Are Antidepressants Effective for Smoking Cessation in African American Smokers Aged 18 and Older?

Jennifer M. Myskowski

Philadelphia College of Osteopathic Medicine, jennifermy@pcom.edu

Follow this and additional works at: http://digitalcommons.pcom.edu/pa_systematic_reviews

Part of the Medicine and Health Sciences Commons

Recommended Citation

Are antidepressants effective for smoking cessation in African American smokers aged 18 and older?

Jennifer M. Myskowski, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013
Abstract

**Objective:** The objective of this selective EBM review is to determine whether or not antidepressants are effective for smoking cessation in African American smokers aged 18 and older.

**Study Design:** Review of two randomized controlled trials published in 2002 and 2011 and one pilot randomized control trial published in 2011, all English language.

**Data Sources:** Two randomized, double-blind, controlled trials comparing bupropion to a placebo group and one pilot randomized controlled trial comparing varenicline with adherence support for smoking cessation to the control without adherence support. All articles were found using Medline, PubMed, and OVID.

**Outcomes Measured:** Smoking cessation was determined on cotinine and/or carbon monoxide verified samples; reduction in cigarettes smoked per day based on patient self-report; adverse effects of treatment were obtained with use of a prompted checklist containing the 10 most common symptoms associated with quitting smoking and smoking cessation pharmacotherapy, and with the National Cancer Institute’s Common Toxicity Criteria for Adverse Events.

**Results:** Cox and Ahluwalia demonstrated that bupropion was effective for smoking cessation over seven weeks, however results were inconclusive for long-term abstinence. Nollen reported that adherence support was ineffective at promoting smoking abstinence in African American smokers utilizing varenicline as a cessation aid.

**Conclusions:** The results of the randomized controlled trials reviewed demonstrate that the antidepressant drug, bupropion, given over seven weeks, was safe and effective for smoking cessation in African American light and heavy smokers. Evidence is inconclusive to support the efficacy of bupropion for long-term smoking cessation. In the pilot trial, there was no significant difference between the treatment receiving varenicline with adherence support and the control, however, there was a significant reduction in cigarettes smoked per day; these results need to be interpreted with caution due to limitations in study design being that the sample size was insufficient and a control arm receiving placebo was not included in the study. Further studies with larger sample sizes are warranted to compare the safety and efficacy of bupropion versus varenicline since limited studies exist surrounding non-nicotine replacement smoking cessation aids in African American smokers.

**Key Words:** smoking cessation, African American, black, bupropion
INTRODUCTION

In the United States, tobacco use continues to be the primary preventable cause of morbidity and mortality for all racial and ethnic groups despite a dramatic decrease in overall smoking prevalence.\(^1\)\(^2\) Of particular concern, African Americans living in the inner city have a smoking rate as high as 45% compared to the national average rate of 25%.\(^2\) African Americans are more likely to attempt to quit smoking in a given year, but have a success rate 34% lower than Caucasians.\(^2\) Cessation is beneficial for smokers of all ages regardless of the extent of their past smoking history. Smoking cessation greatly reduces the risk of developing and prematurely dying from smoking-related malignancy and pulmonary, cardiovascular, or cerebrovascular disease.\(^1,3\) Additionally, African Americans have a 43-55% higher relative risk of smoking-attributable lung cancer when compared to Caucasians. This further validates that this population is a high-risk group and, thus, a national health care priority.\(^4\)

African Americans continue to be significantly underrepresented in smoking cessation research despite suffering greater morbidity and mortality attributed to smoking.\(^1\) Previous research trials investigating smoking cessation aids contained predominately Caucasian moderate to heavy smokers as study participants; therefore, results are not particularly generalizable to the African American smoking community. African American smokers are more likely to be “light” smokers, smoking <10 cigarettes per day, and they tend to smoke high-tar, mentholated cigarettes.\(^1\) Furthermore, African Americans have been found to have slower rates of nicotine metabolism and have higher levels of cotinine (the primary metabolite of nicotine) per cigarette smoked when compared to Caucasian smokers.\(^1\) These differences, coupled with the increased quit attempts with decreased success rates, suggest that with an improved therapeutic aid,
successful smoking cessation can be obtained. This would in turn yield to a decrease in the
degree of disproportional disease-burden attributed to smoking experienced by this population.

