ADHERENCE TO PHARMACOLOGICAL SMOKING CESSATION TREATMENT AMONG WEIGHT-CONCERNED WOMEN

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The concern about weight gain that usually accompanies smoking cessation is a substantial impediment to quitting for many women. Given that sustained-released (SR) bupropion is associated with decreased post-cessation weight gain (Jorenby et al., 1999), this pharmacological agent may be particularly effective in improving quit rates among weight-concerned women. Despite the increasing utilization of smoking cessation medications, such as bupropion, relatively little is known about adherence to these regimens. This study examined the rates, predictors, and sequalae of medication adherence among weight-concerned women participating in a 90-day smoking cessation program. In addition to receiving group behavior therapy, participants were randomized to receive either SR bupropion or placebo. Medication adherence was measured over time with electronic pill cap monitors, smoking cessation was measured by self-report and verified with carbon monoxide readings, and several psychosocial variables were assessed with self-report questionnaires. With 112 participants (91% Caucasian; mean age = 43, SD = 10 years), descriptive statistics were computed to summarize medication adherence, and linear and logistic regression analyses were used to predict medication adherence and prolonged smoking abstinence through the end of treatment, respectively. Overall medication adherence was less than optimal throughout the 90-day study period and adherence rates decreased during each successive 30-day period. Depending on the type of summary index, results indicated that medication adherence ranged from 26% to 73% over the 90-day period. Conscientiousness,

openness to experience, social support and medication outcome expectancies measured at Week 6 were positively associated with 90-day medication adherence. Independent of medication status, medication adherence predicted increased likelihood of maintaining prolonged smoking abstinence. Follow-up cross-lagged panel design analyses indicated that medication adherence significantly predicted subsequent point-prevalence abstinence. Moreover, openness to experience and Week 6 social support predicted increased likelihood of maintaining prolonged smoking abstinence, and post-hoc analyses indicated that medication adherence mediated the associations between openness to experience and prolonged abstinence, and between Week 6 social support and prolonged abstinence. These results suggest that interventions designed either to modify psychosocial variables associated with medication adherence or to match treatments with individual differences may enhance adherence and possibly improve smoking cessation rates among weight-concerned women.

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1 INTRODUCTION

Adherence is the degree to which a person's behavior (e.g., taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice (Haynes, 1979).[1] Unfortunately, adherence is far less than optimal across a wide range of health behaviors and chronic illnesses (Kaplan & Simon, 1990; Dunbar-Jacob, Schlenk, Burke, & Matthews, 1998a). The importance of adherence to smoking cessation treatment is underscored by the fact that cigarette smoking is the single most preventable cause of premature morbidity and mortality in the United States (United States Department of Health and Human Services [USDHHS], 1994). After decades of disproportionately higher rates of male smokers, the prevalence of smoking is now nearly equal between men (25%) and women (21%; Centers for Disease Control, 1999). One reason for the equalization of smoking rates is the failure of women to quit smoking as readily as men (Ockene, 1993). The concern about weight gain that usually accompanies smoking cessation is a substantial impediment to quitting for many women. Given that sustained-released (SR) bupropion is associated with decreased post-cessation weight gain (Jorenby et al., 1999), this pharmacological agent may be particularly effective in improving quit rates among weight-concerned women.

[1]Other terms have been used to describe this process, including noncompliance, non-cooperation, or patient resistance. Since "adherence" suggests more voluntary action on the part of the patient, and for the sake of consistency, this term is used throughout this report.

Despite the increasing utilization of pharmacological agents, such as bupropion, relatively little is known about rates and predictors of smoking cessation pharmacotherapy adherence. A review of the literature on adherence to other health behaviors and chronic disease regimens suggested that six psychosocial characteristics, depressive symptoms, agreeableness, conscientiousness, social support, expectancies, and medication side effects, have conceptual and empirical promise. Thus, two primary aims of the present study were to characterize rates of medication adherence among a sample of female weight-concerned smokers participating in a smoking cessation clinical trial and to examine the extent to which these conceptually relevant psychosocial variables predict medication adherence. In addition, because adherence to the treatment regimen was expected to enhance smoking cessation outcome, the sequelae of treatment adherence were explored. It is important to note adherence to active *and* inactive medication was expected to improve smoking cessation rates. Therefore, another aim of this study was to examine the main effect of medication regimen adherence on smoking cessation. Two final goals were to determine whether any of the aforementioned psychosocial parameters influenced the hypothesized relationship between adherence and smoking cessation or whether medication adherence influenced any observed relationships among the psychosocial variables and smoking cessation.

1.1 SMOKING AND WEIGHT CONCERNS AMONG WOMEN

As noted, concerns about post-cessation weight gain deter many women from quitting smoking. A majority of female smokers state that they have weight concerns related to quitting smoking (Pirie, Murray, & Luepker, 1991). Among young female smokers, almost 40% state that they smoke to manage weight (Klesges & Klesges, 1988) and, in comparison to men, women are three to four times more likely to cite weight gain as a determinant of relapse (Swan, Ward,

Carmelli, & Jack, 1993). Meyers et al. (1997) observed that weight-concerned smokers (80% women) fared significantly worse in quitting at 12 months in comparison to non-weight concerned smokers. Perkins et al. (2001) randomly assigned weight-concerned women to three adjunct treatments accompanying group smoking cessation counseling: (1) behavioral weight control, (2) cognitive-behavior therapy (CBT) to reduce weight concerns, and (3) standard counseling. Although results showed that CBT to reduce weight concerns group improved smoking cessation relative to the other conditions, the overall cessation rates were somewhat disappointing at 12 months follow-up (continuous abstinence rates): behavioral weight control group = 18%, (2) CBT to reduce weight concerns group = 21%, and (3) standard group = 9%. For this reason, Perkins et al. (2001) suggested that conjoint CBT to reduce weight concerns and smoking cessation pharmacotherapy might enhance quit rates to an even greater degree among weight-concerned women.

Bupropion is a pharmacological agent that may be beneficial in ameliorating weight gain and other factors particularly relevant to women's cessation efforts (e.g, depressive symptoms). Originally classified as an antidepressant (Wellbutrin®, GlaxoSmithKline, plc.), bupropion has been shown to be an effective treatment for mild to severely depressed individuals (Feighner, Meredith, Stern, Hendrickson, & Miller, 1984; Pitts et al., 1983; Zung, 1983). Subsequent investigations established the clinical efficacy of bupropion for smoking cessation (Hurt et al., 1997; Jorenby et al., 1999; Hays et al., 2001). The mechanisms by which bupropion facilitates smoking cessation are not known. However, two possible explanations include reductions in negative emotions and weight gain associated with quitting smoking. Shiffman and colleagues (2000) reported that bupropion attenuated negative affect and withdrawal among smokers who quit for a short time. Also, Hurt et al. (1997) observed that bupropion may influence weight gain

associated with smoking cessation. Independent of weight concerns, both men and women gained significantly less weight in a dose-response manner after seven weeks of treatment. That is, after seven weeks of treatment, the placebo group gained 2.9 kg, bupropion 100 mg group gained 2.3 kg, the 150 mg group gained 2.3 kg, and 300 mg group gained 1.5 kg (Hurt et al., 1997). Jorenby et al. (1999) and Hays et al. (2001) also reported that bupropion attenuated post-cessation weight gain, and in two other trials Anderson et al. (2002) and Jain et al. (2002) showed that bupropion facilitates weight loss in obese individuals. Finally, nicotine replacement treatments have not been as successful with women as with men (Perkins, 1996) and bupropion has been shown to be an effective treatment for preventing smoking relapse among women (Gonzales et al., 2002). In summary, bupropion was selected as the pharmacological agent in the larger clinical trial because of its potential utility for smoking cessation in weight-concerned women.[2]

1.2 HEALTH-RELATED ADHERENCE

Health-related adherence is critical for the prevention, treatment, and empirical examination of diseases for many reasons. From a clinical point of view, poor adherence to treatment can lead to incorrect diagnoses and patient and health-care provider frustration (Haynes, Taylor, & Sackett, 1979). In certain circumstances, failure to adhere to medical regimens may result in serious consequences. For instance, low adherence rates among individuals with chronic medical

[2] The overall clinical trial is also designed to examine the efficacy of group smoking cessation counseling: cognitive-behavioral therapy to ameliorate post-cessation weight concerns versus standard smoking cessation counseling. Since the effects of medication and counseling treatments were not the focus of the present study, these factors were assessed for the possibility of confounding medication adherence analyses, and if necessary, statistically adjusted for in such cases (see Data Analytic Plan section).

illnesses have been associated with increased hospital admissions and longer hospital stays (Dunbar-Jacob, Burke, & Puczynski, 1995). Nonadherence may play an important role in the reemergence of drug-resistant organisms, including tuberculosis (Gourevitch, Wasserman, Panero, & Selwyn, 1996) and human immunodeficiency virus (HIV; Mellors, 1997). Nonadherence to treatment requirements for chronic diseases, such end-stage renal disease, is associated with serious medical complications and earlier mortality (Plough, 1992). Unfortunately, satisfactory adherence across a range of chronic disease regimens is as low as 15-20% (Myers & Midence, 1998), and consequently, the annual cost of nonadherence to medical treatment in the United States has been estimated to be $100 billion (Grahl, 1994). Treatment adherence is critical from a research perspective, as well. Poor adherence may complicate and even jeopardize interpretation of findings from clinical trials by reducing the overall group differences in response to treatment. In turn, additional costs may be incurred due to substantial increases in the number of participants required to preserve required statistical power (Dunbar-Jacob, Sereika, Rohay, & Burke, 1998b). In sum, patient nonadherence may significantly contribute to treatment failures in medical and psychological interventions and, thus, poses a significant problem for health care delivery and research.

In light of the potentially severe consequences of nonadherence to health regimens, the identification of factors that predict adherence has received considerable attention. When concomitants of nonadherence are identified, appropriate interventions may be developed to improve patient adherence and ultimately health outcomes (DiMatteo, Lepper, & Croghan, 2000). Unfortunately, relatively little is known about the predictors of adherence to pharmacological smoking cessation treatments.

1.3 PREDICTORS OF ADHERENCE TO PHARMACOLOGICAL SMOKING CESSATION TREATMENT

Recent clinical practice guidelines on treating tobacco dependence indicate that SR bupropion has the highest empirical record of efficacy among first-line cessation-related pharmacotherapies (Fiore et al., 2000). Despite this and other endorsements (e.g., Hughes, Stead, & Lancaster, 2002; Hughes, Goldstein, Hurt, & Shiffman, 1999) and bupropion's increasing popularity[3], published clinical trials examining the effects of bupropion on smoking cessation have not included information about regimen adherence (i.e., Hurt et al., 1997; Jorenby et al., 1999; Hays et al., 2001) Although there are published data on predictors of adherence to antidepressants among depressed individuals (e.g., Demyttenaere, Van Ganse, Gregoire, Gaens, & Mesters, 1998), these findings are inconsistent and have minimal generalizability to the present study, as individuals with current mood disorders were excluded.

Several nicotine replacement studies have included measures of adherence, but for the most part these studies inadequately define and measure adherence (Alterman, Gariti, Cook, & Cnaan, 1999; Fiore, Smith, Jorenby, & Baker, 1994). Two studies have reported on predictors of nicotine replacement adherence. Alterman et al. (1999) examined several potential predictors of nicotine patch adherence, including sociodemographics, nicotine dependence, withdrawal symptomatology, motivation to quit smoking, current and past psychopathology, and level of self-efficacy to quit smoking. Multiple regression analysis revealed three significant predictors of adherence—nicotine dependence, motivation to change, and psychosocial treatment condition—that accounted for 18% of the variance of days of patch use. In a study of nicotine gum adherence, individuals who reported higher self-efficacy to refrain from smoking in tempting

[3] Bupropion is licensed for the treatment of tobacco dependence in over 50 countries worldwide (Hays & Ebbert, 2003); U.S. sales of bupropion (as a smoking cessation aid) exceeded $90 million in 2001 (GlaxoSmithKline, 2002).

situations were more likely to report higher adherence to gum use recommendations (Millard, Waranch, & McEntee, 1992). However, inferences from this study are suspect given the use of self-reported gum usage and the lack of a placebo group. Although the results from these two studies are interesting, it is clear that more research is needed to determine what other variables predict the majority of unaccounted variance in adherence to cessation-related pharmacological treatments, particularly bupropion. For this reason, the present study explored the role of several psychosocial variables that may facilitate the prediction of pharmacotherapy adherence.

1.4 PSYCHOSOCIAL PREDICTORS OF ADHERENCE

Because there are so few published findings on smoking cessation pharmacotherapy adherence, existing "theory" would consist of empirically unsubstantiated hunches about this behavior (Menard, 2002). Fortunately, the research on adherence to other health behavior change and disease treatment regimens has increased dramatically over the past quarter century, with 16,124 articles on medication adherence published between 1976-1999 (Trostle, 2000), and has provided a wealth of information about plausible predictors of adherence to smoking cessation pharmacotherapy. Not surprisingly, there are a substantial number of variables that have been linked with adherence, but consistent findings across studies have been lacking (Dunbar-Jacob et al., 1998b). It has been difficult to interpret available evidence due to the heterogeneous nature of extant studies, including divergent disease characteristics, regimen behaviors, classifications of adherence, and approaches of assessing adherence (Dunbar-Jacob et al., 1998b). The use of several theoretical models, including the Health Belief Model, the Theory of Reasoned Action, the Theory of Planned Behavior, Attrition Theory, and the Self-Regulatory Model, have yielded inconsistent results, and have generally been unsupported in the prediction of adherence to several disease and health behavior change regimens (Clark & Becker, 1998; Horne & Weinman,

1998). Although research with the Stages of Change Model in the prediction of health behavior change has yielded some interesting findings in the area of smoking cessation (DiClemente & Prochaska, 1998), substantial criticism of the model on conceptual grounds has partly undermined the importance of this body of research (e.g., Weinstein, Rothman, & Sutton, 1998). For these reasons, a multivariate, exploratory approach was used in the process of selecting psychosocial predictors for inclusion in this study.

When choosing variables for multivariate research, it is optimal to utilize a small number of valid variables that cover all of the theoretically important dimensions of a research area (Tabachnick & Fidell, 1996). An examination of three notable reviews of predictors of adherence (Haynes, 1979; Kaplan & Simon, 1990; Dunbar-Jacob et al., 1998a) offered several distinct, yet complementary areas of adherence predictors. Specifically, the dimensions of mood, personality, social support, social-cognition, and somatization appeared to be the most relevant and inclusive. Based on empirical and conceptual grounds, several psychosocial characteristics within these five dimensions—depression, conscientiousness, agreeableness, expectations, and side effects—were thought to offer the most promise in explaining individual differences in smoking cessation pharmacotherapy adherence. In the following sections, findings on these putative predictors of adherence are reviewed, including results from a diverse range of health regimens and diseases, and from the smoking cessation literature when available.

