concluded that there was existing evidence supporting the use of bupropion and nortriptyline for smoking cessation regardless of a history of depression but that there was insufficient evidence showing either bupropion or nortriptyline to be superior to nicotine replacement therapy (NRT) or vice versa.<sup>59</sup> Additionally, there has not been research done to evaluate whether bupropion would prevent depressive symptoms or depression relapse better than NRT.<sup>59</sup>

### Effects on sexual functioning

Sexual dysfunction can be due to MDD or the pharmacologic treatment of MDD. Antidepressants such as SSRIs have been shown to be associated with sexual dysfunction, as was reported in a multicenter, prospective, open-label outpatient study where the overall incidence of antidepressant-related sexual dysfunction was 59.1%.<sup>60</sup> When the incidence was compared between the various medications, SSRIs had higher incidences ranging from 58% to 73%.<sup>60</sup> In a later study that examined the prevalence of sexual dysfunction among newer antidepressants, bupropion IR, bupropion SR, and nefazodone were associated with the lowest risk of sexual dysfunction: 22%, 25%, and 28%, respectively.<sup>61</sup> In contrast, SSRIs, mirtazapine, and venlafaxine XR had higher prevalence rates ranging from 36% to 43%.<sup>61</sup> Given the lower sexual risks associated with bupropion treatment, researchers have also examined the effects of transitioning remitted MDD patients with SSRI-induced sexual dysfunction to bupropion SR in an initial feasibility study, with results showing that 6 out of the 11 patients who completed the substitution successfully showed no adverse events or recurrence of MDD and instead had improved sexual functioning





with bupropion SR.<sup>62</sup> When this study was developed into a 4-week placebo-controlled, double-blind comparison of bupropion SR as an added antidote for sexual dysfunction versus placebo, results showed that bupropion SR led to significantly greater self-reported feelings of desire as well as greater frequency of sexual activity compared to placebo ( $P = 0.024$ ).<sup>63</sup>

In order to compare the effects of bupropion on sexual functioning versus other antidepressants, various studies have focused on comparisons with SSRIs such as sertraline,<sup>48,64,65</sup> fluoxetine,<sup>66</sup> paroxetine,<sup>67</sup> and escitalopram.<sup>68</sup> When bupropion SR was compared to sertraline in a randomized, double-blind, multicenter study for 8 weeks, both medications were generally well-tolerated but the sertraline group experienced orgasmic dysfunction significantly more often than the bupropion SR or placebo groups ( $P < 0.05$ ).<sup>64</sup> These results were replicated in another randomized, double-blind, multicenter study that lasted the same duration and that showed similar efficacy results between the two medications but significantly more orgasmic dysfunction in the sertraline group compared to bupropion SR or placebo ( $P < 0.001$ ).<sup>48</sup> When sertraline was again compared to bupropion SR, this time in a longer randomized, double-blind, multicenter trial lasting 16 weeks, patients treated with sertraline were significantly more likely to develop sexual dysfunction compared to the bupropion SR group.<sup>65</sup>

When fluoxetine was compared to bupropion SR in a multicenter, randomized, double-blind, placebo-controlled study for 8 weeks, similar efficacy results were reported but significantly more patients treated with fluoxetine had orgasmic dysfunction compared to bupropion SR or placebo ( $P < 0.001$ ).<sup>66</sup> Bupropion SR, in comparison to paroxetine, did not significantly affect sexual functioning, but men treated with paroxetine did report a worsening of sexual functioning.<sup>67</sup> Finally, in two randomized, double-blind, placebo-controlled studies lasting 8 weeks and comparing bupropion XL to escitalopram, the incidences of orgasm dysfunction and worsened sexual functioning were significantly lower with bupropion XL than with escitalopram ( $P < 0.05$ ) and significantly higher with escitalopram than with placebo ( $P \leq 0.001$ ) with no significant differences between bupropion XL and placebo ( $P \geq 0.067$ ).<sup>68</sup>

## Effects on body weight

Depression can affect body weight through weight gain or loss. The use of antidepressants can also lead to weight changes as a side effect of treatment. For example, tricyclic antidepressants have been shown in various studies to lead to weight gain as an undesirable side effect that can interfere with long-term adherence to treatment.<sup>69,70</sup> When bupropion was studied in relation to its effects on body weight, earlier trials showed that low-moderate and moderate-high doses of bupropion were associated with a lack of weight gain compared to amitriptyline,<sup>71</sup> and when compared to trazodone in a two-center, double-blind, outpatient clinical trial where trazodone had a 1.2-lb average weight gain, there was a 2.5-lb average weight loss with bupropion use.<sup>72</sup> Later when bupropion SR was studied in a longer double-blind clinical trial of 52 weeks to determine its long-term effects on body weight,<sup>73</sup> results showed that bupropion SR, compared to placebo, led to significant rates of body weight loss when organized according to baseline body mass index ( $P < 0.001$ ). Similarly, obese adults with depressive symptoms who were given bupropion SR versus placebo in a randomized, double-blind trial along with a 500 kcal/d-deficit diet were significantly more likely to lose at least 5% of their baseline body weight ( $P < 0.05$  at week 4,  $P < 0.001$  at weeks 6 to 26).<sup>74</sup> According to a recent Cochrane review on smoking cessation interventions that affect body weight, bupropion was also demonstrated in some studies to be able to limit post-cessation weight gain at the end of treatment but this effect was not maintained after one year.<sup>75</sup>