According to the most recent data, in 2010, 201,144 people in the United States were
diagnosed with lung cancer.\textsuperscript{5} Between 2000-2004, cigarette smoking in the United States cost
over $193 billion, with $97 billion in lost productivity and $96 billion in health care
expenditures.\textsuperscript{6} Multiple therapeutic approaches exist to aid smoking cessation, each with a
different mechanism of action. One of the most common therapies is nicotine replacement
therapy (NRT) available in the form of gums, patches, lozenges, and electronic cigarettes.\textsuperscript{7}
Additional smoking cessation aids include non-nicotine pharmacotherapeutics such as
antidepressant medications, like bupropion, which is believed to have dopaminergic and
noradrenergic activity, or partial nicotine agonists, like varenicline. Varenicline is often
associated with antidepressants due to its mood-altering capabilities, however it is not
pharmacologically classified as an antidepressant despite common misperception. Alternative
treatments for smoking cessation include acupuncture, hypnosis, aversive therapy, and
behavioral counseling.\textsuperscript{7}

While there are many treatment options available to aid smoking cessation, the efficacy
and tolerability of antidepressant drugs for smoking cessation in African Americans is
unknown.\textsuperscript{4,2} This paper evaluates two randomized, double-blind, placebo-controlled trials that
examine the efficacy and tolerability of the antidepressant, bupropion, in the treatment of
smoking cessation; additionally, this paper analyzes a pilot study that investigated the use of
varenicline and adherence support for smoking cessation in African American smokers. This
literature review consists of the best available evidence given the population of interest and the
topic in the clinical question.
OBJECTIVE

The objective of this selective EBM review is to determine whether or not the use of antidepressants are effective for smoking cessation in African American smokers aged 18 and older.

METHODS

Specific criteria was designated for the selection of the three trials used in this paper. Criteria for population included African American smokers >18 years old that were interested in quitting smoking. The types of studies included two RCTs (randomized controlled trials) and a pilot RCT. The intervention studied in the two RCTs was bupropion SR in the standardized dosing schedule: 150 mg QD for 3 days, followed with 150mg BID for 7 weeks. In the pilot trial, the intervention studied was varenicline in the standardized dosing schedule: 0.5mg QD for 3 days, followed with 0.5mg BID for 4 days, followed by 1 mg BID for 11 weeks with adherence support for continued encouragement regarding the use of pharmacotherapy. For the RCTs, the treatment group receiving the bupropion was compared to the control group receiving a visually-matched placebo while in the pilot trial, the treatment group receiving varenicline with adherence support was compared to the control group receiving varenicline with standard care. Measured outcomes that were being utilized in this review included biochemically-verified smoking cessation based on cotinine and/or carbon monoxide verified samples, reduction in cigarettes per day (cpd) based on patient self-report, and adverse events.

The study by Cox et al was a randomized, double-blind placebo-controlled trial. The 540 study participants were all African American light smokers (smoked ≤10 cpd) and were randomly assigned to receive bupropion SR or placebo for a treatment period of 7 weeks with up to six health education counseling sessions.
The study by Ahluwalia\(^2\) was a randomized, double-blind placebo-controlled study that involved 600 African American moderate to heavy smokers (smoked \(\geq 10\) cpd). Participants were randomly assigned to receive bupropion SR or placebo for a treatment period of 7 weeks with brief motivational counseling.

In the pilot study by Nollen et al\(^4\), all 72 participants were randomized into two groups and received a one-month supply of varenicline dispensed in a monthly pillbox in addition to verbal instruction on how to properly take the medication. All participants met with a study counselor to gain information regarding the risks of continued smoking, the benefits of cessation, management strategies for coping with withdrawal and cravings, and assistance in developing a quit plan (standard care).\(^4\) The treatment group (adherence support) received five additional counseling sessions on Days 8, 12, 20, 30, and 60 to promote the participants’ motivation to adhere to their medication as prescribed. These participants were also counseled on behavioral techniques to manage the expected adverse events associated with varenicline therapy.\(^4\)