1.4.1 Depression

Individuals with depressive symptomatology and a history of major depression disorder (MDD) have increased risk of poor health outcomes, including higher rates of cardiovascular morbidity and mortality (Musselman, Evans, & Nemeroff, 1998). Although depression may have direct physiological effects on disease pathogenesis, it is also likely that behavioral mediators are also at play (Musselman et al., 1998). Specifically, poor treatment adherence may be a primary

behavioral manifestation of depression. Depression tends to diminish concentration, energy, and motivation, which in turn may negatively influence an individual's willingness and capacity to adhere to a treatment regimen (DiMatteo et al., 2000). Although the link between depression and nonadherence has not been demonstrated consistently (Dunbar-Jacob et al., 1998a), a recent meta-analysis of studies correlating medical patients' treatment nonadherence with depression supports the relationship. DiMatteo et al. (2000) reviewed 12 published studies that examined recommendations given by physicians across several diseases, including end-stage renal disease and kidney transplantation, cancer, general medicine, angina, and rheumatoid arthritis. Eleven of the 12 studies showed a significant negative association between depression (primarily measured symptomatically, e.g., Beck Depression Inventory; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and adherence. Patients with higher levels of depression were three times as likely as patients with lower levels to be poor adherers (DiMatteo et al., 2000).

Few studies have directly examined the association between depression and adherence to pharmacological smoking cessation treatment. Ginsberg et al. (1997), however, in a notable exception, examined whether a history of depression in female smokers (age 18-65) who did not self-report a current MDD episode was associated with adherence to multi-session, multi-component smoking cessation treatment that included nicotine replacement. Results indicated that there was no effect of history of MDD on adherence to treatment, as measured by chewed nicotine gum returned to the clinic and counseling attendance. Unfortunately, depressed symptoms were not assessed, so it is unclear how sub-clinical mood symptoms influenced adherence.

It is plausible that depressive symptomatology may predict treatment adherence among weight-concerned women. History of MDD and level of current depressive symptomatology has

been linked with increased rates of smoking (Acierno, Kilpatrick, Resnick, Saunders, & Best, 1996; Lumley, Downey, Stetner, Wehmer, & Pomerleau, 1994). Individuals with a history of MDD have greater difficulty with quitting smoking (Breslau, Kilbey, & Andreski, 1992). In a previous study with weight-concerned women attempting to quit smoking, 52% had a history of mood disorder and some participants manifested significant current depressive symptomatology (Levine, Marcus, & Perkins, 2003). Although women with current MDD were excluded from the present study, it is likely that many participants had a history of mood disorder and current depressive symptoms. With the exception of the findings by Ginsberg et al. (1997), the weight of the evidence suggests that depression may be associated with poorer adherence to pharmacological smoking cessation treatment among weight-concerned women.

Although depressive and anxiety symptoms often coexist, the meta-analysis by Dimatteo and colleagues (2000) found no consistent relationship between anxiety and treatment adherence. For this reason, anxiety was not examined in this study.

1.4.2 Personality

Several researchers have concluded that the empirical literature provides minimal support for associations between personality traits and treatment adherence (Haynes, Taylor, Snow, & Sackett, 1979, 1979; Kaplan & Simon, 1990; Horne, 1998; Dunbar-Jacob et al., 1998a). However, this conclusion may have been premature given that the personality and health literature has been severely hampered by the use of numerous measures indexing narrowly defined and likely overlapping constructs (Smith & Williams, 1992; Marshall, Wortman, Vickers, Kusulas, & Hervig, 1994). In their extensive review of 853 original articles, methodological articles, and reviews/commentaries, Haynes et al. (1979) found no associations between Minnesota Multiphasic Personality Inventory (MMPI) scales, the most commonly used measure, and patient adherence in the preponderance of studies. Given that the MMPI was

originally constructed to differentiate individuals with and without clinical psychopathology (Butcher, Graham, Dahlstrom, Tellegen, & Kaemmer, 1989), it is not surprising that studies reviewed by Haynes et al. (1979) did not report significant associations between MMPI profiles and adherence among a range of non-clinical populations (e.g., college students, medical populations). In addition, as will be discussed below, the implications of these null findings should not be over-generalized given that reliable and valid measures of adherence were not yet developed and utilized in a majority of the studies conducted in the 1960s and 1970s.

On the other hand, in their extensive review Haynes and Sackett (1976) reported significant, albeit small, correlations between adherence and the wide range of "personality" characteristics, including active vs. passive orientation, futuristic orientation, work orientation, frustration tolerance, feelings of loneliness, motivation, unreliable personality type, immaturity, avoiding responsibility, impulsivity, responsiveness/cooperativeness, authoritariantism, and articulateness/intelligence. Many of these early findings were based on subjective ratings from clinical interviews, which are subject to interviewer biases and lack generalizability across studies (Wiebe & Christensen, 1996). Also, such a hodge-podge of individual difference measures are without a central theoretical schema, so it is difficult to reach firm conclusions about the implications of these findings. Other standardized personality measures have not received much attention in the adherence literature. Therefore, it is possible that applying a more systematic model of personality may be fruitful in the prediction of adherence to treatment regimens.

During the past two decades, there has been a resurgence of interest in a five-factor taxonomy of personality dispositions (Smith & Williams, 1992). The NEO Personality Inventory-Revised (NEO-PI-R) and its short-form, the NEO Five Factor Inventory (NEO-FFI;

Costa & McCrae, 1992), incorporate one of the leading operationalizations of the five-factor model. There are now extensive data supporting the reliability and construct validity of the five NEO factors—conscientiousness, agreeableness, neuroticism, extraversion, and openness to experience (Costa & McCrae, 1992). Concurrently, there has been growing appreciation for the potential utility of a five-factor model in elucidating personality correlates of health-related outcomes (Smith & Williams, 1992). Wiebe and Christensen (1996) proposed that, if used consistently, the five-factor model of personality would bring a central theoretical organization to the personality and health literature. As such, this structure would minimize variability in the field, permit significant accumulation of empirical findings, and organize the direction of future research (Smith & Williams, 1992). Another benefit of using the NEO-FFI is that it does not include any health-related items and therefore obviates confounding with health outcomes (Booth-Kewley & Vickers, 1994). Although the utilization of the five-factor personality model in characterizing patient adherence to health or medical regimens has potential, applications have been relatively few to date. An inspection of the five-factor model reveals two dimensions—conscientiousness and agreeableness—that may most accurately describe qualities important for regimen adherence. Although it is possible that the other three dimensions of the Five-Factor Model of Personality—neuroticism, openness to experience, and extraversion—are relevant to health-related behaviors, these factors seemed less conceptually and empirically relevant to medication adherence. For instance, previous research with the NEO-FFI reported non-significant associations between composite indices of health behaviors and neuroticism, openness to experience, and extraversion (Booth-Kewley & Vickers, 1994; Lemos-Giraldez & Fidalgo-Aliste, 1997). For this reason and for the sake of parsimony, the effects of the latter three

personality dimensions on medication adherence and smoking cessation were assessed in secondary analyses.

1.4.2.1 Conscientiousness

Conscientious is a cluster of traits that include both self-restraint (order, dutifulness, and deliberation) and active striving to achieve goals. Individuals scoring high on this dimension are hardworking, persistent, and highly motivated; individuals scoring low are easygoing and moderately disorganized, and lack a clear direction in their lives (McCrae & Stone, 1997). Conscientious individuals are presumably also the most likely to adhere faithfully to prescribed medical regimens (Christensen & Smith, 1995). A recent seven-decade longitudinal study with 1,178 males and females reported that conscientiousness in childhood was robustly related to survival in middle age and old age (Friedman et al., 1993), and it is possible that various health behaviors, including adherence to medical regimens, were responsible (Friedman et al., 1995). Booth-Kewley and Vickers (1994) found that high conscientiousness scores on the NEO-PI predicted of wellness behaviors (e.g., exercise, vitamin taking), accident control (e.g., learning first aid), and low traffic-related risk-taking. Lemos-Giraldez and Fidalgo-Aliste (1997) reported that conscientiousness scores from a Spanish-translated version of the NEO-FFI predicted a global measure of 15 health-related behaviors, including decreased smoking and alcohol consumption, increased exercise, and a balanced, moderate low-fat diet. Christenesen and Smith (1995) found that the NEO-FFI conscientiousness scale was significantly associated with medication adherence among end-stage renal disease patients, but failed to replicate this direct relationship in another study (Wiebe & Christensen, 1997). Christensen (2000) reported that a patient-by-treatment context interaction might explain their inconsistent findings. That is, among individuals given more responsibility for adhering to their hemodialysis treatment (i.e.,

peritoneal dialysis at home), individuals with a more active coping style were more adherent (Christensen, 2000). Since patients in the present study had complete autonomy for adhering to their medication regimen, it was expected that highly conscientiousness individuals would manifest higher rates of adherence.

1.4.2.2 Agreeableness

Agreeableness is one of the more interpersonal dimensions of the five-factor model (Smith & Williams, 1992). Individuals scoring high on agreeableness are prosocial, compliant, accepting, honest, and straightforward. Individuals scoring low are hostile, suspicious, devious, demanding, and manipulative (McCrae & Stone, 1997). Booth-Kewley & Vickers (1994) found that individuals low in NEO-PI agreeableness engaged in significantly fewer wellness and accident control behaviors, and increased traffic-related risk-taking. Also, as agreeableness is inversely related to hostility (Smith & Williams, 1992), the findings of Booth-Kewley & Vickers (1994) are consistent with other research associating hostility with unhealthy behaviors (e.g., Leiker & Hailey, 1988; Smith, 1992). In the context of research showing that hostility leads to physical disease (Miller et al., 1996), it is possible that hostile individuals have increased health risks due to poor health habits, possibly including poor adherence to medical regimens.

Given that adherence is thought to be partly due to the interaction between a patient and a health care provider (Griffith, 1990), it seems logical to assume that individuals low in agreeableness may not trust in the prescribed treatment regimen and thereby manifest poorer adherence. Few researchers have tested this hypothesis. A literature search revealed only two studies examining the effects of hostility on medication adherence. Lee and colleagues (1992) studied the impact of hostility on adherence to antihypertensive medication among 620 hypertensive men. Individuals scoring high on the Hostility Scale of the Brief Symptom

Inventory (Derogatis & Melisaratos, 1982) reported missing more medication doses compared to those scoring low on the Hostility Scale. Christensen, Wiebe, and Lawton (1997) examined the effect of cynical hostility on regimen adherence among 48 hemodialysis patients. A hierarchical regression analysis revealed that Cook-Medley Hostility (Cook & Medley, 1954) scores significantly predicted poorer medication and dietary adherence. However, an interaction between hostility and Powerful Others Health Locus of Control (Wallston, Wallston, & DeVillis, 1978) scale indicated that the effect of hostility was strongest among individuals believing that positive health outcomes are not a function of powerful others, such as health care providers. The results of these two studies suggest that low levels of agreeableness may lead to poorer medication adherence.

1.4.3 Social Support

Social support is a broad construct that is defined and measured in multiple ways. One popular approach is to operationalize social support as the extent to which an individual perceives various supportive functions to be available from his or her social relationships (Sarason & Sarason, 1994). The supportive functions include emotional (e.g., sharing feelings), informational (e.g., advice), instrumental (e.g., money), and tangible support (e.g., companionship; Sarason & Sarason, 1994). Thus, measures of perceived social support index the extent to which an individual knows other people who could provide these kinds of resources if a need existed. The notion that social support is a determinant of adherence has inherent appeal. That is, the greater the availability of useful help from close others, the more likely that an individual will be motivated and capable of adhering to treatment regimens.

Social support has been associated with a variety of health outcomes, including mortality (House, Landis, & Umberson, 1988; Rosengren, Orth-Gomer, Wedel, & Wilhelmsen, 1993). Health behaviors, in part, may explain these associations. A wide range of studies suggests that

the perceived social support significantly predicts adherence across a variety of health domains (Haynes et al., 1979; Levy, 1983). Moreover, Morisky, DeMuth, Field-Fass, Green, and Levine (1985) randomly assigned hypertensive patients to a program designed to increase family social support for treatment adherence or to a control group. Patients in the support condition demonstrated significantly higher treatment adherence (i.e., with medication, appointment-keeping, and weight control) and reduced blood pressure over a three-year period. More recently, social support has been associated with patient adherence to a variety of chronic disease regimens, including diabetes regimens (Sherbourne, Hays, Ordway, DiMatteo, & Kravitz, 1992), hemodialysis (Christensen et al., 1992), and HIV regimens (Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000). However, an association between perceived support and adherence has not been consistently found (Moran, Christensen, & Lawton, 1997). The equivocal results may be attributable, in part, to the psychometric inadequacy of several social support measures (Heitzmann & Kaplan, 1988). In the current study, the Interpersonal Support Evaluation List (ISEL; Cohen, Mermelstein, Kamarck, & Hoberman, 1985), an instrument with adequate psychometric properties, was used to examine whether perceived social support is predictive of medication adherence.

1.4.4 Expectancies

Bandura's social learning theory (1977) has provided a useful framework for studying a variety of health-related behaviors, including treatment adherence. Two core constructs of social learning theory relevant to adherence are self-efficacy and outcome expectancies. Self-efficacy expectancies are beliefs that one can successfully perform the actions required to achieve valued outcomes. Relative to individuals with low self-efficacy expectations, those with high self-efficacy expectations are thought to be more likely to initiate a behavior, expend more effort, and sustain a behavior while experiencing obstacles (Bandura, 1977). Accordingly, individuals

possessing greater adherence-related self-efficacy beliefs would be expected to exert more effort and persist more in the face of obstacles, resulting in higher adherence to the treatment regimen. In fact, lower self-efficacy expectations for treatment adherence have been related with subsequently poorer adherence to a variety of disease regimens, including fluid intake adherence among chronic hemodialysis patients (Brady, Tucker, Alfino, Tarrant, & Finlayson, 1997), adherence to a rheumatoid arthritis medication (Brus, van de Laar, Taal, Rasker, & Wiegman, 1999), adherence to home glucose testing, diet, and exercise behaviors among individuals with type 2 diabetes (Skelly, Marshall, Haughey, Davis, & Dunford, 1995), and antiretroviral medications among HIV+ patients (Catz et al., 2000).

Although there is a substantial literature on the relationship between self-efficacy expectancies and smoking cessation (often referred to as "abstinence self-efficacy;" Gwaltney, 2000), these efficacy expectancies often pertain to perceived coping abilities across a range of conditions (e.g., feelings, arousal levels, environmental stressors) that may lead to smoking relapse (Gwaltney et al., 2001). However, there have been no apparent attempts to examine how self-efficacy expectancies affect adherence to smoking cessation treatments, including bupropion. Since self-efficacy expectancies are behavior specific and are not considered to comprise a trait (Maddux, 1999), a goal of the present study was to examine the extent to which adherence-related self-efficacy expectancies prospectively influence actual adherence to the medication regimen.

