The Association Among Depressive Symptoms, Smoking Status and Antidepressant Use in Cardiac Outpatients

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Abstract

Both depression and smoking are highly prevalent and related to poorer outcomes in cardiac patients. In this study, the authors examined the association between depressive symptoms and smoking status, described the frequency and type of antidepressant use, and prospectively tested the effects of antidepressant use in smokers on smoking status and psychosocial outcomes. Participants comprised 1498 coronary artery disease (CAD) outpatients who completed a baseline survey which assessed depressive symptoms, current medications, and smoking status. A second survey was mailed 9 months later that assessed depressive symptoms, anxiety, insomnia, current medications and smoking status. Results showed that current and former-smokers had significantly greater depressive symptoms than non-smokers. Ten percent of patients were taking antidepressants, most frequently SSRIs, with significantly more smokers on antidepressants than former and non-smokers. At follow-up, smokers on antidepressants were less likely to have quit, had greater anxiety, depressive symptoms and insomnia than smokers not using antidepressants. This study demonstrated that smokers and quitters with CAD had greater depressive symptoms and use of antidepressants than non-smokers, but that the antidepressants utilized may not be optimizing outcomes.

Keywords

Smoking; Depression; Antidepressants; Coronary artery disease (CAD); Outpatients

Introduction

Smoking is associated with increased all-cause morbidity and mortality in the general population (Health Canada, 2008; Centers for Disease Control and Prevention (CDC), 2002) and has adverse prognostic consequences in patients with established coronary artery disease (CAD) (Prugger et al., 2008; Daly et al., 1983; De Bacquer et al., 2003). For example,

continued smoking in CAD patients is associated with non-fatal myocardial infarctions, recurrent coronary events, the lowering of high-density lipoprotein cholesterol, restenosis and all-cause mortality (Critchley and Capewell, 2004; Rea et al., 2002; Johansson et al., 1985; Ronnevik et al., 1985; Salonen et al., 1980; Wilson et al., 2000; Perkins and Dick, 1985; Kinjo et al., 2005; Serrano et al., 2003; Kwiterovich et al., 1998). Previous studies show that approximately 14–37% of the cardiac population are current smokers (Attebring et al., 2004; Hasdai et al., 1997; Huijbrechts et al., 1996; Kronish et al., 2006; Taira et al., 2000).

Smoking cessation is the most effective lifestyle modification in the management of patients with CAD (Critchley and Capewell, 2004; Daly et al., 1983) as smoking-related cardiovascular events are significantly reduced within one year (Thomson and Rigotti, 2003). Further, quitting smoking can reduce the risk of MI to that of a non-smoker over time (Health Canada, 2008; Wilhelmsen, 1998; Thomson and Rigotti, 2003).

Despite the evidence of adverse consequences of continued smoking, the literature shows that the rate of self-initiated smoking cessation after a cardiac event is not optimal. In a review of smoking cessation following an MI (Burling, et al., 1984), the quit rate ranged from 27% to 62%. The wide range is likely due to methodological differences between studies (i.e. criteria to define abstinence). More recent evidence demonstrates that only 30–40% stop smoking spontaneously after a coronary event (Quist-Paulsen et al., 2003; Dornelas et al., 2000). With a treatment program (i.e. inpatient smoking cessation program, counselling etc.), smoking cessation following a cardiac event reaches approximately 50% (Dawood et al., 2008; Dornelas et al., 2000; Weiner et al., 2000). Although treatment programs have been shown to increase quit rates, many cardiac patients that are current smokers are not offered treatment for smoking-cessation (Van Spall et al., 2007; Weiner et al., 2000). Moreover, many hospitals do not provide such programs as part of routine care (Dawood et al., 2008).

The literature has shown many factors that are associated with continued smoking. Some of these characteristics include weight gain (Blitzer, Rimm, and Giefer, 1977; Cordoba et al., 1994; Detry et al., 2001; Grunberg, Bowen, and Winders, 1986; Wack and Rodin, 1982) and insomnia (Udner, 2006; Colrain, 2004) after quit attempts, personal and sociodemographic factors (Bjornson et al., 1995; Blake et al., 1989; Pomerleau, Pomerleau, and Garcia, 1991; Rosal et al., 1998; Royce et al., 1997; van Berkel et al., 1999; Waldron, 1991), history of a cardiac event (Attebring et al., 2004), hostility, tension and depressive symptoms (Perez et al., 2008; Brummett et al., 2002; Glassman, 1993; Attebring et al., 2004; Kronish et al., 2006; Schrader et al., 2006; Thorndike et al. 2008; Dawood et al. 2008). Over the last few decades, research has shed light on depression in particular, and its' association with continued smoking. For instance Anda et al. (1990) examined epidemiologic data from the United States, and suggested that multiple studies indicate that depression plays a role in continued cigarette smoking. They reported that depressed smokers were significantly less likely to quit compared with nondepressed smokers (relative risk, 0.6).