Keywords used in literature search were “smoking cessation”, “African American”, “black” and “bupropion”. All articles were published in peer-reviewed journals in the English language. Literature searches were conducted via Medline, PubMed, and OVID and articles were selected based on their relevance to the clinical question and inclusion of patient-oriented outcomes (smoking cessation, reduction in cigarettes smoked per day, adverse events). Studies included in the search were randomized controlled trials published after 1996 that included patient-oriented outcomes, and a study population of African American adult smokers >18 years of age. Exclusion criteria consisted of studies that the patient population was <18 years of age and non-African American. The statistics reported in these studies included mean change from baseline, 95% confidence interval (CI), and p-value.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>TYPE</th>
<th>PTS (n)</th>
<th>AGE</th>
<th>INCLUSION CRITERIA</th>
<th>EXCLUSION CRITERIA</th>
<th>W/D at wk</th>
<th>INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahluwalia et al, 2002</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>600</td>
<td>Mean = 44</td>
<td>Self-identified &quot;African American or black;&quot; ≥ 18 years old; ≥10 cigarettes per day; interested in quitting in next 30 days; spoke English; has a permanent home address with working telephone.</td>
<td>Contraindication for bupropion SR (predisposition to seizures, excessive alcohol use, bulimia or anorexia nervosa, current use of bupropion or psychoactive medication, pregnant, use of other tobacco forms or NRT in past 30 days); in drug treatment during past 6 months; or being treated for depression.</td>
<td>189</td>
<td>Bupropion SR; dosage: 150 mg QD x3 days, then 150mg BID x7 weeks</td>
</tr>
<tr>
<td>Cox et al, 2012</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>540</td>
<td>Mean = 46</td>
<td>Self-identified African American, aged ≥18 years, interested in quitting smoking, smoked ≤10 CPD x ≤2 years, smoked on ≥25 days in past month, smoked ≥ 3 years; had a home address and functioning telephone; willing to attend scheduled study visits and to provide biological samples for genetic analyses related to nicotine and bupropion metabolism.</td>
<td>Current use of bupropion; use of psychoactive medications, NRT, fluoxetine, clonidine, buspirone, or doxepin in past 30 days; hx of alcohol or substance abuse within past year; current drinking of ≥14 alcoholic drinks Q week and/or drinking ≥5 drinks on one occasion ≥2 times in past month; hx of seizures or head trauma; hx of bulimia or anorexia nervosa; current pregnancy (verified by OTC test kit) or contemplating pregnancy; breast feeding; MI in past 30 days; use of other tobacco forms in past 30 days; use of opiates, cocaine, or stimulants; or diabetes treated c oral hypoglycemics or insulin; intention to move from Kansas City region in next 12 months; or presence of another study participant in household.</td>
<td>161</td>
<td>Bupropion SR; dosage: 150 mg QD x3 days, then 150mg BID x7 weeks</td>
</tr>
<tr>
<td>Nollen et al, 2011</td>
<td>Pilot study</td>
<td>72</td>
<td>Mean = 46.8</td>
<td>African American; ≥18 years of age; smoking &gt;10 cpd; wanting to quit, and willing to take varenicline.</td>
<td>Planning to move from the area within 3 months or had contraindications to use of varenicline (CV event in month prior to enrollment; renal impairment, taking insulin for diabetes but unwilling to closely monitor BS); or hx of clinically significant allergic reactions to varenicline; MDD in past year requiring tx; hx of alcohol or drug dependency in past year; hx of psychosis, panic disorder; bipolar disorder or any eating disorders; or current breastfeeding, pregnancy or plan to get pregnant in next 3 months.</td>
<td>12, 15, 11 at Mon 1, 2, and 3</td>
<td>Adherence support (single counseling session focused on making a quit plan &amp; 5 additional counseling sessions to encourage medication use) with varenicline.</td>
</tr>
</tbody>
</table>
OUTCOMES MEASURED

Outcomes measured were those of patient-oriented evidence that matters (POEMs). Smoking abstinence was measured via patient self-report and biochemically confirmed through salivary cotinine and expired carbon monoxide verified samples. Reduction of cigarettes smoked per day was self-reported. Medication adverse events were measured through a prompted questionnaire containing the top ten common symptoms associated with quitting smoking and smoking cessation pharmacotherapy (Nollen et al⁴), self-report (Ahluwalia²) and via the National Cancer Institute’s Common Toxicity Criteria for Adverse Events with Grade ≥3 indicating a serious adverse event analyzed using Pearson $X^2$ test (Cox et al¹).

RESULTS

The two randomized, controlled trials compared bupropion to placebo, and the pilot randomized, controlled trial compared varenicline and adherence support to varenicline and standard care.