Outcome expectancies are the beliefs that certain actions will led to specific outcomes in particular situations (Bandura, 1977). With respect to treatment adherence, individuals who believe that taking their medication will lead to better health outcomes may be more likely to adhere to their medication regimen than those who do not hold this belief. Outcome

expectancies, or perceived benefits, are a central component of the Health Belief Model (HBM), one of the most commonly applied models to adherence (Clark & Becker, 1998). Janz and Becker (1984) reviewed 46 studies of adherence to preventive health and disease regimens, and found that positive outcome expectancies or perceived benefits were significant in 78% of the studies. In a meta-analysis of the studies in Janz and Becker's (1984) review, Booth-Kewley and Vickers (1994) reported a significant relationship ($\underline{r} = .33$) between positive outcomes expectancies and health-promoting behaviors.

In the nicotine literature, the focus of research has been on the expectancies of smoking itself (e.g., smoking as a stress reliever) and how these beliefs affect a range of smoking behaviors, including current nicotine use and dependence, the initiation of smoking, cessation attempts and outcomes, and nicotine withdrawal symptoms (Brandon, Juliano, & Copeland, 1999). For instance, Gottlieb, Killen, Marlatt, and Taylor (1987) used a balanced placebo design to manipulate expectancies and pharmacological treatment for smoking cessation. In this study, 109 smokers attempting to quit were randomly assigned to nicotine gum or placebo gum and were randomly told they were receiving nicotine gum or placebo. Participants who reported that they were receiving nicotine gum smoked fewer cigarettes during the first week of quitting in comparison to those who believed they were receiving placebo gum. Interestingly, the actual nicotine content of gum did not affect relapse. Despite the assessment of smoking expectancies in several other experimental and observational studies, outcome expectancies in reference to behaviors involved with quitting smoking, such as adherence to pharmacotherapy, apparently have not been examined.

Bandura's social learning model (1977) posits that self-efficacy and outcome expectancies are orthogonal and should be examined conjointly in the prediction of behavior

change. However, the two variables are often correlated and, as a result, it is common that only one predicts the health outcome. For instance, Skelly et al. (1995) examined the relationships between self-efficacy and outcome expectancies and adherence to a diabetes regimen consisting of home glucose testing, medication/insulin administration, diet, and exercise. The correlation between outcomes and efficacy expectancies was .75, and when both variables were entered into a multiple regression model, only efficacy expectations were a significant predictor of adherence. Similarly, in a study of fluid intake adherence among hemodialysis patients, adherence self-efficacy and outcome expectancies were both entered into multiple regression model, but only self-efficacy expectancies significantly predicted adherence (Brady et al., 1997). In that study, self-efficacy and outcome expectancies were uncorrelated ($\underline{r} = .20$, $\underline{p} > .05$), but inspection of the three outcome expectancy items indicated that they might have not actually indexed beliefs that adhering to the hemodialysis regimen would improve their health status (e.g., "If I had a way to keep track of how much liquid I drink, I would be able to drink less").

It is possible that certain characteristics of the adherence regimen may influence the explanatory power of outcome versus self-efficacy expectancies. In their review of studies examining self-efficacy and health behaviors, Strecher, DeVallis, Becker, and Rosenstock (1986) concluded that self-efficacy expectancies are probably predominant when the health behavior is thought to lead to preferred consequences but the change is not easy to achieve. In the two studies examining self-efficacy and outcome expectancies discussed above (Skelly et al., 1995; Brady et al., 1997), the diabetes and hemodialysis regimens were characterized by considerable complexity or difficulty with implementation. Therefore, it is not surprising that self-efficacy expectancies had greater predictive power. However, the inverse of the above conclusion by Strecher et al. (1986) may be true for adherence to less challenging regimens, such as the

standard bupropion regimen which consists of two pills per day. Stated differently, it is plausible that outcome expectancies may be paramount when the health behavior (e.g., medication adherence) is not necessarily expected to lead to the desired consequences (e.g., smoking cessation) and the change (e.g., taking one pill twice per day) is relatively easy to make. Since this hypothesis is speculative, the present study examined the extent to which both self-efficacy and outcome expectancies predict adherence to the medication regimen.

1.4.5 Side Effects

Medication side effects, defined as actions of a drug that are different from its intended use (Barsky, Sainfort, Rogers, & Borus, 2002), are quite common among individuals taking an active or inactive drug. Barsky et al. (2002) differentiate two types of medication side effects: (1) "specific side effects are symptoms or physiological changes that result directly from the specific biological and pharmacological activity of the drug and tend to be dose-dependent and predictable," and (2) "nonspecific side effects are symptoms or physiological changes that cannot be explained on the basis of the known pharmacology of the drug and are idiosyncratic and not dose-dependent" (p. 622). Although either type of side effects may be construed as indication that the medication is active and beneficial (Hitsman, Spring, Borrelli, Niaura, & Papandontos, 2001), it is probable that most are adverse in nature. A small subset of individuals consuming bupropion is expected to suffer relatively severe adverse side effects, such as hypertension, hives, and possibly seizure (Micromedex, 2003). In these circumstances, the health care provider often discontinues the regimen, and consequently, this would not be classified as nonadherence. Other individuals taking an active or inactive medication may experience specific or nonspecific side effects that are less severe and not contraindicative (Hurt et al., 1997; Jorenby et al., 1999; Hays et al., 2001), but are still perceived as a nuisance. It is these situations when individuals may decide that the benefits of the medication do not outweigh the costs of negative

side effects and in turn may voluntarily under-dose or discontinue taking the medication. As a smoking cessation aid, antidepressants in high doses led to increased side effect levels and higher incidence of dropout (Jorenby et al., 1999; Niaura et al., 2002). Side effects deterred adherence among adolescents taking medication for iron deficiency (Cromer, Steinberg, Gardner, Thornton, & Shannon, 1989) and adult women taking the infertility drug ethinylestradiol (Kruse, Eggert-Kruse, Rampmaier, Runnebaum, & Weber, 1993). Moreover, in a randomized clinical trial comparing hypertensive pharmacotherapies (Preston, Materson, Reda, & Williams, 2000), adverse, nonspecific side effects to placebo medication led to a discontinuation rate (13%) that was comparable to the mean rate of six active antihypertensives (12%). Thus, it was posited that side effects would be inversely associated with medication adherence in the present study.

1.4.6 Covariation among Psychosocial Predictors

The mixed and often unreplicated findings on the associations between psychosocial variables and adherence in the extensive adherence literature may be attributed in part on the use of univariate research strategies. That is, many studies have explored the associations between adherence and individual psychosocial variables (e.g., DiMatteo et al., 2000). However, examining one psychosocial predictor in the absence of other theoretically and empirically-related factors fails to control for related variables and therefore reduces the validity of any observed correlations. In other words, the overlap between many health-related psychosocial parameters raises questions about the extent to which the relationship between a single variable and adherence is confounded by the role of a third (i.e., "hidden") variable. Although true experiments provide the only basis for definitive causal inferences, inferences from correlational research may be strengthened when confounding variables are ruled out. For example, examining the discrete effects of depression on adherence would negate the possibility of examining whether an observed correlation was accounted for in part or completely by other related

constructs. In the aforementioned meta-analysis on depression and adherence, DiMatteo et al. (2000) relied on zero-order correlations to support the conclusion that depression increased the risk of nonadherence among several medical regimens. However, it is plausible to hypothesize on a variety of conceptual grounds that a third variable, such as social support or hostility, caused both depression and poor adherence. Raynor, Pogue-Geile, Kamarck, McCaffery, and Manuck (2002) posited that, "Those who are depressed may view the world in a cynically hostile manner by virtue of their negative affective state. Hostile individuals may drive people away or may not accurately perceive others' affiliative intentions. Individuals lacking the perception that support is available may be lonely and depressed as a result" (p. 191). In this vein, the Big Five factors of personality are thought to be conceptually distinct, but empirical evidence suggests that they are not orthogonal. For instance, Shadel, Niaura, Goldstein, and Abrams (2000) reported a significant overlap between Extraversion and Openness to Experience (r = .58) and between Neuroticism and Agreeableness (r = -.37). Importantly, the use of multivariate strategies, such multiple regression modeling, facilitates the examination of related variables by providing statistical information about the unique predictive utility of each variable in the context of every other included variable (i.e., with partial t-tests).

It is also possible that psychosocial variables account for variance in adherence in an additive or interactive manner (Rozanski, Blumenthal, & Kaplan, 1999; Burns & Katkin, 1993). An interaction, or moderational effect, takes place when a third variable influences the direction and/or strength of the relation between a predictor and criterion variable (Baron & Kenny, 1986). An advantage of including several plausible psychosocial factors simultaneously is that the overall predictive utility of a block of these variables can be assessed and potentially important potentiation among psychosocial parameters can be tested. Although there were too many

possible interactions among the six aforementioned psychosocial parameters to test, a few notable possibilities were considered. Since individuals lacking social support may be at increased risk for manifesting and recovering from depression (Roberts & Gotlieb, 1997), the possibility that high levels of depression and low levels of social support would potentiate the risk of nonadherence was explored. Secondly, individuals experiencing depressive symptoms tend to be vulnerable to medication side effects. That is, a subset of depressed individuals may be "... somatically preoccupied, expect to suffer and experience discomfort, and don't feel they deserve to get better" (Barsky et al., 2002, p. 625). Thus, depressed individuals experiencing high levels of medication side effects were expected to manifest relatively poor medication adherence. Thirdly, individuals experiencing a *sustained change* in aversive physical symptoms after initiating the medication regimen would be expected to manifest less favorable medication adherence. Stated differently, individuals who tend to experience relatively few ambient physical symptoms at pretreatment but then experience several negative, non-remitting medication side effects after starting the medication may decide to underdose or discontinue their medication. On the other hand, those who experience high levels of pretreatment physical symptoms may not attribute specific side effects to the new regimen given the "background noise" or lack of change from baseline. Similarly, those who experience a change in physical symptoms from pretreatment but then experience attenuation shortly thereafter may think that they are habituating to the medication (as instructed by the project nurse) or are overcoming the nicotine withdrawal stage. Thus, it was posited that individuals experiencing a higher number, more severe, and long-lasting side effects would manifest poorer medication adherence relative to those experiencing less aversive side effects.

1.4.7 Summary of Putative Psychosocial Predictors

Although smoking cessation pharmacotherapy is increasingly prevalent, relatively little is known about correlates of adhering to this important health behavior. The larger health-related adherence literature provided some conceptual and empirical support for the predictive utility of several psychosocial parameters. The issues of confounding and potentiation among psychosocial variables provided a basis for using a multivariate approach in the present study, as well as motivating the choice of specific psychosocial variables and hypothesizing moderating patterns among some of them.

1.5 MEASUREMENT OF ADHERENCE

The inability to precisely measure adherence has hindered attempts to identify consistent predictors of this behavior. The numerous ways to assess adherence are not always accurate, and each one provides its own set of problems.[4] For the most part, self-reported adherence is not an accurate measure. Whereas patient reports of poor adherence are usually reliable, reports of proper adherence are often inflated (Epstein & Cluss, 1982). Similarly, there is evidence that physicians tend to overestimate their patients' rates of adherence (Rand & Weeks, 1998).

More objective measurements seem to be slightly better, but they remain questionable as well. One of the more widely used of these objective methods is counting pills remaining in a patient's prescription. This quantitative approach documents whether the proper amount of medication was removed from its container between clinic visits (Dunbar-Jacob et al., 1998b). Unfortunately, patients are able to deceive investigators by creating the impression that they consumed the prescribed amount (e.g., by throwing away remaining medications, sharing

[4] For an extensive review, see Rand and Weeks (1998).

medications with family members, etc.), and these counts do not allow any inferences about whether the medication was taken on schedule or all at once (Rand & Weeks, 1998).

The use of clinical outcomes (i.e., whether or not the patient improves) to index adherence is problematic in that this measure is based on the assumption that proper adherence will always lead to a better health outcome and that health outcomes are always a function of adherence (Myers & Midence, 1998). This assumption is faulty in that treatment adherence is only one of many factors affecting patients' progress (e.g., individual differences in medication responsiveness, proper diagnosis, etc.).

Another, more direct means to assess adherence is to measure levels of a prescribed medication in blood or urine. This method is the only type to verify that medications have actually been consumed and, as a result, have yielded somewhat more reliable estimates of adherence than other methods (Rand & Weeks, 1998). However, there are several problems with this approach, as well. There are individual differences in how patients absorb, metabolize, and excrete medications and, as a result, the quantity of ingested drug is unknown (Myers & Midence, 1998). This approach does not provide information about the temporal patterns of medication taking, resulting in the possibility that a patient consumes the medication directly before known assessments ("white-coat adherence"). Furthermore, biological verification is only available for a few drugs (Rand & Weeks, 1998). Not surprisingly, available evidence suggests that there are several limitations to therapeutic drug monitoring of bupropion (Preskorn, Fleck, & Schroeder, 1990). There exists wide variability in plasma levels of bupropion and its metabolites among patients (Preskorn & Katz, 1989). The assay used to verify these levels is technically complex, and results may differ as a function of the capacities of the laboratory employed. In addition, buproprion is not stable in plasma and, unless the sample is immediately frozen, it will

degrade (Preskorn et al., 1990). Due to the relative weaknesses of the aforementioned adherence measures, an indirect method, electronic event monitoring (EEM), was used as the primary measure of adherence in the present study.

EEM is widely considered the best available method for measuring medication adherence (Dunbar-Jacob et al., 1998b; Farmer, 1999), and not surprisingly, its utilization has increased greatly over the past 15 years. A common attribute of electronic monitoring devices is that they are able to record date and time of each monitor activation via a microprocessor chip (Dunbar-Jacob et al., 1998b). These are the only type of data that provide information about the temporal patterning of medication taking. Such devices have been developed for a range of medication adherence behaviors, including opening a pill bottle or box, removal of tablets from a blister pack, releasing eye drops, and discharging inhaled medications (Rand & Weeks, 1998). The device used in the present study was the Medication Event Monitoring System (MEMS, AARDEX Ltd, Zug, Switzerland). The MEMS cap contains a microprocessor that electronically logs each instance the medication bottle is opened and records the date, time, and duration of opening. In turn, these data are downloaded onto a personal computer for subsequent analysis (Rand & Weeks, 1998). Importantly, efforts to mislead the investigators or clinicians by patients (e.g., by repeatedly opening MEMS cap in a short period of time) are identified and ruled out in the editing process (Dunbar-Jacob et al., 1998b).

Although the MEMS and other electronic devices do not provide actual data on medication ingestion, the activation of these monitors serves as a proxy of consumption. Therefore, it is still possible that patients do not actually take the medication when the cap is opened. For instance, this approach would be inaccurate if patients took the medication from the MEMS bottle and stored it in another bottle. This would result in the lower estimation of pill

consumption (Dunbar-Jacob et al., 1998b). Nonetheless, as the monitors log each cap opening, "patients would need to exert considerable, deliberate effort to fool the system; that is, they would have to activate the medication monitor at each correct administration time. This is unlikely…" (Dunbar-Jacob et al., 1998b, p. 99). In the present study, participants were instructed to use only the MEMS bottle to hold their study medication and to consume the prescribed amount directly upon opening the cap.