There are several potential reasons for this relationship. Depression is associated with maladaptive coping strategies and negative cognitions, such that patients may continue to

smoke to regulate their emotions (Barth and Bengel, 2007; Herrmann-Lingen, 2001; Pomerleau et al., 2005). Moreover, depressive symptoms are often exacerbated in quitters, causing difficulties in abstaining (Breslau, Kilbey, and Andreski, 1991; Glassman, et al., 2001; Murphy et al., 2003). Given the evidence that there is a significant association between smoking and depression, and that depression is 3 times more common in patients after an acute myocardial infarction (AMI) than in the general community (Lichtman et al., 2008; Thombs et al., 2006), it is important to further examine smoking behaviour in depressed patients with established CAD. Moreover, the association between smoking and depression is particularly worrisome, given that cardiac patients with depression have two times greater morbidity and mortality than cardiac patients without depression (Lett et al., 2004; van Melle et al., 2004).

While studies have examined the association between smoking and depression, few have investigated this association among patients with established CAD. Further, to our knowledge, there have been no studies that have examined the association between antidepressant use and smoking cessation or psychosocial outcomes in cardiac smokers. The objectives of this study were to (1) examine the association between depressive symptoms and smoking status in a large multi-site CAD outpatient population, (2) describe the frequency and type of anti-depressant use by smoking status, and (3) prospectively describe the effect of antidepressant use in smokers on smoking status and psychosocial outcomes.

Methods

Procedure and Design

This study represents secondary analyses from a study on utilization of cardiac rehabilitation (Grace et al., 2008). The sample is composed of cardiac outpatients nested within cardiologists (see Figure 1). Upon receiving ethics approval from participating institutions, a list of all Ontario cardiologists (N=384) was generated through a national physician registry, CMD Online (www.mdselect.com). Basic sociodemographic data were extracted. Consenting cardiologists were visited by a research assistant to extract a random retrospective sample of approximately 25 each of their CAD outpatients. Patients were invited by mail to participate; cardiologists were not aware which patients were invited. Written informed consent was obtained from patients who wished to participate. Basic clinical and demographic data were extracted from the outpatient medical charts, and a self-report survey was mailed that assessed smoking status, depression and anti-depressant use. A second survey was mailed nine months later that assessed depressive symptoms, anxiety, insomnia, medication use and smoking status. The test of the main objectives in this study is cross-sectional in design; however the final test of effects of antidepressant use on smoking status and psychosocial outcome is prospective and non-randomized.

Participants

Ninety-seven cardiologists consented to participate (14 [14.4%] women, mean graduation year 1982 ± 8.57 ; 33% response rate). Inclusion criteria consisted of having a nonpediatric practice, located in a major centre in the Windsor to Ottawa corridor of Ontario and actively treating CAD outpatients.

Patients that had been seen by the cardiologist in the outpatient clinic between 2004 and 2006 with a confirmed diagnosis of CAD were eligible for participation. Diagnosis was confirmed by the indication in patients' charts of a detailed history, focused physical examination, diagnostic electrocardiographic changes (Q waves, and/or ST-T segment changes), and/or troponin levels above the 99th percentile of normal. Patients who had undergone percutaneous coronary intervention (PCI), acute coronary bypass (ACB), concurrent valve repair/replacement, or received a concomitant diagnosis of heart failure, angina or arrhythmia were also eligible.

Of the 2486 CAD outpatients mailed, 1498 consented to participate (429 women [28.6%]; 72% response rate). This represents a mean of approximately 15 patients per cardiologist. Participants per cardiologist ranged from 8–20, while the response rates ranged from 47%–100%. Three hundred and ninety-eight patients were deemed ineligible for the study. Reasons for ineligibility were based on exclusion criteria for the larger study as follows: lack of English language proficiency (n = 145; 36.4%), incorrect address and/or could not locate the patient (n = 87; 21.9%), no formal CAD diagnosis (n = 38; 9.5%), orthopedic, neuromuscular, cognitive or vision impairment (n = 36; 9.0%), death (n = 34; 8.6%), non-recent index event or treatment (n = 20; 5.0%), patient resides outside of province (n = 12; 3.0%), patient's survey returned to non-participating healthcare provider and thus misplaced (n = 4; 1.0%), comorbid non-dysphoric psychiatric condition (n = 3; 0.8%) and other (the patient is following up with a non-participating cardiologist, the patient is terminally ill; n = 19; 4.8 %)

Twelve hundred and seventy-six patients completed the 9-month follow up survey (137 declined and 87 were ineligible; 90% retention rate). Reasons for ineligibility at follow-up were: unable to reach/incorrect contact information (n=37; 42.5%), deceased (n=24; 27.6%), new onset of an orthopedic, neuromuscular, cognitive, psychiatric or vision impairment (n=6; 6.8%), and other reasons (n=20; 23.1%) such as too ill to participate or moved out of the province/country.