## Tolerability

The safety profile of bupropion has been studied in various trials and reported in several reviews. In one series of randomized, double-blind, parallel-group, placebo-controlled trials on bupropion SR,<sup>76</sup> headache, dry mouth, and nausea were the most frequently reported adverse side effects with incidences similar to placebo except for dry mouth (bupropion SR, 16%; placebo, 7%). Additionally, dry mouth, nausea, and insomnia occurred significantly more often with bupropion SR compared to placebo ( $P < 0.05$ ), but sexual dysfunction was reported in less than 1% of patients in either group.<sup>76</sup> Despite the adverse events, less than 10% of patients in either group discontinued



treatments due to the side effects with no deaths or serious adverse events reported.<sup>76</sup> A review of bupropion has also similarly stated that bupropion IR, SR, and XR are generally well-tolerated with the most common adverse events being headache, dry mouth, and nausea.<sup>9</sup> Other reported side effects include sweating and tremors.

More serious risks include a dose-dependent risk of seizures which has been studied in several prospective surveillance studies and which indicate that bupropion IR has a seizure incidence of 0.4% at the maximum recommended dosage of 450 mg/day and that bupropion SR has a seizure incidence of 0.1% for dosages up to 300 mg/day.<sup>77</sup> With regards to induced mania, expert consensus guidelines for the treatment of bipolar depression indicate that experts prefer the use of bupropion or SSRIs as first line treatment with the belief that bupropion is the least likely among antidepressants to induce mania.<sup>78</sup> As for extrapyramidal symptoms (EPS) associated with antidepressants, a recent review stated that there has been 1 report of EPS associated with bupropion and 6% of EPS cases found in the FDA's Adverse Event Reporting System were due to bupropion, compared to 66% with duloxetine, 10% with sertraline, and 7% with escitalopram.<sup>79</sup> Contraindications to bupropion include current or prior diagnosis of bulimia nervosa, anorexia nervosa, or seizure disorders, allergy to bupropion, abrupt discontinuation of alcohol or sedatives including benzodiazepines, and taking MAOIs or other bupropion formulations. Overall, bupropion is well tolerated with less sexual, gastrointestinal, and sedation side effects than SSRIs.<sup>7,9,80</sup> Bupropion is also well tolerated in the elderly.<sup>50</sup>

## Patient Preference

The issues of treatment adherence, patient preferences, and quality of life (QOL) improvement following treatment with bupropion have been addressed in multiple studies. When researchers conducted a web-based survey on patient preferences and adherence to bupropion treatment, fewer patients who were once-daily users were non-adherent (15%) compared to twice-daily users (37%) and thrice-daily users (65%) with the most common reason being forgetting to take the medication (49% of twice-daily users and 65% of thrice-daily users).<sup>81</sup> When asked if they would prefer once-daily regimens, 77% of twice-daily users and

94% of thrice-daily users expressed interest, leading the researchers to conclude that once-daily bupropion is more favored by users and a reduction in dosing frequency could lead to improved adherence to therapy and better outcomes.<sup>81</sup>

In assessing QOL outcomes following bupropion treatment, multiple studies have been conducted on the general and elderly populations. The trial conducted by Fortner et al<sup>51</sup> on elderly patients with MDD and medical co-morbidities as well as trials by Doraiswamy et al<sup>52</sup> and Hewett et al<sup>50</sup> on geriatric depression and QOL are discussed in more detail in the section entitled *Role in Geriatric Depression*. When the QOL of adult patients with MDD who were treated with bupropion SR for 8 weeks was examined in another study, results showed that there were significant improvements in the Quality of Life in Depression Scale (QLDS) scores ( $P < 0.001$ ) as well as in work productivity as shown by fewer missed hours of work due to depression, increased effectiveness on the job, and fewer hours of overall lost productivity ( $P < 0.001$  for each variable).<sup>82</sup> The improvements in QOL and work productivity were significantly greater for bupropion SR responders who had scores of "very much improved" or "much improved" on the Clinical Global Impressions scale for Improvement of Illness (CGI-I) during the last 3 weeks of treatment compared to those who were non-responders ( $P < 0.001$ ).<sup>82</sup>

## Conclusions

In the treatment of MDD, bupropion has shown comparable therapeutic efficacy to other antidepressants including SSRIs, SNRIs, and TCAs as well as effectiveness in treating fatigue, hypersomnia, anhedonia, and anxiety symptoms associated with major depression. It is generally well tolerated with minimal undesirable side effects that have been associated with other antidepressant use, including sexual dysfunction and weight gain. In patients who failed antidepressant trials, augmentation with as opposed to switching to bupropion was generally more promising. Due to its favorable side-effect profile, bupropion has been used in the treatment of geriatric depression with good therapeutic efficacy and health outcome measurements related to QOL and daily functioning. For patients with co-morbidities such as asthma, HIV, or nicotine dependence, bupropion has also been shown to help with depression



severity that correlated significantly with asthma improvement and smoking cessation. Quality of life and work productivity improvements have also been reported in the general adult population treated with bupropion. Despite the multitude of studies that have been done on bupropion since its first introduction as an antidepressant, larger randomized clinical trials are still needed to confirm the benefits of bupropion use and examine the full scope of its potential.

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