Dunbar-Jacob and colleagues (1998b) reviewed evidence comparing the accuracy of adherence measures, including self-report, pill counts, and EEM. In short, EEM usually offers a lower estimate of adherence in relation to other measures, particularly self-report. The reviewers concluded that EEM measures are the most accurate, and other measures may overestimate adherence, with potentially undesirable consequences. In addition, Dunbar-Jacob et al. (1998b) discussed how measurement of adherence has a major influence on the significance of psychosocial predictors of adherence. In an earlier study, Dunbar-Jacob and her colleagues (as cited in Dunbar-Jacob et al., 1998b) compared a set of potential predictive factors across three measurement methods: EEM, 24-hour recall, and an interview reviewing the previous month. When using the 24-hour recall and the interview, the psychosocial characteristics did not predict adherence, but social support and pain significantly predicted adherence measured with EEM. Therefore, the inconsistent results in the prediction of adherence across studies may be a function of diverging methods of assessing adherence. Dunbar-Jacob et al. (1998b) suggested that "the electronic event monitors cause us to reexamine what we know about predictors of adherence. Our data suggest that many of the findings on adherence predictors may be related to the measurement method rather than the actual behavior… Clearly, more work is indicated in separating out the predictors of adherence behavior and the correlates of each measurement

method" (p. 110). For these reasons, evaluating predictors of EEM-measured medication adherence was a relative strength of this study.

In addition to the wide array of methods for assessing medication adherence, there are multiple ways of defining medication-taking behavior. The most basic dimension of adherence may be considered medication "completion" versus "non-completion." In the present study, medication completion was defined as manifesting greater than or equal to 14 days of correct intake. That is, participants who failed to take any medication or who discontinued medication within two weeks of initiating the regimen were classified as non-completers. The rationale for establishing this threshold was based on following reasons: (1) it is possible that psychosocial factors associated with failure to take a minimum amount of mediation may differ from factors associated with future discontinuation or deviation from the prescribed regimen; (2) the intent to treat approach of classifying smoking relapse dictates that non-completers are classified as having relapsed (Hughes et al., 2003), and as a result, an association between medication adherence (including non-completers) and smoking relapse would be highly conflated; and (3) evidence suggests that medication adherence during the first several weeks of the regimen is one of the strongest predictors of long-term health outcome, e.g., initial adherence to an anti-cholesterolemia regimen predicted five-year mortality in the Lipid Research Clinics Coronary Primary Prevention Trial (Dunbar-Jacob et al., 1998a).

Among completers, medication adherence is often operationalized by the quantity of medication-taking events. This type of adherence definition reflects the total amount of medication taken over a cumulative time span (Martin, Bowen, Dunbar-Jacob, & Perri, 2000). The typical manner of defining adherence in this manner is by dividing the number of dose self-administrations by the prescribed number of doses during the specific time period and

multiplying by 100%. This statistic is referred to as the "percentage of prescribed administrations taken" (Sereika & Dunbar-Jacob, 2001). Although this index provides gross information about whether a patient took too much or too little medication during the regimen period, it does not include information about the timing of medication intake. As a result, a patient who opened the MEMS cap multiple times in one day but skipped several days may still be considered a good adherer (Sereika & Dunbar-Jacob, 2001). Moreover, adherence definitions based solely on quantity of administrations over an extended period of time fail to allow for the possibility that adherence may change over the course of a health-related behavior or chronic disease regimen. For instance, Myers and Branthwaite (1992) found that patients typically terminated treatment altogether at the beginning of a regimen, became more casual about the treatment during the middle and often forget, and began varying the dosage themselves as the regimen moved into a long-term maintenance phase.

EEM-assessed medication adherence also permits the operationalization of several other distinct types of nonadherence, including errors of omission, dosage, or timing. Since the time of cap openings/closings is recorded in real time, information about the timing of events between (e.g., two pills per day) and/or within (e.g., two pills in a day separated by a lag of 8-14 hours) days may be compared against the actual medication prescription. One such summary index is referred to as the "percentage of days with the prescribed number of administrations" or "percentage of days with correct intake" (Sereika & Dunbar-Jacob, 2001). With this measure, a patient is dichotomously classified as either adherent or nonadherent each day as a function of whether he or she took the correct number of pills that day. The sum of total adherent days is then divided by the total days in the regimen and is multiplied by 100% to arrive at this summary measure of correct intake. Although this statistic does not provide information about timing of

pill consumption within the day, it does provide substantially more temporal information than the aforementioned measure of "percentage of prescribed administrations taken."

An extension of the measure of correct daily intake is the "percentage of days with the correct number of administrations and timing" (Sereika & Dunbar-Jacob, 2001). Specifically, in addition to providing information about correct number medication-taking behaviors in a day, it also takes into consideration the relative timing of proximate medication doses. The determination of correct timing between doses within a given day is inexact, but Sereika and Dunbar-Jacob (2001) suggested, "a 'near' optimal interval [should be] based on the prescribed daily frequency of doses with a clinically reasonable window of medication-taking about the targeted time of administration. A standard convention is to set the dosing window within 20% to 25% of the prescribed interval..." (p. 147). Since the half-life of 150mg sustained release bupropion is 14 hours (Micromedex, 2003), a window of 8 to 14 hours (11 hours ± 27.3%) was established for the present study. This index may provide a relatively conservative index of medication adherence in that there is minimal forgiveness for minor deviations from the exact medication regimen.

It is important to note that the two indices incorporating timing of medication events, the "percentage of days with the prescribed number of administrations" and "percentage of days with the correct number of administrations and timing," do not provide information about days of underdosings, overdosings, and drug holidays (i.e., one or more consecutive days of no medication-taking events; Sereika & Dunbar-Jacob, 2001). Fortunately, EEM-measured adherence data allows for the operationalization of such indices.

Conducting multiple analyses with each summary measure of adherence as a criterion would have led to an unacceptably high experimentwise Type I error rate. Therefore, the pros

and cons of several candidate indices were weighed before deciding on the summary index to be used in the primary analyses. As mentioned previously, the "percentage of prescribed administrations taken" index may overestimate medication adherence because the timing of dose administrations is not incorporated into its definition. On the other hand, "percentage of days with the correct number of administrations and timing" index may underestimate an adequate level of medication adherence because both timing across and within days are incorporated into its definition. The of "percentage of prescribed administrations taken" index may be the optimal index of medication adherence because it evaluates correct dosage for each day of the regimen but does not incorporate a potentially conservative inter-dose interval within each day. Thus, although all of the previously described summary indices were used to describe the rates of medication adherence, the latter one was chosen as the summary measure for use in the primary analyses on the predictors and consequences of medication adherence.

To recapitulate, the use of EEM to assess medication adherence and the inclusion of multiple summary measures of medication-taking behavior were expected to provide a relatively accurate measure of medication consumption, provide a broader depiction of multifaceted medication-taking behavior, and possibly provide unique information in the prediction of medication adherence. Importantly, the use of the percentage of days with the correct intake index over an extended period allowed for the break down of the larger study period (90 days) into shorter periods (of 30 days). Consistent with previous research (e.g., Myers and Branthwaite, 1992), it was expected that sample averages would decrease over each of these 30-day periods.

1.6 SEQUELAE OF ADHERENCE

Patients who manifest better adherence are thought to benefit more from medical treatments than patients who manifest poorer adherence. It is widely assumed by many clinical researchers and practitioners that resulting positive health outcomes are a function of adherence to a medication with an active, specific pharmacological effect. The following sections will explore the validity of this assumption in the context of smoking cessation and other health behavior and disease regimens.

1.6.1 Smoking Cessation

A nicotine patch intervention study provides a test of this assumption. Killen, Fortmann, Davis, and Varady (1997) reported that among high adherers to a nicotine patch regimen, 70% were abstinent at 100 days and 42% of high adherers were abstinent at 200 days, respectively. In contrast, 32% and 20% of poor adherers were abstinent at 100 and 200 days, respectively. Importantly, the assumption that adherence only to the active nicotine patch led to increased smoking cessation rates would have led to an erroneous conclusion. This is because adherence to the patch regimen, independent of active or placebo condition, had an important effect on relapse. Killen et al. (1997) used Cox proportion hazards analysis to examine time to relapse, with treatment condition (nicotine or placebo patch), adherence with counseling treatment manual, and adherence with patch regimen included as independent variables. At 2 months, patch adherence status and patch treatment condition were significant predictors in the model, but at 6 and 12 months, patch adherence status was the only significant predictor. The Killen et al. (1997) finding that adherence to patch regimen had a direct effect on smoking cessation is consistent with a small but growing body of research supporting the main effect of medication adherence on a variety of health outcomes, independent of whether the patient is taking the active drug or placebo.

In order to examine the main effect of adherence, independent of active medication, the reporting of adherence behavior in both active medication and placebo groups is necessary. A recent report comparing the effects of fluoxetine versus placebo on smoking cessation demonstrates why this information is important. Hitsman et al. (2001) investigated the influence of serum fluoxetine levels (i.e., an index of adherence to an active medication) on adherence to behavioral smoking cessation treatment and smoking cessation outcome. Results showed that individuals with higher levels of fluoxetine were less likely to drop out of behavioral treatment and more likely to maintain prolonged abstinence over 10 weeks. The limited utility of indexing medication adherence solely via drug levels in plasma is underscored by the lack of information about placebo regimen adherence. The authors pointed out that, as a result, it is impossible to rule out that fluoxetine levels were a proxy for a general tendency to adhere to treatment, which may have led to enhanced behavior therapy adherence and prolonged smoking abstinence. Unfortunately, with the exception of the Killen et al. study (1997), no studies in the smoking cessation literature have presented information on adherence to active and placebo medications.

1.6.2 Other Health Behavior and Disease Regimens

Epstein (1984) identified six experimental studies in the broader health outcomes literature in which active pharmacological agents were compared against placebos. The health outcomes included cardiovascular mortality, weight loss, alcohol abstinence, psychosis relapse, and fever or infection among cancer patients. An adherence vs. nonadherence dichotomization was made either by the original authors or by Epstein. When comparing the effect of the medication against the placebo, only half of the studies reported a significant improvement of the medication groups (the rest were null). However, a main effect of adherence was found in five of the six studies. It is important to note that, in order to demonstrate this effect, patients who were adherent in both the active medication and placebo groups were required to achieve better health outcomes.

Several pertinent studies were published after Epstein's (1984) review. For example, adherence data was available for 2175 post-myocardial infarction (MI) patients who participated in the β-Blocker Heart Attack Trial (BHAT; Horwitz et al., 1990). Patients who were randomly assigned to propranolol or placebo were assessed at one year. Adherence was assessed with pill counts. Even after controlling for MI severity, patients who were classified as poor adherers (took less than or equal to 75% of their medication) were 2.6 times more likely than good adherers to die within the follow-up year. Analysis of the propranolol group revealed that the mortality rate was 4.2% for poor adherers and 1.4% for good adherers. In the placebo group, the mortality rates were 7.0% and 3.0% for poor and good adherers, respectively. There was no significant difference between treatment groups on mortality. Horwitz et al. (1990) used a series of multiple regression models to determine whether sociodemographic variables, psychosocial variables (i.e., life stress and social isolation), and smoking accounted for the main effect of adherence. Some of these predictors were related to mortality, but the main effect of adherence could not be explained by these variables.

McDermott, Schmitt, and Wallner (1997) reviewed several studies examining the effects of medication adherence on cardiovascular morbidity and mortality among patients with or at risk for coronary artery disease and congestive heart failure. Twelve studies were identified that compared hospitalization rates and mortality between adherers and nonadherers. Seven studies found that adhering to medication positively affected health outcomes, and three studies showed that adhering to placebo regimens was predictive of positive outcomes. More recently, Irvine et al. (1999) examined the association between adherence and mortality among 1141 patients in the randomized, double-blind Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT). Results indicated that poor adherence to either amiodarone or placebo was

associated with increased risk for sudden cardiac death, total cardiac mortality, and all-cause mortality. Again, no differences were found between treatment groups on mortality, and several medical, demographic, or psychosocial characteristics were not able to account satisfactorily for the main effect of adherence on outcome.

These studies provide convincing evidence for the main effect of adhering to medical regimens on a range of treatment outcomes, independent of whether the patient is taking the active study medication or placebo. Taken together, these findings are promising, but additional research with a variety of populations, medications, and health outcomes is needed to add reliability and generalizability to this effect. Thus, one of the goals of the present study was to examine the main effect of adherence to the study medication (i.e., independent of bupropion or placebo status) on smoking cessation among women who were engaged in smoking cessation clinical trial. Interestingly, many of the aforementioned studies did not consistently demonstrate that medication adherence interacted with the level of medication (active or placebo) to produce positive treatment results. These mixed results may be due to a reduced effect size of the specific, pharmacological agent. This explanation is consistent with findings from a recent meta-analysis by Kirsch and Sapirstein (1999) indicating that approximately 25% of the response to antidepressant medications is due to the administration of an active medication, 50% due to a placebo effect, and the remaining 25% due to other nonspecific factors. Thus, the assumption that adhering to medical regimens enhances specific, active pharmacological effects requires further empirical validation.

1.6.3 Main Effect of Adherence: Possible Mechanisms

The vast majority of studies in this area have not focused on adherence as an independent predictor of health outcome. These randomized, double-blind studies were designed to compare medication versus placebo effects (Epstein, 1984). In fact, the observation of the adherence

effect in the Coronary Drug Project (1980), one of the first studies to report this finding, was apparently discovered serendipitously. For this reason, most of these studies did not discuss or include measures of possible mechanisms underlying the main effect of adherence. As discussed above, the BHAT (Horwitz et al., 1990) and CAMIAT (Irvine et al., 1999) are two exceptions, but none of the medical, demographic, or psychosocial characteristics assessed in these trials accounted for the main effect of adherence on mortality. Furthermore, as with the literature on predictors of adherence, all of the studies examining adherence, health outcomes, and potential mechanisms were observational. For these reasons, the mechanisms underlying the nonspecific effect of adherence are presently unknown.

Although there are no published findings indicating what active ingredients account for the main effect of adherence on health outcome, several alternative explanations exist. The main effect of adhering to placebo on health-related behavior change or clinical status suggests that factors other than just the effectiveness of the specific, pharmacological agent are functioning. The active, specific components of a medication may be maximized by good adherence, but such behavior may also activate nonspecific effects that lead to treatment success. Therefore, it has been suggested that the ingredients driving the nonspecific adherence effect are analogous to the ingredients underlying the placebo effect (Czajkowski, Chesney, & Smith, 1998). As the placebo effect is believed to be a function of nonspecific components of treatment, Czajkowski et al. (1998) posited that positive outcome expectancies and social support are the active ingredients of the main effect of adherence. On the other hand, it is possible that particular characteristics of good treatment adherers predispose them to profit more from nonspecific aspects of treatment (Czajkowski et al., 1998; Horwitz & Horwitz, 1993). For instance, conscientious individuals,

who may be more apt to adhere to treatment, may seek out more social support from friends and family, which in turn leads to better health outcomes.