Measures

Smoking Status—Self-report questionnaires to ascertain smoking history were administered. Smoking status was self-reported at baseline and follow-up through forced-choice options. Participants were classified as current smokers, former-smokers or non-smokers. Current smokers were smoking at the time of the baseline survey administration, and former-smokers had quit prior to the first survey assessment.

Clinical Variables—Clinical and risk factor data extracted from outpatient medical charts included sex, age, date of the last outpatient visit or cardiac event or procedure, Canadian Cardiovascular Society (CCS) angina class (Canadian Association of Cardiac Rehabilitation, 2004), New York Heart Association class (NYHA) class (The Criteria Committee of the New York Heart Association, 1994), blood pressure, lipids, family history of CAD, diabetes and medications (inclusive of antidepressants). On the baseline survey, patients self-reported height and weight (to compute body mass index), comorbid illness, and all current medications.

The Duke Activity Status Index (DASI) (Hlatky et al., 1989) is a brief 12-item, self-administered survey to determine functional capacity. Participants were asked about their ability to perform common activities of daily living, such as personal care, ambulation, household tasks, sexual function, and recreational activities, which are each associated with specific metabolic equivalents (METs). This valid and common tool correlates highly with peak oxygen uptake (Nelson et al., 1991). This was administered at both time points.

Sociodemographic Variables—The baseline patient survey assessed sociodemographic characteristics. These included ethnocultural background, marital status (married vs. not), gross family income (\$49,999 or less vs. \$50,000 or more), work status (full/part-time vs. other) and education (less vs. greater than high school) through forced-choice responses.

Psychosocial Variables—The Beck Depression Inventory-II (BDI-II) (Beck, Steer, and Brown, 1996; Beck et al., 1961) was used to assess depressive symptoms. It is a reliable and well-validated 21-item scale that uses a forced-choice 4-alternative response format. It has been widely used in the general population and in populations with long-term illness, including cardiac problems. (Beck, Steer and Garbin, 1988; Bhattacharyya et al., 2007; Caulin-Glaser et al. 2007; Dias et al., 2005; Frasure-Smith, Lesperance, and Talajic, 1993; Shnek et al., 2001; Steer, et al. 1999) Higher scores reflect greater depressive symptomatology, with scores >14 reflecting mild to severe symptomatology. The internal consistency was excellent, with a Cronbach's α value of .90 in the present sample. This scale was administered at both time points.

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) was used to assess emotional distress and was administered at follow-up. The HADS is a 14-item self-report questionnaire, with seven items assessing anxiety and seven items assessing depressive symptoms. There are four response options for each item, scored from 0 to 3, for a scoring range of 0 to 21 for each subscale. A subscale score of 0 to 8 represents subthreshold symptoms, a score of 9 to 10 represents moderate anxiety or depressive symptoms, and a score of 11 or greater represents severe symptoms. The HADS has been widely used as an anxiety and depressive symptom screening measure in hospital settings and has previously been used in cardiac research (Bjelland et al., 2002; Carless et al., 2006; S. L. Grace et al., 2005; Hevey, McGee, and Horgan, 2007; Murphy et al., 2007; Stafford, Berk, and Jackson, 2007). In the current study, the internal reliability of the depression and anxiety subscale were $\alpha=.87$ and $\alpha=.83$ respectively.

The Women's Health Initiative Insomnia Rating Scale (WHIIRS) (Levine et al., 2005) was used to assess sleep disturbances, and was administered at follow-up. The WHIIRS consists of five items, four of these items are related either to initiation insomnia, maintenance insomnia, or early morning awakening and the last item is related to sleep quality. Each item is scored on a 5-point Likert scale. The last item on sleep quality is reversed scored and then the items are summed. Scores range from 0–24. Scores ≥ 9 indicate clinically significant insomnia. The internal reliability of this scale was very good with a Cronbach's α value of .83 in the present sample.