The study by Cox et al¹ found at week 3, the bupropion group had significantly higher levels of cotinine-verified 7-day point prevalence abstinence versus the placebo (21.5% vs 9.6%, OR=1.39, 95% CI= 1.56-4.22, p <.001). At the end of the medication phase, week 7, the treatment group was again found to have significantly higher cotinine-verified smoking abstinence over the placebo (23.7% vs 9.6%, OR= 2.92, 95%CI= 1.78-4.77, p<.001). This study found no statistically significant differences between bupropion SR and placebo at week 26 (13.3% vs 10.0%, OR= 1.39, 95%CI=0.82-2.35, p=.23).¹ Overall, this study concluded that bupropion SR was effective for short-term smoking abstinence in African American light smokers. Particular efficacy was notable at initial abstinence early in the treatment phase, during
week 3, and following the completion of the medication phase at week 7, but not in achieving long-term smoking abstinence at week 26.

The study by Cox et al. assessed the prevalence of adverse events at week 3 by utilizing the National Cancer Institute’s Common Toxicity Criteria for Adverse Events with Grade ≥3 indicating serious adverse events. The incidence and severity of adverse events in the intervention group were similar to those seen in the placebo group; therefore, no significant difference was reported between bupropion SR and the placebo (32.6% vs 28.5%, p>.05 for all grades).

The study by Ahluwalia determined that bupropion SR was effective for smoking cessation versus placebo at week 7 of the medication phase (36.0% vs 19.0%, mean difference of 17.0%, 95%CI=9.7-24.4, p<.001) and this progress was maintained over 26 weeks (21.0% vs 13.7%, p=.02). For analysis of the safety of treatment, adverse events were reported through week 6. The treatment group reported significantly more problems sleeping (29.3% vs 20.7%, p=.02 by 2-tailed Fisher exact test). All other adverse events were not deemed significant in this study. Most commonly reported adverse events included “problems sleeping” and “dry mouth.”

The study by Nollen et al. reported that there were no significant differences in smoking abstinence rates or reduction in cigarettes smoked per day between the treatment group, medication adherence support, and the control group, standard care. At Month 3, cotinine-verified (<20 ng/ml) smoking abstinence was 23.6% (n=17). Among the remaining participants that failed to reach abstinence, there was a significant reduction in cigarettes smoked per day (cpd). At baseline, participants smoked 16.1 cpd (SD=5.6) and at Month 3, reduced to 4.5 cpd (SD=5.3), for a mean decrease of 12.2 cpd (SD= 6.5; p<.0001). To summarize these results, the
Nollen _et al_ study demonstrated that adherence support was ineffective at promoting smoking abstinence in African American smokers utilizing varenicline as a cessation aid.

In this pilot study, there were no significant relationships established between adverse events, medication adherence, or smoking abstinence (p> .05). Study participants reported an average of 2.9 (SD=1.8) adverse events on a prompted checklist. These adverse events were attributed to the use of varenicline over the duration of the 3-month treatment phase. The highest reported adverse events were abnormal dreams (86.0%), nausea (77.0%), and gas (63.2%).

Table 2. Efficacy of bupropion drugs for smoking cessation 6 weeks after quit date

<table>
<thead>
<tr>
<th>Study</th>
<th>CER</th>
<th>EER</th>
<th>RRR (EER-CER/CER)</th>
<th>ABI (EER-CER)</th>
<th>NNT (1/ABI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox <em>et al</em></td>
<td>0.096</td>
<td>0.237</td>
<td>0.1469</td>
<td>0.14</td>
<td>8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ahluwalia</td>
<td>0.19</td>
<td>0.36</td>
<td>0.8947</td>
<td>0.17</td>
<td>6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

_RRR_ = Relative Risk Reduction; _ABI_ = Absolute Benefit Increase; _NNT_ = Numbers Needed to Treat; _CER_ = Control Event Rate; _EER_ = Experimental Event Rate

Table 2 displays the treatment effects of the studies. ABI shows the increase in successful smoking cessation in the bupropion group compared to the placebo group. RRR determines the effectiveness of bupropion therapy when compared to the placebo. NNT reports the number of patients that need to be treated with bupropion to produce one good outcome (i.e. smoking cessation).