Thus, another objective of including several promising psychosocial variables in the present study was to help to characterize the active ingredients of the hypothesized relationship between adherence to the medication regimen and the health outcome, smoking cessation. Exploratory regression analyses were used to determine whether psychosocial parameters were associated with both medication adherence and prolonged smoking abstinence. Adjustment for such parameters factors in subsequent hierarchical regression analyses provided information about whether the main effect of adherence could be accounted by one or more of these psychosocial characteristics.

1.7 STUDY AIMS

The aims of this study were to examine rates, predictors, and sequelae of adherence to a smoking cessation medication regimen among weight-concerned women engaged in a smoking cessation intervention study. There is little empirical or conceptual research on adherence to smoking cessation pharmacotherapy, and as such, this exploratory study provided the first extensive look at adherence to a regimen of bupropion versus placebo. The following research questions and hypotheses were addressed:

Question 1. What are the rates of adherence to a medication regimen among a sample of female weight-concerned smokers participating in a smoking cessation clinical trial?

Hypothesis 1a. The primary composite index of medication adherence, which emphasizes the correct number of daily doses, was expected to be suboptimal over the 90-day period and was also expected to decrease over each successive 30-day period.

Hypothesis 1b. Medication adherence was expected to progressively decrease when operationalized as (a) percentage of prescribed doses taken over the study period, (b) percentage of days with the correct number of doses taken, and (c) percentage of days with the correct number of doses taken *and* correct timing between doses, respectively.

Question 2. To what extent do individual differences in depressive symptoms, agreeableness, conscientiousness, social support, medication side effects, and medication efficacy and outcome expectancies predict adherence to the medication regimen?

Hypothesis 2. Higher levels of depressive symptoms and medication side effects were expected to be negatively associated with medication adherence, whereas agreeableness, conscientiousness, social support and optimistic medication efficacy and outcome expectancies were expected to be positively associated with medication adherence. An interaction between depressive symptoms and medication side effects was expected to significantly predict medication adherence. Individuals with high levels of depressive symptoms and medication side effects were expected to be more likely to manifest poorer medication adherence relative to individuals with low levels of depressive symptoms or medication side effects. Moreover, individuals experiencing a sustained change in side effects from basal levels were expected to manifest poorer adherence than those whose symptoms did not change from pretreatment levels or remitted over time.

Question 3. To what extent does adherence to the medication regimen predict smoking abstinence, independent of medication treatment?

Hypothesis 3. High levels of medication adherence were expected to be positively associated with prolonged smoking abstinence and point prevalence abstinence rates over time.

2 METHOD

2.1 PARTICIPANTS

One hundred-and-fifty-five adult women participated in the smoking cessation program.[5] Participants were recruited primarily via newspaper, bus, and television advertisements to take part in a smoking cessation treatment program designed to assess counseling and pharmacological approaches to assisting weight-concerned women quit smoking. All participants in the smoking cessation program smoked at least 10 cigarettes per day for at least one year and reported considerable concerns about post-cessation weight gain. All women were required to be healthy, not pregnant, lactating or interested in becoming pregnant during the clinical trial, and employing suitable birth control. Individuals with current Axis I psychiatric disorders were ineligible. Individuals with current or recent (in the past year) in-patient hospitalization for psychiatric, drug, or major medical problems were also ineligible. Other exclusionary criteria included history of seizure, serious head injury, and current or historical eating disorders. Lastly, women were also excluded if they were currently taking medications that may lower the seizure threshold, psychotropic medications, or nicotine replacement therapy.

Participants were initially screened over the telephone for inclusion/exclusion criteria. Next, participants attended an information session at which signed informed consent was

[5] The present study was part of a larger clinical trial that will ultimately recruit 450 participants over a four-year period. The larger trial has a longer period of intervention (26 weeks) and follow-up assessment (52 weeks). Procedures from the larger clinical trial that are beyond the scope of this "sub-study" are not presented.

obtained and screening information was documented. Participants were then scheduled for individual telephone appointments for the administration of the Structured Clinical Interview for DSM-IV, Version 2 (SCID; First, Spitzer, Gibbon, & Williams, 1998). Finally, individuals were scheduled for a physical examination to make sure that health-related eligibility criteria were met. The study was approved by the University of Pittsburgh Biomedical Institutional Review Board.

The age range was 19 to 62 years old, with a mean age of 43 (SD = 9.7 years). Participants were 87% Caucasian, 12% African-American, and 1% Pacific Islander/Native Hawaiian. Nearly all participants (98.7%) completed high school and 33.5% completed at least a four-year college degree. On a Likert scale ranging from 0 (not at all) to 100 (extremely), the mean rating of participants' pretreatment desire to quit smoking was 85.6 (SD = 14.5) and the mean concern about gaining weight after quitting smoking was 73.50 (SD = 24.3). Additional descriptive characteristics of the participants are displayed in Table 1.

Table 1

Participant Characteristics

Characteristic	Mean	Standard Deviation
Age (years; N = 155)	43.19	9.69
Years of smoking (N = 150)	25.07	10.18
Cigarettes/day (N = 150)	20.89	8.23
Fagerstrom tolerance (0-10; N = 150)	5.11	2.08
Body Mass Index (N = 155)	27.32	5.45

Characteristic	Percentage
Race (N = 155)	
Caucasian	87.1
African-American	12.3
Native Hawaiian or other Pacific Islander	0.6
Highest education level (N = 150)	
Grade school or some high school	1.3
High school graduate	13.5
Some college/technical school	49.0
Four-year college graduate	24.5
Post-graduate degree	9.0

2.2 PROCEDURE

2.2.1 Research Design

All participants were randomized into a larger double-blinded RCT examining the effects of medication (bupropion versus placebo) and counseling (weight-focused CBT versus standard support) on smoking cessation. The psychosocial treatments were not designed to influence medication adherence differentially (see Perkins et al., 2001). Given that medication adherence was observed over time but not manipulated, the research design for the present study was longitudinal and passive-observational (Kazdin, 1992).

2.2.2 Pharmacotherapy

Participants were randomly assigned to receive bupropion or an identical appearing placebo at Week 2 of treatment (six days before the quit date). Participants took the study drug for the remaining 12 weeks of treatment. All women were directed to take one 150 mg capsule daily for the first three days and then two 150 mg capsules each day for the remainder of the study. A 300 mg daily dose was chosen based on safety and published smoking cessation findings (e.g., Glaxo Wellcome Inc., 1999; Hurt et al., 1997). All participants were seen individually by a project nurse five times over the 12-week period. These clinic visits were scheduled at Weeks 2, 3, 5, 8, and 10. During each visit, the project nurse completed a Medication Management Form, which included information about medication side effects. Treatment was free, but a small, refundable deposit of $25 was requested from participants to increase counseling session attendance.

2.3 MEASURES

The primary measures of depression, personality, social support, and self-efficacy and outcome medication expectancies were assessed at the pretreatment information session. Medication side effects were assessed at Weeks 2 (pretreatment), 3, and 5 nurse visits. Secondary measures of

depression, social support, and medication outcome expectancies were collected at Week 6. Unless otherwise specified, all subsequent references to these psychosocial parameters pertain to baseline measurements.

2.3.1 Depression

The BDI (Beck et al., 1961) is a 21-item self-report scale that includes descriptions of typical symptoms of depression (i.e., fatigue, hypochondriasis, insomnia, pessimism, sadness, self-dislike, and suicidal ideation) experienced over the past two weeks. The BDI has been used extensively in both clinical and nonclinical populations as a measure of depressive symptomatology (Beck, Steer, & Garbin, 1988). Test-retest reliability of the BDI ranges from .62 (4 months) to .90 (2 weeks) in nonpsychiatric undergraduate students (Beck et al., 1988). The BDI has an internal consistency of 0.86 for psychiatric patients and .81 for nonpsychiatric individuals (Beck et al., 1988).

2.3.2 Personality

The personality factors of conscientiousness and agreeableness were assessed with the NEO-FFI (Costa & McCrae, 1992). The NEO-FFI is a short-form measure (60 items) of the NEO-PI-R (Costa & McCrae, 1992), which indexes the Big Five Personality factors of neuroticism, conscientiousness, extraversion, openness to experience, and agreeableness. The conscientiousness scale of the NEO-FFI is highly associated with the conscientiousness scale of the longer version, NEO-PI-R ($\underline{r}$ = .87) and internal consistency is high ($\underline{\alpha}$ = .81; Costa & McCrae, 1992). Similarly, the agreeableness scale of the NEO-FFI is highly associated with the agreeableness scale of the NEO-PI-R ($\underline{r}$ = .77); internal consistency is acceptable ($\underline{\alpha}$ = .68; Costa & McCrae, 1992).

2.3.3 Social Support

The ISEL (Cohen et al., 1985) is a 40-item measure of perceived availability of specific forms of social support, including appraisal, belonging, self-esteem, and tangible support. Internal consistency reliabilities for the ISEL range from .88 to .90 (Cohen et al., 1985). Cohen et al. (1985) reported adequate test-retest reliability of the ISEL, with a six-month reliability of .74. Given that the four types of support are highly intercorrelated (Sarason, Shearin, Pierce, & Sarason, 1987) and confirmatory factor analysis results are consistent with the existence of an underlying second-order general factor of support (Brookings & Bolton, 1988), the total ISEL score was used in this study.

2.3.4 Expectancies

There have been few attempts to investigate pharmacotherapy-related efficacy and outcome expectancies in health domains, and no published works on expectancies for smoking cessation medications. For this reason, a measure indexing medication outcome (items 1-13) and self-efficacy (items 14-24) expectancies was developed for this study. The Study Medication Expectancies Questionnaire (SMEQ; see Appendix A) was loosely based on several relevant sources, including two previously used measures assessing outcome expectancies of arthritis medication, the Perceived Therapeutic Efficacy Scale (Dunbar-Jacob et al., 1993), and self-efficacy to adhere to an HIV+ medication regimen, the Treatment Self-Efficacy scale (Catz et al., 2000; S.L. Catz, personal communication, July 27, 2000). In addition, outcome expectancy items were developed to assess several response expectancies (e.g., cravings, weight control, etc.), the type of outcome expectancy most commonly assessed in smoking research (Brandon et al., 1999). Many of the specific response expectancies were derived from the DSM-IV (American Psychiatric Association, 1994) criteria for nicotine withdrawal.

Likewise, self-efficacy items were based in part on others' works. These items were designed to assess an individual's confidence in her ability to take the study medication in contexts of varying difficulty, which is consistent with Bandura's (1997) suggestions on how to develop a self-efficacy questionnaire. Although several high-risk situations were based on those from Catz et al.'s (2000) questionnaire on HIV medication adherence, several others were culled from Gwaltney et al.'s (2001) smoking cessation-specific Relapse Situation Efficacy Questionnaire.

Reliability analyses indicated that the medication outcome expectancies subscale (α = .89), the medication self-efficacy expectancies subscale (α = .88), and the entire SMEQ (α = .88) had adequate internal consistencies. As expected, the medication outcome and self-efficacy sub-scales were moderately and positively correlated ($\underline{r}$ = .24, p = .004, $\underline{N}$ = 147). Taken together, the strong internal consistencies and the relatively minimal shared variance ($\underline{R}^2$ = 5.8%) of the two subscales provided support for the psychometric adequacy of this measure.

2.3.5 Side Effects

Medication side effects were assessed at Weeks 2, 3, and 5 with an investigator-designed 38-item questionnaire based on symptom lists used in Federal Drug Administration drug trials. For Week 2, or pretreatment, participants were asked to check off any problems that they had experienced in the previous week. For Weeks 3 and 5, participants were asked to check off any symptoms that they had experienced since their previous medication check-up/refill visit. Then the study nurse asked participants to rate each positively endorsed symptom on a 1-6 Likert scale, with 1 = very mild or only happened once and was not bothersome, 4 = present on more than half the days or somewhat bothersome in intensity, and 6 = it happened every day or was very bothersome. Since the Week 2 symptoms were assessed prior to initiating the medication regimen, this information more accurately indexes ambient physical symptoms. Still, for the sake of

consistency, pretreatment physical symptoms are referred to as Week 2 side effects throughout the remainder of this report.

2.3.6 Nicotine Dependence

Participants completed the Fagerstrom Tolerance Questionnaire (Fagertrom, 1978) at pretreatment. This eight-question measure is designed to assess nicotine dependence on a scale ranging from 0 (no dependence) to 11 (high dependence).

2.3.7 Medication Adherence

Adherence to the medication regimen was assessed with the Medication Event Management System (MEMS) Smart Cap (AARDEX Ltd, Zug, Switzerland). The MEMS consists of a medication bottle that contains a pressure-activated microprocessor in the cap. This microprocessor automatically records each opening of the medication bottle (i.e., an event), providing the number of times opened each day and the hours since the bottle was last opened. The MEMS Smart Caps were also equipped with a digital display indicating to participants in real-time the number of daily cap openings and time elapsed since the previous opening. The digital display was pre-programmed to reset automatically each day at 3AM. Participants were instructed to use this information to facilitate proper adherence and were also told that these data would be used for research purposes. Data from the microprocessor were downloaded to a personal computer for later analysis at Weeks 3, 5, 10, and 14. The total number of doses prescribed during the 12-week period was 177, although this number was smaller for some participants if their dosage was reduced by the project physician.

Consistent with the recommendations of Sereika and Dunbar-Jacob (2001), six summary measures were used to explain the EEM data. Each index was computed for the entire 90-day period as well as for the three 30-day periods. Specifically, the adherence summaries measured were: (1) the percentage of prescribed doses taken during the time periods, (2) the percentage of

days with the correct number of doses, (3) the percentage of drug holidays (i.e., no doses taken for one or more consecutive days), (4) the percentage of days with underdosing (i.e., less than the correct number of doses was recorded), (5) the percentage of days with overdosing (i.e., more than the correct number of doses was recorded), and (6) the percentage of days with the correct number of doses and correct timing between doses.

2.3.8 Smoking Cessation

Smoking status was assessed at each of the 12 behavior therapy sessions. There was one meeting during the 1st week of treatment, two meetings each during the 2nd and 3rd weeks (immediately prior to and after the smoking quit date), one meeting during the 4th, 5th, and 6th weeks, and three more bi-weekly meetings during the 8th, 10th, 12th and 14th weeks. Using an intent to treat approach, any participant who failed to maintain regular attendance at study visits was considered to have relapsed (Hughes et al., 2003).