Statistical Analyses

SPSS 16.0 (SPSS Inc., 2008) was used for all analyses, and data were thoroughly cleaned and screened. The frequency of antidepressant use was explored by type and smoking status. Demographic and clinical differences were compared by smoking status using the Chi-square test for discrete variables and Analysis of Variance (ANOVA). Where significance was found, Bonferroni post-hoc tests were used to test differences by smoking status. Multinomial logistic regression analysis was used to examine the association between depressive symptoms and smoking status, after controlling for demographic and clinical differences identified through bivariate analyses. These included age, sex, comorbid conditions, overweight/obesity, index MI, work status, marital status, education and dyslipidemia. Family income was excluded from the analysis due to a low rate of completion on the self-report survey. Non-smokers were used as the reference group. Odds ratios (OR) with 95% confidence intervals (CI) are reported. Finally, current smokers from the baseline assessment were selected from the sample, and the data were stratified by anti-depressant use. A non-parametric test (Mann-Whitney Test) was used to describe the effect of antidepressant use in smokers on smoking status and psychosocial outcomes at the 9-month follow-up assessment. All statistical tests were two-tailed. $P < 0.05$ was used for all tests to indicate statistical significance.

Results

Respondent Characteristics

Participating patient characteristics are shown in Table I. Age ranged from 28 to 104 years old. The mean number of days between the participant's last outpatient visit or a cardiac event or procedure and baseline survey completion was 200.0 ± 136.0 (median = 172.0 days, or approximately 6.5 months). Overall, there were 148 (9.9%) current smokers, 486 (32.4%) former-smokers, and 864 (57.7%) non-smokers.

As shown in Table I, smoking status was related to some clinical and demographic characteristics. Overall significance is denoted in the total column, while post-hoc multiple comparisons where significant are denoted in the central columns of the table. Smokers were significantly younger, less likely to be married, have an education less than high school and more likely to have dyslipidemia, have a current MI, work full/part time and have depressive symptoms compared to non-smokers. Further, smokers were significantly younger and more likely to work full/part time, have a current MI and have higher depressive symptoms than former-smokers. Finally, former-smokers were more likely to be male, overweight, have a lower income, have an education less than high school, and have a comorbid condition and higher depressive symptoms than non-smokers.

Depressive Symptoms and Antidepressant Usage by Smoking Status

Table I displays the mean BDI-II scores by smoking status, and shows that at baseline assessment, current smokers had significantly greater depressive symptoms than former and non-smokers. Further, former-smokers had higher depressive symptoms compared to non-smokers. Women had significantly greater depressive symptoms than men. Of the overall sample, 386 (26.3%) indicated elevated depressive symptoms (BDI-II > 14). By smoking

status, 56 (38.6%) of current smokers, 141 (29.7%) of former-smokers and 189 (22.7%) of non-smokers had elevated depressive symptoms.

A total of 156 (10.4%) participants reported taking an anti-depressant at baseline. Table II displays the class of antidepressants used by smoking status, in descending frequency. An analysis of variance showed that significantly more smokers were on antidepressants than former and non-smokers ($F=15.37$; $p < .001$).

The Association Between Depressive Symptoms and Smoking Status

As shown in Table III, a multinomial logistic regression analysis was used to examine the association between depressive symptoms and smoking status. The results revealed that smokers had significantly greater depressive symptoms, were significantly younger, had lower education, were less likely to be married and were more likely to have dyslipidemia than non-smokers. Former-smokers had significantly greater depressive symptoms, were younger, male, had lower education, more comorbid conditions, were more often overweight or obese and less likely to be married than non-smokers.

The Effect of Antidepressant Use in Smokers on Smoking Status and Psychosocial Outcome at Follow-up

At the 9 month follow-up, participants were again asked to report their smoking status. Of the 148 smokers at baseline, 127 (85.8%) were still smokers and 21 (14.2%) reported that they had quit.

Non-parametric tests were used to describe the effect of antidepressant use in smokers (both as reported in baseline survey) on smoking status and psychosocial outcomes at the 9-month follow-up assessment. As shown in Table IV, smokers taking antidepressants at the time of baseline assessment had mean scores that were above scale cut-off scores indicative of psychosocial distress on the HADS anxiety subscale, the BDI-II and insomnia scale. Further, a significantly greater number of smokers that did not report taking an antidepressant at baseline, quit smoking by follow-up compared to smokers who were taking antidepressants. Finally, smokers on antidepressants had significantly higher anxiety levels and depressive symptoms on the HADS subscales, higher depressive symptoms measured by the BDI-II and higher rates of insomnia than smokers who did not report taking antidepressants at baseline.