Table 3. Safety of bupropion in the treatment of smoking cessation

<table>
<thead>
<tr>
<th>Study</th>
<th>CER</th>
<th>EER</th>
<th>RRI (EER-CER/CER)</th>
<th>ARI (EER-CER)</th>
<th>NNH (1/ARI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox <em>et al</em></td>
<td>0.285</td>
<td>0.326</td>
<td>0.1439</td>
<td>0.041</td>
<td>25</td>
<td>p&gt;.05</td>
</tr>
<tr>
<td>Ahluwalia</td>
<td>0.207</td>
<td>0.293</td>
<td>0.4155</td>
<td>0.086</td>
<td>12</td>
<td>.02</td>
</tr>
</tbody>
</table>

_RRI_ = Relative Risk Increase; _ARI_ = Absolute Risk Increase; _NNH_ = Numbers Needed to Harm; _CER_ = Control Event Rate; _EER_ = Experimental Event Rate
Table 3 displays the safety of bupropion therapy. RRI determines the safety of bupropion therapy and also the likelihood of experiencing an adverse event during therapy. ARI shows the increase in amount of adverse events in the bupropion group compared to the placebo group. NNH reports the number of patients that need to be treated with bupropion to cause an adverse event; 12-25 patients need to be treated to get one adverse event.

**DISCUSSION**

This literature review investigated the safety and efficacy of antidepressants for smoking cessation in African American smokers >18 years of age. Evidence from the studies by Cox *et al*¹ and Ahluwalia² studies showed that the antidepressant, bupropion, was safe and effective for smoking cessation through 7 weeks of medication therapy in both light and heavy African American smokers. Evidence was conflicting, and therefore inconclusive, about successful long-term cessation at week 26.

Limitations were present in each study that affect their validity and generalizability to the clinical question of concern. The greatest limitation for this literature review is the scant amount of RCTs previously conducted studying the population of interest. This dramatically narrowed the sources available for reference data. Furthermore, the study conducted by Cox *et al*¹ is generalizable to light smokers, whereas the study by Ahluwalia² is specific for heavy smokers. Additionally, the study by Nollen *et al*⁴ was a pilot study that had a very small sample size of 72 participants, therefore the results must be interpreted with caution. This study also did not include a placebo to adequately measure the efficacy or safety of varenicline.

The Nollen *et al*⁴ study was a pilot trial that investigated adherence support with use of varenicline in African American smokers. Varenicline is not pharmacologically classified as an
antidepressant medication; it is classified as a partial nicotine agonist that additionally stimulates dopamine activity. Bupropion is classified as an antidepressant medication that functions as a dopamine-reuptake inhibitor. Although both of these pharmacologic smoking cessations aids affect the dopamine pathway and have mood-altering capabilities, they exert very different mechanisms of action. Both medications are first-line non-nicotine replacement therapies often prescribed as smoking cessation aids. Because limited studies exist in the population at question and the common fallacy of varenicline as an antidepressant medication, this pilot study was included in this literature review.

Bupropion is believed to have both dopaminergic and noradrenergic activity. One of the most serious adverse events of therapy is lowering of the seizure threshold. A Black Box warning has been issued for serious neuropsychiatric events including depression, suicidal thoughts and suicide. Serious hypersensitivity reactions have been reported with bupropion use. These side effects are very rarely seen in the treatment of smoking cessation. In general, side effects are minor: CNS stimulation (restlessness, anxiety, insomnia), anorexia, cognitive impairment, seizures, weight loss, and sexual dysfunction. Bupropion is contraindicated in patients who have a history of seizure disorder, anorexia/bulimia, and patients undergoing abrupt discontinuation of ethanol or sedatives including benzodiazepines.

Varenicline has a dual mechanism of action. As a partial nicotine receptor agonist, it reduces nicotine withdrawal by plugging into the alpha 4, beta 2 nicotinic receptors of the brain. If the patient continues to smoke, the nicotine in the cigarette is unable to reach the receptor since it is blocked by the drug. This removes the feel good, rewarding sensation that the patient typically experiences from smoking a cigarette. Varenicline, like bupropion, has a Black Box
warning for neuropsychiatric effects including depression, suicidal thoughts and suicide. Additional side effects include CNS depression, hypersensitivity reactions, and nausea.9

CONCLUSION

The studies reviewed collectively are inconclusive regarding safety and efficacy of antidepressants for smoking cessation in African American adult smokers. Although there was no difference in smoking cessation with adherence support, the pilot study that examined varenicline showed significant reduction in cigarettes smoked per day. This may be promising for discovering successful methods to help African American smokers. Additional methods and combinations of therapeutic modalities need to be explored that can compliment or enhance the effects of varenicline. Future study is necessary to evaluate the efficacy of bupropion versus varenicline to determine which non-nicotine replacement pharmacotherapy is better able to assist this population in achieving smoking abstinence. Additionally, further trials are warranted that compare varenicline to a placebo in African American smokers to better assess adverse events attributed to therapy before routine use can be recommended.
References