All smoking cessation definitions were based on recent recommendations from the Society of Research on Nicotine and Tobacco (SRNT) subcommittee on abstinence measures (Hughes et al., 2003). The efficacy of smoking cessation was evaluated with rates of prolonged abstinence over the 12-week period. Relapse was defined as (1) seven consecutive days of smoking, or (2) smoking at least once each week on two consecutive weeks, including an initial two-week grace period. The two-week grace period meant that any smoking during the first 14 days after the quit date was not considered a relapse. According to SRNT guidelines, the rationale for this grace period is twofold: (1) a subset of individuals who a few cigarettes after quitting will go on to maintain permanent abstinence, and (2) the effects of treatment may not be fully effective until at least a few weeks of therapy (Hughes et al., 2003). Only those participants who self-reported abstinence and provided biochemical verification at each visit were classified as manifesting prolonged abstinence. Biochemical verification of abstinence included expired-air

carbon monoxide concentrations below eight parts per million (ppm) Although perfect attendance was not expected, participants were nonetheless required to provide negative CO measurements at ≥ 75% of the eight post-quit sessions in order to be considered abstinent.

Point prevalence abstinence rates were also computed at Weeks 6, 10, and 12 as secondary outcome measures. Point prevalence abstinence rates were defined more conservatively than prolonged abstinence in that no smoking at all was permitted during the day of the assessment as well as the previous seven days. Although SRNT subcommittee recommended the inclusion of survival analysis as a nontraditional measure of smoking relapse (Hughes et al., 2003), the relatively short follow-up in the present study (90 days) was not of sufficient duration to provide clinically meaningful information. For example, a difference of 30-50 days in time to relapse between individuals with "good" versus "poor" adherence rates may be statistically significant, but such a small difference would be relatively unimportant given that prolonged abstinence of at least one year is the hallmark of successfully quitting smoking. For this reason, survival analyses were not included in this report.

2.4 DATA ANALYSIS

2.4.1 Statistical Analysis Plan

After descriptive statistics were computed, hierarchical multiple linear regression model building was performed to examine the hypothesized predictors of medication adherence. The procedure of automatic stepwise selection was used to ascertain the best subset of predictor variables. Although exploratory studies typically utilize a relatively liberal alpha level (i.e., entry criterion of .20 and elimination criterion of .25; Tabachnick & Fidell, 1996) to reduce Type II error rate, the entry and elimination criteria were set conservatively at .05 and .10, respectively. These criteria were chosen to minimize the experiment-wise Type I error rate that could be inflated due

to multiple analyses. A preliminary multiple linear regression model was fit to determine whether potentially confounding variables should be entered in the final model. Specifically, medication group, counseling group, age, race, education status, and Fagerstrom tolerance scores were entered simultaneously as predictors and medication adherence was set as the criterion of this regression equation. Dichotomous variables, including medication and counseling groups, race, and education status, were dummy coded. Then multiple regression model building was conducted with 90-day medication adherence entered as the dependent variable and the pool of predictor variables entered in three steps. Any potentially confounding variables found to be associated with medication adherence in the prior analysis were entered in the first step of the regression equation. Main effect terms of BDI, agreeableness, conscientiousness, ISEL, medication efficacy expectancies, medication outcome expectancies, and Weeks 2, 3 and 5 side effects were entered in the second step. A priori designated interaction effects comprised the third step, including a two-way interaction of BDI-by-Week 5 side effects and a three-way interaction of Week 2-by-Week 3-by-Week 5 side effects. The overall model fit was examined via an F-test and the significance of individual predictors was evaluated with partial t-tests and R^2 change values. The reported betas are the standardized regression coefficients for the final model. Several diagnostic procedures were used to examine and verify assumptions of linear regression model building (see Appendix B for procedural details).

Next, multiple logistic regression analysis was performed to examine the main effect of medication adherence on smoking cessation. The dichotomous outcome of prolonged smoking abstinence was entered as the criterion variable and 90-day medication adherence was entered as the predictor variable. The same potentially confounding variables assessed with linear regression model building were examined for their association with smoking cessation and, if

significant, were entered as covariates in the logistic model. The model χ^2 test, the Hosmer-Lemeshow goodness-of-fit index, and R^2_L (i.e., a hand-calculated coefficient of determination analogous to R^2 in linear regression; Menard, 2002) were used to evaluate the overall fit of the model, and the likelihood ratio test was used to assess the significance of including a predictor to the overall model. See Appendix B for diagnostic procedures used for examining and verifying logistic regression assumptions.

Tests for statistical mediation and moderation were conducted in cases where a psychosocial variable was associated with both medication adherence *and* prolonged smoking abstinence. A mediator variable is responsible partly or completely for the process by which one variable significantly influences another (Baron & Kenny, 1986). When testing for mediational effects, the following criteria were assessed for statistical significance ($p < .05$): (1) the predictor was significantly associated with the criterion, (2) the predictor was significantly associated with the mediator, and (3) after controlling for the predictor, the mediator was significantly associated with the criterion (Baron & Kenny, 1986). If these criteria were upheld, then a statistical test was conducted to determine whether the association between the predictor and criterion was significantly attenuated after controlling for the mediator (Holmbeck, 2002). A moderator variable influences how a predictor is associated with a criterion. A moderational effect is also commonly referred to as a statistical interaction, such that the association between the predictor and criterion varies significantly at different levels of the moderator (Baron & Kenny, 1986). Post-hoc probing based on Holmbeck's (2002) guidelines was conducted if mediation or moderation was found to be significant. Post-hoc probing of a mediational effect involves the hand-calculation of a z-test (i.e., $b_{\text{indirect effect}}/se_{\text{indirect effect}}$). Post-hoc probing of a moderational

effect consists of computation and plotting of the simple regression slopes. See Holmbeck (2002) for detailed procedures of post-hoc probing of significant mediational or moderational effects.

Unless otherwise stated, all statistical analyses were performed with SPSS for Windows, Version 8.5.

2.4.2 Missing or Incomplete Data

Like most prospective RCTs, data were missing or incomplete for a subset of participants. Five participants experienced severe medication side effects within the first 14 days of the medication regimen. In each case, the medication randomization blind was broken for provision of medical care. All five participants were taking bupropion and were withdrawn due to following reasons: hypertension (N = 3), depression (N = 1), and edema (N = 1). Since their medication non-completion was involuntary, these participants were excluded from all primary and secondary analyses.

Self-report scales were classified as missing if greater than or equal to 25% of its items were missing. If scales were missing less than 25% of its items, missing questions were conservatively coded as neutral or asymptomatic (e.g., a missing BDI question was entered as zero). Thirty-one of the remaining 150 participants (20.7%) did not complete or were not administered one or more of the primary predictors of adherence. Nearly all missing data were due to failure of participants to complete one or more self-report measure. The proportions of participants with missing data for the primary predictors of adherence were as follows: (1) BDI = 0.7%, (2) ISEL = 3.3%, (3) NEO/agreeableness and conscientiousness = 3.3%, (4) medication efficacy and outcome expectancies = 6% (of which 2% was due to experimenter error), (5) Week 2 side effects = 1.3%, (6) Week 3 side effects = 6%, and (7) Week 5 side effects = 15.3%. Additionally, missing data existed for two potential covariates, including: (1) education status = 2.7%, and (2) Fagerstrom Tolerance = 3.3%. Four participants were missing all of the following

data: ISEL, NEO/agreeableness and conscientiousness, medication efficacy and outcome expectancies, education status, and Fagerstrom tolerance.

Finally, one participant with complete self-report data was withdrawn from the medication regimen after 16 days due to an adverse medication reaction to bupropion. Since the listwise mean number of prescribed days for the sample was 88 (SD = 8.3) and the second fewest number of prescribed days was 61, this participant was considered an outlier and excluded from subsequent analyses.

To minimize the possibility of nonrandom missing data, the pattern of missingness was analyzed carefully using a series logistic regression analyses. The level of missingness of the psychosocial predictors of medication adherence and two possible covariates (education level and nicotine dependence) were re-coded as dummy variables (0 = non-missing, 1 = missing) and entered in separate hierarchical logistic regressions as dependent variables. Sociodemographic variables (age, race, education level, and body mass index), medication group, and counseling group, and nicotine dependence[6] were entered as predictors in each of these models. Results from each of these logistic regression analyses were non-significant, indicating that missingness among the predictors was unrelated to several important characteristics. Given the relatively small proportions of missingness per individual variables and the fact that the predictors and possible covariates were apparently missing at random, listwise deletion was used in the primary analyses below.

[6] Education level and nicotine dependence were not simultaneously entered as predictors and criterion variables.

3 RESULTS

3.1 PRIMARY ANALYSES

Initial data screening was conducted on all psychosocial variables. Descriptive statistics are presented in Table 2. All means and standard deviations were within valid ranges and were comparable to another sample of weight-concerned female smokers participating in a smoking cessation trial (e.g., Perkins et al., 2001) and to other non-clinical samples (Costa and McCrae, 1992; Cohen et al., 1985). Although pretreatment side effects levels between the bupropion ($\underline{M}$ = 8.89) and placebo ($\underline{M}$ = 4.90) groups were inexplicably different, $\underline{F}(1,116) = 5.51$, $\underline{p} = .02$, mean side effect levels at Week 5 were not significantly different between groups, $\underline{F}(1,116) = .732$, $\underline{p} = .394$, bupropion $\underline{M}$ = 13.63, placebo $\underline{M}$ = 11.56. Pretreatment and Week 5 side effects levels were collapsed across medication groups and are presented in Table 3. The pretreatment rates are comparable to ambient physical symptom levels of non-medical patients (Khosla, Bajaj, Sharma, & Mishra, 1992; Reidenberg & Lowenthal, 1968) and the Week 5 side effects levels are not substantively divergent from those reported by other individuals taking bupropion in clinical trials (Hurt et al., 1997; Jorenby et al., 1999; Hays et al., 2001). Given that there are no previous investigations of smoking cessation pharmacotherapy efficacy and outcome expectancies, a meaningful comparison with other samples was not possible.

Table 2

Psychosocial Variables at Baseline

Variable	Mean	Standard Deviation
Beck Depression Inventory	6.26	5.85
Interpersonal Support Evaluation List	94.18	14.93
Medication efficacy expectancies	66.61	7.98
Medication outcome expectancies	58.64	11.59
NEO—Conscientiousness	33.88	5.67
NEO—Agreeableness	33.51	5.25
NEO—Extraversion	29.05	6.57
NEO—Openness to Experience	27.06	6.01
NEO—Neuroticism	18.69	6.23

Note. N = 118.

Table 3

Self-Reported Medication Side Effects

Side Effect	Percent Reporting	
	Pretreatment	Week 5
Headache	27	12
Blurred vision	3	2
Anxious/nervous	20	28
Tremor/shakiness	0	6
Muscle spasms/muscle tension	13	7
Drowsy	9	18
Agitated/restless	13	27
Dizzy	4	4
Inability to sleep/insomnia	11	32
Excessive sleep	5	5
Increased saliva flow	2	3
Poor concentration	4	15
Disturbed concentration	7	13
Irritability/anger/hostility	17	30
Sweating	4	6
Feeling too happy (feeling high)	1	7
Hot flashes	14	9
Short of breath	10	5
Rapid or fluttering heart	3	2

Chest pain	2	2
Strange taste in mouth	2	13
Excessive thirst	3	13
Dry mouth	2	21
Poor appetite	3	6
Increased appetite	7	20
Heartburn	6	6
Stomach pain	3	8
Nausea/vomiting	1	6
Excessive gas	4	11
Inc. urinary frequency	1	12
Dec. urinary frequency	1	3
Inc. sex drive	1	1
Dec. sex drive	0	4
Itchy skin	6	6
Skin rash or hives	3	2
Muscle pain	13	5
Joint pain	6	2
Fever/chills	0	1

Note. Pretreatment indicates prior to initiating the study medication. N = 112.

3.1.1 Description of Medication Adherence

A relatively small proportion (6/118, or 5.1%) of participants were medication non-completers (i.e., less than 14 days with correct intake). The sample size of medication completers was 112. Given the relatively small size of this non-completer group and possible substantive differences between medication non-completers and completers, descriptive statistics are provided here for medication completers only (tests for differences between completers and non-completers are presented in the Prediction of Medication Adherence section below). As a check of MEMS methodology, participants were asked two self-report questions at medication check-ups/refills: (1) "Have you been using the MEMS bottle to dispense you medication? (yes/no)" and (2) "To what extent have you been using the MEMS cap to keep track of your pills? (1 = not at all, 7 = completely)." At Week 5, a large proportion (93/112) responded "yes" to the first question, and the mean response was 4.80 (SD = 2.18) to the second question. Thus, a majority of participants reported using the electronic cap and accompanying pill bottle, whereas the MEMS' digital display was used to a moderate degree. As the MEMS' digital display was intended to facilitate medication adherence, it is not surprising that the correlation between self-reported use of the electronic cap to keep track of pill intake and 90-day medication adherence was significant, albeit of modest magnitude, $r = .25$, $p = .01$.

Descriptive statistics for the full 90-day period, the 1st 30-day period, the 2nd 30-day period, and the 3rd 30-day period are presented in Table 4. As predicted, medication adherence defined with a variety of summary measures was far less than optimal over the full 90-day period. Each medication index also decreased over each of the three consecutive 30-day periods. For example, the mean of the most stringently defined adherence measure, incorporating both the prescribed number of doses and timing between doses, was 26.2% over the 90-day period and 32.2%, 25.4%, and 19.1%, respectively, over the corresponding three 30-day periods. Even the

Table 4

Descriptive Statistics for Summary Measures of Medication Adherence

Time Period	Mean # of prescribed days	Mean % of prescribed doses taken	Mean % of days with correct intake	Mean % of days with drug holidays	Mean % of days with underdosing	Mean % of days with overdosing	Mean % of days with correct intake & timing between doses
90-days	88.5 (5.02)	72.8 (25.6)	58.0 (24.3)	21.8 (25.1)	15.6 (13.6)	4.6 (3.0)	26.2 (17.7)
1st 30-days	29.6 (2.1)	95.4 (12.8)	78.8 (15.8)	3.6 (8.4)	10.3 (12.4)	7.4 (4.2)	32.2 (17.3)
2nd 30-days	29.7 (1.5)	73.2 (32.3)	55.6 (29.9)	20.3 (29.9)	19.1 (17.8)	5.0 (5.5)	25.4 (21.1)
3rd 30-days	29.2 (3.8)	50.7 (41.4)	39.5 (37.5)	41.6 (44.8)	17.5 (22.7)	1.4 (3.2)	19.1 (24.1)

Note. N = 112. Standard deviations in parentheses.

least stringent adherence measure, indexing the percentage of prescribed doses taken, yielded a less than perfect rate of 72.8%. As expected, medication adherence progressively decreased over the 90-day period when operationalized with increasingly stringent criteria: % of prescribed doses taken: 72.8% > % of days with correct intake: 58.0% > % of days with correct intake and timing between doses: 26.2%.

A correlation matrix among the summary measures of medication adherence is displayed in Table 5. The multicollinearity among these measures was quite variable, with a low correlation of $|\underline{r}| = .03$, $\underline{p} = .74$, and a high correlation of $|\underline{r}| = .95$, $\underline{p} = .000$. Despite near perfect multicollinearity among a few of these indices, most correlations were moderate to moderately strong in magnitude, suggesting that the use of multiple indices of medication adherence provided partially overlapping but not redundant information.