Discussion

The current study examined the relationship between depressive symptoms and smoking status in a multi-site CAD outpatient population. The results showed that current and former-smokers had greater depressive symptoms than non-smokers at baseline. This association held after controlling for other factors, although the authors concede that the degree of clinical significance may be low. Further, of the overall sample, nearly one-third of patients indicated elevated depressive symptoms, while 40% of the current smokers indicated elevated symptoms above the BDI-II clinical cut-off. This suggests that smokers may be using cigarettes to regulate mood, and that attempts to quit may be undermined by depressive symptoms (West et al., 1984; Miyata, H. 2008; Breslau et al., 2000; Anda et al., 1990; Pomerleau et al., 2005). Moreover, significantly more smokers were on

antidepressants than former and non-smokers. By follow-up, smokers on antidepressants were less likely to have quit, and had greater anxiety, depressive symptoms and insomnia than smokers not using antidepressants.

Antidepressant Use Among Cardiac Patients

Smoking cessation can be considered the most effective lifestyle modification in the management of patients with CAD (Critchley and Capewell, 2004; Daly et al., 1983; Quist-Paulsen et al., 2005). There are several safe and effective means to support quit attempts in the general population such as behavioral counselling (Barth et al., 2006; Vidrine, et al., 2006), nicotine replacement therapy (NRT) (Fiore, 2000; Hurt, 1999; Kozłowski et al., 2007) and psychoactive medication (Aubin et al., 2004; Bolin, Lindgren, and Willers, 2006; Boshier, Wilton, and Shakir, 2003; Mansourati et al., 2005; Tonnesen et al., 2003; Tonstad and Johnston, 2004; Wilkes et al., 2005; Wu et al., 2006). Within cardiac samples, psychoactive medications may have the benefit of addressing both the hazardous burden of depression and smoking. There is however a dearth of published evidence that exists on the use of antidepressant drugs for smoking cessation in patients with CAD (Frasure-Smith and Lesperance, 2006). This is a major gap in knowledge, considering the role of depression in undermining quit attempts, and the potential of these medications to address two prevalent risk factors in CAD patients.

In the current study, 10% of the outpatient CAD sample was taking an antidepressant, with smokers more likely to be taking an antidepressant than former and non-smokers. In fact, almost one-quarter of smokers were taking an antidepressant. The most frequently prescribed class of antidepressants were Selective Serotonin Reuptake Inhibitors (SSRIs), followed by tricyclics/tetracyclics (TCAs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), with 6% of the total sample using bupropion. The most frequent class of antidepressants used in smokers was the SSRI citalopram (Celexa).

Until the last decade, there were virtually no studies or clinical trials that tested the safety and effects of antidepressant use in cardiac populations. However, a large clinical trial that evaluated the SSRI sertraline in depressed cardiac patients (SADHART) (Glassman et al., 2002) demonstrated that it is a safe and effective treatment for recurrent depression in patients with recent MI or unstable angina. Further, in the more recent CREATE study (Lesperance et al., 2007), the SSRI citalopram was also demonstrated to be safe and effective in reducing depression in a cardiac population. In addition, the American Academy of Family Physicians (Post-Myocardial Infarction Depression Clinical Practice Guideline Panel, 2009) and the American Heart Association (Lichtman et al., 2008) have established evidence-based clinical practice guidelines that recommend SSRIs for depressed patients after a MI. Therefore, the prevalence of SSRI use, sertraline or citalopram in particular, in this population is highly appropriate.

Although often prescribed after the failure of SSRI and SNRI antidepressants, TCA antidepressants remain a common cause of fatal drug poisoning as a result of their cardiovascular toxicity evident by ECG abnormalities, arrhythmias and hypotension (Pentel and Benowitz, 1986; Thanacoody and Thomas, 2005). As evidence shows that there is a cardiac danger in TCA use, it is disconcerting that 20% of the CAD population in this study

on antidepressants reported the use of a TCA. It can be noted however, that the frequency reported in CAD patients in this and other studies (Feinstein et al., 2006; Grace, Leung, and Stewart, 2008) represents a lower rate of TCA use when compared to previous reports (Benazon, Mamdani, and Coyne, 2005).