Given the previously documented difficulties with the normality assumption for EEM-measured adherence measures (Dunbar-Jacob et al., 1998b), the univariate normality of 90-day medication adherence was assessed by examining its distribution graphically (see histogram in Figure 1) and by performing formal inference tests of skewness and kurtosis.[7] Although not perfectly bell-shaped, the distribution approximated normality and the $\underline{z}$ tests for skewness and kurtosis did not exceed the conventional but conservative .01 alpha level (Tabachnick & Fidell, 1996). Consequently, the normality assumption was presumably supported, transformation was considered unnecessary, and linear regression modeling was used in subsequent analyses of medication adherence (i.e., percentage of days with correct intake).

[7] Skewness: $\underline{z}$ = Skewness – zero / standard error of skewness; kurtosis: Kurtosis: $\underline{z}$ = Kurtosis – zero / standard error of kurtosis (Tabachnick & Fidell, 1996).

Table 5

Correlations among Summary Measures of 90-Day Medication Adherence

	1	2	3	4	5	6
1. % of prescribed doses taken	1.0	---	---	---	---	---
2. % of day with correct intake	.94* (.000)	1.0	---	---	---	---
3. % of days with drug holidays	-.95* (.000)	-.84* (.000)	1.0	---	---	---
4. % of days with underdosing	-.03 (.737)	-.29* (.002)	-.26* (.007)	1.0	---	---
5. % of days with overdosing	.48* (.000)	.29* (.002)	-.37* (.000)	-.05 (.602)	1.0	---
6. % of days with correct intake & timing between doses	.64* (.000)	.72* (.000)	-.55* (.000)	-.29* (.002)	.14 (.139)	1.0

Note. N = 112. Two-tailed tests. Exact significance levels in parentheses below correlation coefficients
* $p < .01$

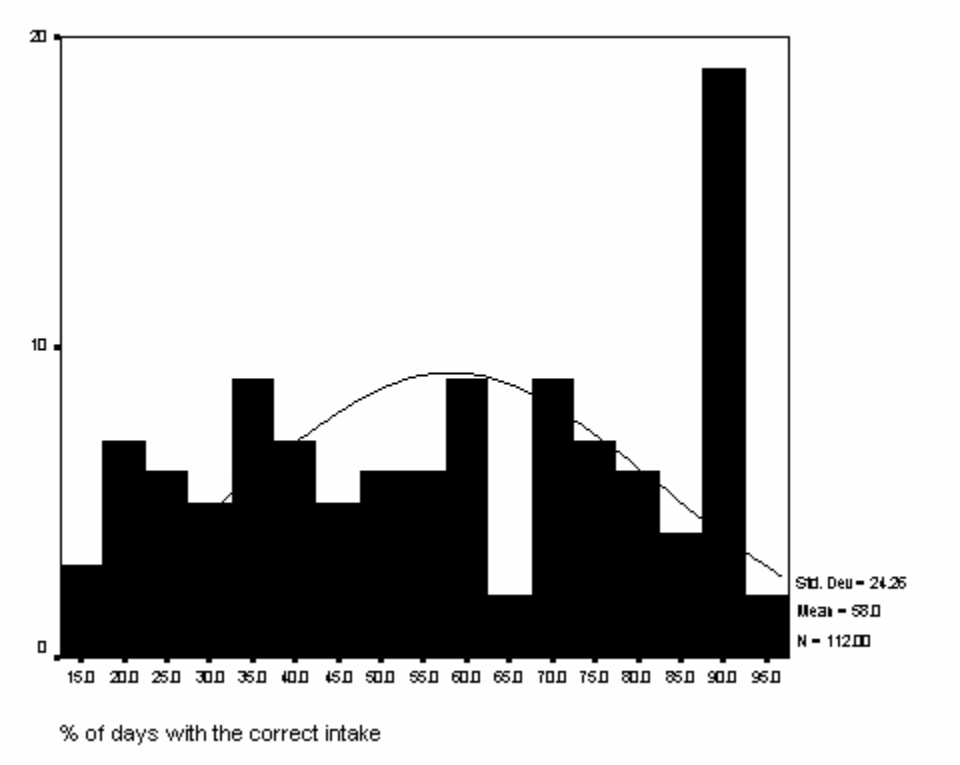

Figure 1

Histogram of the frequency distribution of the percentage of days with correct intake (with a superimposed normal curve).

3.1.2 Prediction of Medication Adherence

A multiple regression logistic regression analysis was performed in order to characterize differences between medication completers and non-completers. Category of medication completion was entered as the criterion, and in order to maximize information about medication completion, several variables, including medication group, counseling group, age, race, education status, and Fagerstrom tolerance scores, were entered as predictors in the first step. First- and second-order psychosocial parameter terms were entered as predictors in the second and third steps, respectively. The final model is summarized in Table 6. The overall model was significant, χ^2 (2) = 17.32, p = .000, R^2_L = .37, Hosmer-Lemeshow goodness-of-fit, χ^2 (8) = 6.21, p = .624 (i.e., a well-fit model produces a non-significant χ^2). Two variables were included in the final model: (1) race, unstandardized β = -2.97, p = .006, odds ratio (OR) = .051, 95% confidence interval (CI) = .006-.434, and (2) conscientiousness, unstandardized β = .322, p = .005, OR = 1.38, 95% CI = 1.102-1.728. Likelihood ratio tests indicated that the removal of race or conscientiousness from the model resulted in significant decrements in model fit, Δ in –2 log likelihood (1) = 7.33, p = .007, and Δ in –2 log likelihood (1) = 16.74, p = .000, respectively. Thus, this fitted model indicates that individuals who are non-Caucasian or less conscientiousness were more likely to not complete the minimum threshold of medication adherence. Although the proportion of non-Caucasian participants was small (13/118, or 11.0%), the proportion of non-completers who were non-Caucasian was relatively large (3/6, or 50%). Given these differences, all subsequent analyses were conducted with medication completers (N = 112).

Prior to performing linear regression analyses to predict medication adherence among completers, power analysis estimation for the linear regression model was computed using

Table 6

Results of Regression Model on Medication Completion

Variable	β	Odds Ratio	95% CI	p-value
In model				
Race/ethnicity	-2.97	.051	.006-.434	.006
Conscientiousness	.322	1.38	1.102-1.728	.005
Failing to enter model ($p > .10$)				
Medication group, Counseling group, Age, Education status, Fagerstrom tolerance scores				
BDI, Agreeableness, ISEL, Medication efficacy expectancies, Medication outcome expectancies, Week 2 (baseline) side effects, Week 3 side effects, Week 5 side effects				
BDI-by-Week 5 side effects				
Week 2-by-Week 3-by-Week 5 side effects				

Note. Overall Model A: χ^2 (2) = 17.32, p = .000. N = 112. β is the unstandardized regression coefficient for the final regression model. Medication Completion: 0 = non-completion, 1 = completion; race/ethnicity: 1 = White, 2 = Black or Native Hawaiian/Pacific Islander.

Power Analysis and Sample Size Software 2000 (PASS, Kaysville, Utah). A two-sided .05 alpha level and a sample size of 112 participants were assumed. When predicting medication adherence, an R^2 of .12 attributed to nine independent variables achieves 81% power, even after adjusting for an additional three covariates with an R^2 of .10. Given that a recent meta-analysis of 12 studies assessing the association between depression and adherence to a variety of disease regimens reported that the pooled difference in risk of nonadherence between depressed and nondepressed patients was 27% (i.e., nondepressed patients manifesting better adherence; DiMatteo et al., 2000), power with the current sample size was deemed adequate.

A multiple linear regression model was fit to determine whether any of the potentially confounding variables should be included in the final model. Specifically, medication group, counseling group, age, race, education status, and Fagerstrom tolerance scores were entered as predictors and 90-day medication adherence was set as the criterion. The overall model was significant, $F(6, 105) = 2.27$, $p = .042$, but age was the only significant predictor of medication adherence, $t(111) = 2.10$, $p = .038$, $\beta = .21$. In the subsequent hierarchical regression model of medication adherence, age was force entered in the first block of predictors and the first- and second-order psychosocial parameters were entered in the second and third blocks, respectively. The final model is summarized in Table 7. Although the overall model was significant, $F(2,109) = 7.23$, $p = .001$, age was not significantly associated with medication adherence, $R^2 \Delta = .028$, $t(111) = 1.47$, $p = .14$. As predicted, conscientiousness scores accounted for a significant increment in the variance in medication adherence, $R^2 \Delta = .089$, $t(111) = 3.32$, $p = .001$, $\beta = .30$. This effect indicates that higher levels of conscientiousness were associated with more favorable adherence, relative to lower levels of conscientiousness. Terms reflecting all other predictor

Table 7

Results of Regressing Primary Psychosocial Variables on 90-Day Medication Adherence

Variable	β	R^2 Δ	Significance of change
In model			
Conscientiousness	.30	.089	$t(111) = 3.32$, $p = .001$
Overall model		.117	$F(2,109) = 7.23$, $p = .001$
Failing to enter model ($p > .10$)			
Age			
BDI, Agreeableness, ISEL, Medication efficacy expectancies, Medication outcome expectancies Week 2 (baseline) side effects, Week 3 side effects, Week 5 side effects			
BDI-by-Week 5 side effects, Week 2-by-Week 3-by-Week 5 side effects			

Note. $N = 112$. β is the standardized regression coefficient for the final regression model.

variables and interactions failed to approach significance (i.e., $\underline{p} > .10$) and were eliminated from the final regression model.

3.1.3 Prediction of Smoking Abstinence

Prior to performing analyses to predict smoking cessation, a power analysis was conducted using an effect size from previous research on adherence and smoking cessation (Killen et al., 1997). A logistic regression of a binary response variable (smoking abstinence) on a continuous predictor with a sample size of 112 achieves 83% power to detect a 15% change in probability of smoking abstinence between mean medication adherence and one standard deviation above the mean. Killen et al. (1997) reported a 30% difference in smoking relapse at 3-month follow-up between those who adhered to the nicotine patch treatment instructions (40% relapsed) compared to those who did not adhere (70% relapsed). Thus, power to detect a moderate effect of adherence on smoking cessation with the present study was deemed adequate.

Four logistic regression analyses were performed to examine the effects of 90-day medication adherence and the only significant psychosocial predictor of adherence, conscientiousness, on smoking cessation. In these smoking cessation analyses, prolonged smoking abstinence entered as the dichotomous criterion variable. Again, an initial logistic regression model was fit to determine whether any of the potentially confounding variables should be included in the final model. A final solution for the overall model could not be fit as none of the predictors (including medication and counseling treatments) significantly predicted prolonged abstinence ($\underline{p} > .065$). As a result, no covariates were entered into subsequent models.

A second logistic regression model was analyzed with the main effect of medication adherence entered as the only predictor variable. As seen in Table 8A, results indicated that the model was a good fit, χ^2 (1) = 13.18, $\underline{p} = .000$, $\underline{R}^2_L = .087$, Hosmer-Lemeshow goodness-of-fit,

Table 8

Results of Two Logistic Regression Models on Prolonged Smoking Abstinence

	Predictor	β	Odds Ratio	95% CI	p-value
A.	90-day medication adherence	.031	1.031	1.013-1.049	.000
B.	Conscientiousness	.035	1.036	.967-1.110	.320

Note. Overall Model A: χ^2 (1) = 13.18, p = .000; Overall Model B: χ^2 (1) = 1.00, p = .317. N = 112. β is the unstandardized regression coefficient for the final regression model.

χ^2 (8) = 7.04, p = .532, and that medication adherence was significantly associated with increased likelihood of prolonged smoking abstinence, unstandardized β = .031, p = .000, OR = 1.031, 95% CI = 1.013-1.049. The likelihood ratio test indicated that the removal of medication adherence from the model resulted in significant decrement in model fit, Δ in –2 Log Likelihood (1) = 13.24, p = .000.

A third logistic regression model was analyzed with the main effect of conscientiousness entered as the predictor variable. The model was not significant, χ^2 (1) = 1.00, p = .317, indicating that inclusion of conscientiousness did not improve the prediction of prolonged smoking abstinence (see Table 8B). This null finding suggests that conscientiousness did not mediate the relationship between medication adherence and smoking abstinence in this study.

Finally, to assess for a possible moderational effect on smoking cessation, a multiple logistic regression model was analyzed with the main effects of medication adherence and conscientiousness entered as predictor variables in the first step and the interaction between medication adherence and conscientiousness entered in the second step. In order to remove potentially high levels of non-essential multicollinearity between the main effects and the interaction term (Aiken & West, 1991), 90-day medication adherence and conscientiousness were centered about their respective means before testing the significance of the interaction term. The overall model was a significant fit, χ^2 (3) = 13.65, p = .003, R^2_L = .090, Hosmer-Lemeshow goodness-of-fit, χ^2 (8) = 6.91, p = .55, but the interaction term was not a significant predictor of smoking abstinence, χ^2 (1) = 0.449, p = .503. Medication adherence again accounted for a significant proportion of the variance in prolonged smoking abstinence, unstandardized β = .031, OR = 1.031, 95% CI = 1.013-1.051. Thus, these results suggest that conscientiousness and medication adherence did not form a moderating relationship.

3.2 SECONDARY ANALYSES

3.2.1 Prediction of Medication Adherence with Alternative Psychosocial Factors

Although conscientiousness and agreeableness were the only personality factors tested in primary analyses, the effects of all Big Five dimensions were assessed concurrently in secondary analyses. A multiple stepwise linear regression model was computed with 90-day medication adherence entered as the dependent variable and the five personality factors entered as the predictor variables. The overall model fit the data well, $\underline{R}^2 = .187$, $\underline{F}(3, 108) = 8.27$, $\underline{p} = .000$, and is summarized in Table 9. Age was again force entered in the first step and in this instance was significantly associated with medication adherence, $\underline{R}^2 \Delta = .028$, $\underline{t}(108) = 2.12$, $\underline{p} = .037$, $\underline{\beta} = .189$. As in the primary analyses, conscientiousness was positively associated with medication adherence, $\underline{R}^2 \Delta = .089$, $\underline{t}(108) = 3.68$, $\underline{p} = .000$, $\underline{\beta} = .32$. Openness to experience also accounted for a significant increment in the variance in medication adherence, $\underline{R}^2 \Delta = .070$, $\underline{t}(108) = 3.04$, $\underline{p} = .003$, $\underline{\beta} = .27$. This result indicates that higher levels of openness to experience were associated with more favorable adherence, relative to lower levels of openness. Terms reflecting all other Big Five factors failed to approach significance (i.e., $\underline{p} > .40$) and were eliminated from the final regression model.