While TCAs and SSRIs have been a proven means to combat depression, and depression plays a role in smoking behaviour, there is no evidence that these antidepressants aid in smoking cessation. Bupropion (Zyban, Wellbutrin) however is an antidepressant that is approved for smoking cessation (Jorenby, 2002) and has been shown to be effective in promoting cessation (Aubin et al., 2004; Bolin et al., 2006; Boshier et al., 2003; Mansourati et al., 2005; Tonnesen et al., 2003; Tonstad and Johnston, 2004; Wilkes et al., 2005; Wu et al., 2006). One of the mechanisms involved with successful quit rates is the ability of bupropion to target physiological and psychological nicotine withdrawal symptoms. For example, preclinical studies demonstrate that in rats experiencing nicotine withdrawal, bupropion can dose-dependently lower changes in brain-reward threshold and somatic signs of nicotine withdrawal. Moreover, in human laboratory studies, the administration of bupropion has demonstrated that it can alleviate some nicotine withdrawal symptoms, including depressed mood, irritability, difficulty concentrating and increased appetite (Mooney & Sofuoglu, 2006). While bupropion has been established to be safe and effective with fairly minimal adverse side effects in the general smoking population (Hurt et al., 1997; Tonstad et al., 2003), its' safety and efficacy for smokers with CAD still remains somewhat understudied (Rigotti et al., 2006). Potential side effects such as increases in blood pressure (Roose et al., 1991) and chest pain (de Graaf and Diemont, 2003) warrant future investigation; however, some studies have demonstrated safety and lack of serious adverse events and show that bupropion is well tolerated in CAD populations (Rigotti et al., 2006; Tonstad et al., 2003; Tonstad and Andrew Johnston, 2006).

Effects of Antidepressants Among Smoking Cardiac Patients

Overall, 14% of the smokers in this study reported that they quit smoking nine months later. While smoking patients were not randomized to receive antidepressant therapy, the prospective results from this study surprisingly did not support the notion that smokers with CAD are more likely to quit if using an antidepressant. The results showed that significantly more smokers who were not taking an antidepressant at baseline managed to quit at follow-up. This finding is similar to the study by Attebring et al. (2004) where the use of sedatives/antidepressants at time of admission for an acute cardiac event predicted continued smoking at 3-months follow-up (Attebring et al., 2004). Moreover, the results in the current study showed that smokers on antidepressants had greater negative affect and more insomnia when compared to smokers who were not on antidepressants.

There are several plausible explanations for these findings. First, smokers on antidepressants may have had greater nicotine dependence and more psychosocial distress at baseline compared to those smokers that did not indicate the use of an antidepressant. Second, there are several measurement issues that may have affected the results. We failed to assess antidepressant dosage and length of treatment, therefore it is possible that the dose of antidepressants was insufficient to result in cessation or improved psychosocial well-being.

Further, a lack of diagnostic interviews precludes any conclusions on appropriateness of the antidepressant prescribing or the degree of remission afforded by treatment. Other measurement limitations relate to lack of data on unfilled prescriptions, titration of dosages, side effects leading to discontinuation, and psychotherapy or other treatment referrals (Grace et al., 2008). It is possible that patients who were not on antidepressants were more often accessing other therapies, which may have had positive effects on their cessation and psychosocial well-being. Third, the failure of smokers on antidepressants to quit may be related to unmeasured motivational issues (Zerwic, King and Wlasowicz, 1997) or health beliefs (Marshall, 1990; Bolman and de Vries, 1998). For instance, perhaps patients on antidepressants have lower motivation to quit and asked their physician for a “wonder pill”. Fourth, individuals on antidepressants may have had greater depressive symptoms before using these medications; if so, the antidepressants may have indeed effectively helped to decrease their depression symptoms but left them with few mental resources left to attempt or succeed at smoking cessation. Finally, perhaps these associations are spurious but could be explained by unmeasured personal preferences of physicians for the prescription of antidepressant medication leading to medical practice variation. Physicians may prefer one type of antidepressant over another (i.e. a TCA over a SSRI), or may have a relationship with a pharmaceutical company which may preclude following the current recommended clinical practice guidelines (Post-Myocardial Infarction Depression Clinical Practice Guideline Panel, 2009). In contrast, some physicians may be inclined not prescribe antidepressants at all.

Caution is warranted when interpreting these results, mainly due to design, measurement issues and generalizability. First, the assessment of the association between smoking and depression was cross-sectional in nature, and therefore no causal conclusions can be drawn. Moreover, while the examination of effects of antidepressant use among smokers was prospective, due to the non-randomized nature of the design, again causal conclusions cannot be drawn.

Second, with regard to measurement issues, the assessment of smoking status, depression and antidepressant use were self-report, and therefore may be biased due to social desirability for example. However, self-report of smoking behavior has been shown to be unbiased in most studies (Patrick et al., 1994). In future, biochemical assessment should be undertaken for objective smoking and medication status evaluation. Moreover, use of structured clinical interviews to assess depression is advocated. Third, we did not assess length of time since quitting; therefore the group of former-smokers may have been quite heterogeneous. Nor did we assess what length of time constitutes quitting. Fourth, we did not assess other cessation aids such as NRT or counselling which may have affected outcomes. Fifth, information regarding antidepressant dosage, timing of use, and adherence were not collected. Therefore, the results herein should be interpreted with caution. Finally, the nature of this outpatient sample may limit the generalizability of the results.

In conclusion, smokers and quitters with CAD had greater depressive symptoms than non-smokers. Smokers were more likely to use antidepressants, SSRIs in particular, than both former and non-smokers. Smokers on antidepressants were less likely to quit, significantly more anxious, depressed and had higher levels of insomnia than those not taking

antidepressants. Future studies are needed to determine the optimal combination of treatments for concomitant smoking and depression in cardiac populations.

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Figure 1.
Participant Recruitment Flow Diagram

Table I

Participant characteristics stratified by smoking status

	Current Smokers	Former Smokers	Non-smokers	Total
N (%)	148 (9.9)	486 (32.4)	864 (57.7)	1498
Demographic Characteristics				
Age, mean, $\pm$ SD	59.53 $\pm$ 10.27 ^{***}	67.24 $\pm$ 11.14	68.13 $\pm$ 11.30	66.99 $\pm$ 11.42 ^{***}
Sex (% women)	41 (27.7)	113 (26.3) ^{**}	275 (31.8) ^{**}	429 (28.6) ^{**}
Ethnocultural background (% white)	133 (89.9)	417 (86.0)	717 (83.0)	1267 (84.6)
Education (% greater than high school)	62 (42.5) ^{**}	219 (46.1) ^{***}	502 (58.9) ^{**}	783 (53.1) ^{***}
Family income (% \$50,000 or more)	58 (40.6)	184 (42.1) [*]	390 (50.2) [*]	632 (46.6) ^{**}
Work status (% FT/PT)	70 (47.9) ^{***}	137 (28.5)	281 (32.7)	488 (32.9) ^{***}
Marital Status (% married)	88 (59.5) ^{**}	331 (68.8)	630 (73.3) ^{**}	1049 (70.5) ^{**}
Clinical Characteristics				
Index MI (%yes) [†]	63 (42.6)	155 (32.0) [*]	260 (30.1) ^{**}	478 (31.9) [*]
Hypertension (%yes) [†]	98 (66.7)	303 (62.6)	524 (60.8)	925 (62.0)
Family history of heart disease(%yes) [†]	92 (69.7)	282 (64.7)	490 (64.3)	864 (65.0)
Diabetes mellitus (%yes) [†]	36 (24.5)	134 (27.6)	216 (25.1)	386 (25.9)
Dyslipidemia(%yes) [†]	100 (67.6) [*]	300 (61.7)	481 (55.7) [*]	881 (58.8) [*]
Overweight/obesity (%yes)	68 (46.9)	259 (54.3) ^{**}	380 (44.8) ^{**}	707 (48.1) ^{**}
Co-morbid Conditions (% yes)	129 (87.8)	437 (90.9) ^{***}	707 (82.9) ^{***}	1274 (86.0) ^{***}
Duke Activity Status Index, mean $\pm$ SD	37.63 $\pm$ 16.67	35.66 $\pm$ 15.78	36.61 $\pm$ 16.34	36.41 $\pm$ 16.20
Depressive Symptoms, mean $\pm$ SD	13.07 $\pm$ 10.16 ^{***}	10.60 $\pm$ 8.51 ^{**}	9.12 $\pm$ 7.81 ^{***}	9.97 $\pm$ 8.39 ^{***}
Women	15.54 $\pm$ 10.37 [*]	12.69 $\pm$ 9.64	10.42 $\pm$ 8.52 [*]	11.53 $\pm$ 9.07 ^{**}
Men	12.72 $\pm$ 9.34 ^{***}	9.97 $\pm$ 8.12 ^{**}	8.50 $\pm$ 7.45 ^{***}	9.35 $\pm$ 8.02 ^{***}

MI = myocardial infarction; FT/PT = Full-time/Part-time,

^{*}
p < .05;^{**}
p < .01;^{***}
p < .001.

⁷ Present if being treated for condition or noted in medical chart.
 Note: Percentages take into account missing values for some variables.

Table II

Frequency of Anti-Depressant use by Type and Smoking Status at Baseline

Type of Anti-Depressant	Current Smokers (N=148)	Former Smokers (N=486)	Non Smokers (N=864)	Total (N=1498)
Use of an Antidepressant (% yes)	35 (23.6)***	52 (10.7)	69 (8.0)	156 (10.4%)***
SSRIs	19(54.2%)	27(51.9%)	41(59.4%)	87 (55.8%)
Citalopram (Celexa)	4(21.0%)	11(40.7%)	15(36.6%)	30 (34.4%)
Paroxetine (Paxil)	8(42.1%)	7(26.0%)	7(17.1%)	22 (25.0%)
Trazadone (Desyrel)	3(15.8%)	4(36.4%)	7(17.1%)	14 (16.1%)
Sertraline (Zoloft)	3(15.8%)	4(14.8%)	5(12.2%)	12 (13.8%)
Fluoxetine (Prozac)	1(5.2 %)	1(3.7 %)	7(17.1 %)	9 (10.3)
Tricyclics/Tetracyclics	7(20.0%)	12(23.1%)	12(17.4%)	31 (19.9)
Amitriptyline	5(71.4%)	8(66.7 %)	8(66.7 %)	21 (67.7%)
Nortriptyline	0(0 %)	3(25.0 %)	1(8.3 %)	4 (12.9%)
Mirtazapine *	1(14.3 %)	0(0 %)	2(16.7 %)	3 (9.7%)
Desipramine	1(14.3 %)	0(0 %)	1(8.3 %)	2 (6.5%)
Trimipramine	0(0 %)	1(8.3 %)	0(0 %)	1 (3.2%)
SNRIs	4(11.4%)	7(13.5%)	11(15.9%)	22 (14.1%)
Venlafaxine (Effexor)	4(100 %)	7(100 %)	11(100 %)	22 (100%)
Bupropion (Wellbutrin)	2(5.7%)	3(5.8%)	4(5.8%)	9 (5.8%)
More than 1 Type	3(8.6%)	3(5.8%)	1(1.4%)	7 (4.5%)

SSRIs, Selective Serotonin Reuptake Inhibitors; SNRIs, Serotonin Norepinephrine Reuptake Inhibitors

* Mirtazapine has a tetracyclic chemical structure and is classified as a noradrenergic and specific serotonergic antidepressant. Because of its unique pharmacologic profile, mirtazapine does not have the true effects of a TCA.

Table III

Multinomial Logistic Regression Analysis: Correlates of Smoking Status, N = 1383

Smoking Status	Correlate	OR	P	95% Confidence Interval	
				Lower Bound	Upper Bound
Current smokers vs. Non-smokers	Depressive Symptoms	1.04	< .001	1.02	1.06
	Age	0.93	< .001	0.91	0.95
	Sex (women)	0.79	0.28	0.51	1.21
	Work status (FT/PT)	1.11	0.64	0.72	1.72
	Education (Greater than HS)	0.41	< .001	0.28	0.61
	Marital Status (Married)	0.52	0.001	1.35	0.78
	Index MI (yes)	1.42	0.08	0.96	2.11
	Co-morbid conditions (yes)	1.49	0.12	0.82	2.50
	Overweight/obesity (yes)	0.70	0.07	0.48	1.03
	Dyslipidemia (yes)	1.69	0.01	1.13	2.52
	Depressive Symptoms	1.02	0.02	1.00	1.03
	Age	0.99	0.03	0.97	1.00
Former vs. Non-smokers	Sex (women)	0.56	< .001	0.43	0.75
	Work status (FT/PT)	0.77	0.08	0.57	1.04
	Education (Greater than HS)	0.61	< .001	0.45	0.77
	Marital Status (Married)	0.74	0.03	0.57	0.97
	Index MI (yes)	1.14	0.30	0.89	1.48
	Co-morbid conditions (yes)	2.00	< .001	1.406	3.091
	Overweight/obesity (yes)	1.32	0.02	1.04	1.68
	Dyslipidemia (yes)	1.23	0.09	0.97	1.57

OR, Odds Ratio; vs., versus; DASI, Duke Activity Status Index; MI, Myocardial Infarction; FT/PT, Full-time/Part-time; HS, High School;

Table IV

Nine Month Effect of Antidepressant Use on Smoking Status and Well-Being Among Smokers with CAD, N=127

	Antidepressants (n=34)	No Antidepressants (n=93)	p
Smoking Status (% quitter)	1 (2.7)	20 (17.7)	0.03
HADS Anxiety, Mean $\pm$ SD	9.42 $\pm$ 4.23	5.94 $\pm$ 4.39	0.001
HADS Depression, Mean $\pm$ SD	6.89 $\pm$ 4.52	3.96 $\pm$ 3.69	0.001
BDI-II, Mean $\pm$ SD	17.59 $\pm$ 12.73	8.82 $\pm$ 9.38	0.001
Insomnia, Mean $\pm$ SD	12.30 $\pm$ 4.99	7.97 $\pm$ 5.35	0.001

HADS, Hospital Anxiety and Depression Scale; BDI, Beck Depression Inventory