With the exception of side effects, all primary analyses were conducted with predictors measured prior to initiating medication or counseling treatments and attempting to quit smoking. Although not hypothesized, it is possible that individual differences in psychosocial variables measured a few weeks after beginning treatment and quitting smoking influenced medication adherence and/or prolonged smoking abstinence distinctly from the same variables measured

Table 9

Results of Regressing All Dimensions of the Five-Factor Model of Personality on 90-Day Medication Adherence

Variable	β	R^2 Δ	Significance of change
In model			
Age	.19	.028	$t(108) = 2.12$, $p = .037$
Conscientiousness	.32	.089	$t(108) = 3.68$, $p = .000$
Openness to Experience	.27	.070	$t(108) = 3.04$, $p = .003$
Failing to enter model ($p > .40$)			
Agreeableness, Extraversion, Neuroticism			

Note. $N = 112$. Overall model, $F(3, 108) = 8.27$, $p = .000$. β is the standardized regression coefficient for the final regression model.

before treatment. For this reason, the effects of Week 6 BDI, Week 6 medication outcome expectations, and Week 6 ISEL were analyzed in secondary analyses. Given the prospective nature of this assessment, it is not surprising that missing data existed among the sample of 112 medication completers. The proportions of participants with missing data were as follows: Week 6 BDI = 11.6%, Week 6 medication outcome expectancies = 11.6%, and Week 6 ISEL = 18.8%. To maintain an N of 112, missing data were imputed with the means of the non-missing cases. Then, a stepwise linear regression model was computed with 90-day medication adherence entered as the criterion variable, age entered in the first predictor step, and the three Week 6 psychosocial parameters entered in the second predictor step.[8] The final model is summarized in Table 10. The overall model was significant, $R^2 = .107$, $F(2, 109) = 6.50$, $p = .002$. Age did not account for a significant amount of variance in medication adherence, $R^2 \Delta = .028$, $t(109) = 1.86$, $p = .065$, but Week 6 ISEL scores were positively associated with increased medication adherence, $R^2 \Delta = .079$, $t(109) = 3.10$, $p = .002$, $\beta = .28$. For heuristic purposes, the correlation between Week 6 ISEL and Week 6 BDI scores was computed. Since it was moderately strong, $r = -.45$, $p = .000$, a univariate model with Week 6 BDI as the sole predictor was computed. Interestingly, Week 6 BDI scores would have been significantly and negatively associated with medication adherence had Week 6 ISEL scores not been entered concurrently, $R^2 \Delta = .084$, $t(109) = -2.59$, $p = .011$, $\beta = -.24$. These results suggest that social support accounts for variability in medication adherence over and above depressive symptoms but not vice versa.

[8] This analysis was also conducted using participants with complete data only and the results were comparable, i.e., the overall model was significant, $R^2 = .123$, $F(2, 78) = 5.48$, $p = .006$; age did not account for a significant amount of variance in medication adherence, $R^2 \Delta = .021$, $t(78) = 1.59$, $p = .115$; Week 6 ISEL scores were positively associated with increased medication adherence, $R^2 \Delta = .102$, $t(78) = 3.01$, $p = .004$, $\beta = .32$.

Table 10

Results of Regressing Week 6 Psychosocial Variables on 90-Day Medication Adherence

Variable	β	R^2 Δ	Significance of change
In model			
Week 6 ISEL	.28	.079	$t(109) = 3.10$, $p = .002$
Failing to enter model ($p > .10$)			
Age, Week 6 BDI, Week 6 medication outcome expectancies			

Note. $N = 112$. Missing data for Week 6 ISEL, BDI, and medication outcome expectancies were imputed with means of respective non-missing cases. Overall model, $F(2, 109) = 6.50$, $p = .002$. β is the standardized regression coefficient for the final regression model.

3.2.2 Prediction of Smoking Abstinence with Alternative Psychosocial Factors

In order to test for mediational or moderational effects related to smoking abstinence, a series of logistic regression models were computed with alternative psychosocial variables found to be associated with medication adherence entered as predictors. First, a logistic regression model was analyzed with the main effect of openness to experience entered as the predictor variable and prolonged smoking abstinence entered as the criterion variable. Results indicated that the model was a good fit, χ^2 (1) = 4.50, p = .034, R^2_L = .0295, and Hosmer-Lemeshow goodness-of-fit, χ^2 (8) = 6.08, p = .638, and that openness to experience was significantly associated with increased likelihood of prolonged smoking abstinence, unstandardized β = .069, p = .039, OR = 1.072, 95% CI = 1.003-1.145. To test whether medication adherence mediated the association between openness to experience and smoking abstinence, the effect of medication adherence on prolonged smoking abstinence was assessed, controlling for openness to experience. A logistic regression model was fit, χ^2 (2) = 15.41, p = .000, R^2_L = .1011, Hosmer-Lemeshow goodness-of-fit, χ^2 (8) = 7.92, p = .442, showing that medication adherence predicted increased smoking abstinence, unstandardized β = .028, p = .002, OR = 1.029, 95% CI = 1.011-1.047, after controlling for openness to experience. Since the three pre-conditions of mediation were achieved (Baron & Kinney, 1986), post-hoc probing of the indirect effect was conducted. The statistical test for mediation (Holmbeck, 2002) demonstrated that the indirect effect was significant, z = 2.00, p = .023, indicating that the drop in the total effect (i.e., the path between openness to experience and smoking abstinence) was statistically significant upon inclusion of medication adherence in the model. Thus, medication adherence was a significant mediator of the openness to experience/smoking abstinence relationship, accounting for 39.7% of the variance.

Next, a logistic regression model was computed with Week 6 ISEL entered as the predictor variable and smoking abstinence as the criterion. The model fit adequately, $\underline{\chi}^2$ (1) = 5.88, $\underline{p}$ = .015, $\underline{R}^2_L$ = .0386, Hosmer-Lemeshow goodness-of-fit, $\underline{\chi}^2$ (7) = 7.77, $\underline{p}$ = .354, and results indicated that social support was significantly associated with increased likelihood of prolonged smoking abstinence, unstandardized $\underline{\beta}$ = .036, OR = 1.037, 95% CI = 1.006–1.069. When controlling for Week 6 ISEL, a model with 90-day medication adherence predicting prolonged smoking abstinence was a significant fit, $\underline{\chi}^2$ (1) = 15.623, $\underline{p}$ = .000, $\underline{R}^2_L$ = .1025, Hosmer-Lemeshow goodness-of-fit, $\underline{\chi}^2$ (7) = 9.007, $\underline{p}$ = .342, unstandardized $\underline{\beta}$ = .027, $\underline{p}$ = .003, OR = 1.028, 95% CI = 1.010-1.046. The statistical test for mediation showed that the indirect effect was significant, $\underline{z}$ = 2.14, $\underline{p}$ = .016, indicating that medication adherence was a significant mediator of the Week 6 ISEL/smoking abstinence relationship (accounting for 37.2% of the variance). As previously mentioned, Week 6 BDI scores were significantly associated with prolonged smoking abstinence when entered as the sole predictor (i.e., without Week 6 ISEL). For heuristic purposes, a mediational test involving BDI/medication adherence/prolonged smoking abstinence was explored. The test was significant, $\underline{z}$ = -1.81, $\underline{p}$ = .035, indicating that medication adherence significantly mediated the association between depressive symptoms and prolonged smoking abstinence (accounting for 22.48% of variance), but only when ISEL scores were precluded.

Finally, an exploratory hierarchical logistic regression analysis was conducted to determine whether any of the psychosocial parameters unrelated to medication adherence were associated with prolonged smoking abstinence. Specifically, the following main effect terms were entered in the first step of the model: agreeableness, neuroticism, extraversion, baseline BDI, baseline ISEL, baseline and Week 6 medication outcome expectations, baseline self-efficacy

expectations, and Weeks 2, 3, and 5 side effects. The overall model was significant, χ^2 (2) = 15.45, p = .000, R^2_L = .1014, Hosmer-Lemeshow goodness-of-fit, χ^2 (8) = 6.75, p = .564, and is summarized in Table 11. Two variables were included in the final model: (1) agreeableness, unstandardized ß = .096, p = .018, OR = 1.101, 95% CI = 1.016-1.192, and (2) Week 6 medication outcome expectations, unstandardized ß = .048, p = .005, OR = 1.049, 95% CI = 1.015-1.085. Likelihood ratio tests indicated that the removal of Agreeableness or Week 6 medication outcome expectations from the model resulted in significant decrements in model fit, Δ in –2 Log Likelihood (1) = 6.04, p = .014, and Δ in –2 Log Likelihood (1) = 9.42, p = .002, respectively. Thus, individuals with higher agreeableness scores and Week 6 medication outcome expectations tended to maintain smoking abstinence more successfully than individuals scoring low on either of these variables.

In order to better characterize the openness to experience/smoking cessation relationship, another possible mediator was examined, that is, Week 6 medication outcome expectancies. The zero-order correlation between openness to experience and Week 6 medication outcome expectations was in fact significant, r = .24, p = .012, so a test for statistical mediation was conducted. The indirect effect was significant, z = 1.76, p = .039, indicating that Week 6 medication outcome expectations significantly mediated the openness to experience/smoking abstinence relationship (accounting for 32.8% of the variance).

Finally, the possibility that Week 6 ISEL mediated the agreeableness/prolonged smoking abstinence association was explored. Although two pre-conditions of mediation were achieved, (1) agreeableness was significantly associated with Week 6 ISEL, r = .28, p = .003, and (2) agreeableness was significantly associated with prolonged smoking abstinence (see above), Week 6 ISEL scores did not predict prolonged smoking abstinence when adjusting for

Table 11

Results of Regressing Psychosocial Variables Unrelated with Medication Adherence on Prolonged Smoking Abstinence

Variable	β	Odds Ratio	95% CI	p-value
In model				
Agreeableness	.096	1.101	1.016-1.192	.018
Week 6 medication outcome expectancies	.048	1.049	1.015-1.085	.005
Failing to enter model ($p > .10$)				
Neuroticism, Extraversion, Baseline BDI, Baseline ISEL, Baseline medication outcome expectations Baseline self-efficacy expectations, Weeks 2 side effects, Week 3 side effects, Week 5 side effects				

Note. Overall Model χ^2 (2) = 15.45, p = .000. N = 112. Missing data for Week 6 medication outcome expectancies were imputed with means of non-missing cases. β is the unstandardized regression coefficient for the final regression model.

agreeableness, ß = .029, p = .069. Thus, this later null finding suggested that Week 6 ISEL was not a significant mediator.

3.2.3 Main Effect of Medication Adherence on Smoking Abstinence: Possible Influences

The aim of the next set of logistic regression analyses was to shed light on possible explanations for the main effect of medication adherence on prolonged smoking abstinence. If the main effect of 90-day medication adherence lost its statistical significant when adjusting for potentially important psychosocial variables, this would suggest a plausible, but not causal, psychosocial mechanism underlying the influence of adherence. As described above, the main effect of medication adherence on prolonged smoking abstinence was not attenuated when entering conscientiousness prior to medication adherence. Two more multiple logistic regression model were fit with psychosocial parameters related to medication adherence (openness to experience and Week 6 ISEL) entered prior to medication adherence as predictors and prolonged smoking abstinence entered as the criterion. When adjusting for openness to experience, the overall model was statistically significant, χ^2 (2) = 15.41, p = .000, but the main effect of medication adherence on smoking cessation was not attenuated, unstandardized ß = .028, p = .002, OR = 1.029, 95% CI = 1.011-1.047. Similarly, when adjusting for Week 6 ISEL, the overall model was statistically significant, χ^2 (2) = 15.62, p = .000, but the main effect of medication adherence on smoking cessation remained significant, unstandardized ß = .027, p = .003, OR = 1.028, 95% CI = 1.010-1.046.

A final stepwise multiple logistic regression model was fit with all remaining first-order psychosocial terms entered prior to 90-day medication adherence. Again, the overall model was a good fit, χ^2 (2) = 25.14, p = .000, and the main effect of medication adherence was still significant, unstandardized ß = .028, p = .003, OR = 1.028, 95% CI = 1.010-1.047. In sum, these

results did not implicate any measured psychosocial mechanisms that may underlie the main effect of adherence on smoking cessation.

3.2.4 Prediction of Smoking Abstinence with all Six Summary

In the primary analyses, medication adherence was operationalized with the "percentage of prescribed administrations taken" summary index. In order to compare the relative predictive utility of the numerous summary measures of medication adherence that were computed, a stepwise multiple logistic regression analysis was conducted with all six summary measures of 90-day medication adherence entered as predictors and prolonged smoking abstinence entered as the criterion. The final model is summarized in Table 12. The overall model was significant, χ^2 (1) = 17.84, $\underline{p}$ = .000, $\underline{R}^2_L$ = .12, Hosmer-Lemeshow goodness-of-fit, χ^2 (7) = 3.82, $\underline{p}$ = .800. Interestingly, the measure indexing percentage days with drug holidays was significantly associated with decreased likelihood of maintaining prolonged smoking abstinence, unstandardized $\underline{ß}$ = -.037, $\underline{p}$ = .000, OR = .963, 95% CI = .945-.982. The likelihood ratio test showed the dropping the drug holiday index from the model resulted in significant decrement in model fit, Δ in –2 Log Likelihood (1) = 18.27, $\underline{p}$ = .000. None of the other five summary measures of adherence remained in the final model ($p \geq .10$), suggesting that failure to take medication for one or more consecutive days was the most robust predictor of failing to maintain prolonged smoking abstinence.

3.2.5 Temporal Nature of the Medication Adherence-Smoking Abstinence Relationship

In primary analyses, logistic regression modeling showed that 90-day medication adherence (i.e. percentage of days with correct intake) was positively related to prolonged smoking abstinence. However, those results were not capable of differentiating direction of causality, that is, medication adherence may have led to enhanced smoking abstinence, smoking abstinence may

have led to enhanced medication adherence, or both may have been antecedents of one another. A cross-lagged panel design was used to test hypotheses regarding the temporal nature of the relationship between medication adherence and smoking abstinence. It is important to note that the plausibility of a causal relationship is strengthened, but by no means proved, by utilizing this quasi-experimental design in which variables are collected at least twice over time (Kenny, 1975).

Since medication adherence and prolonged smoking abstinence were global measures of the entire study period, they do not provide information about fluctuations of these behaviors over time. Therefore, the three 30-day measures of medication adherence and point-prevalence smoking abstinence measures taken during each of these 30-day periods were designated as the components of the cross-lagged panel design.[9] For simplicity, the 1st, 2nd, and 3rd 30-day medication adherence periods are referred to as A1, A2, and A3, respectively, and point-prevalence smoking abstinence at day 28, 56, and 84 are referred to as P1, P2, and P3, respectively, in this cross-lagged panel design. The design is outlined in Figure 2. Tentative conclusions about the direction of medication adherence—smoking abstinence associations can be established by comparing the correlation coefficients representing A1-P2 versus P1-A2, as well as the cross-lagged correlations of A1-P3 versus P1-A3 and A2-P3 versus P2-A3. Assuming that presumed causal variables precede presumed effect variables in time (Leary, 1995), hypotheses regarding medication adherence causing increased smoking abstinence are supported

[9] It is important to note that point-prevalence abstinence is measured independently over repeated occasions. Although having one cigarette is a strong predictor of relapse over time, it is possible to be classified as having been non-abstinent at one point-prevalence abstinence time point but abstinent at a subsequent time point.

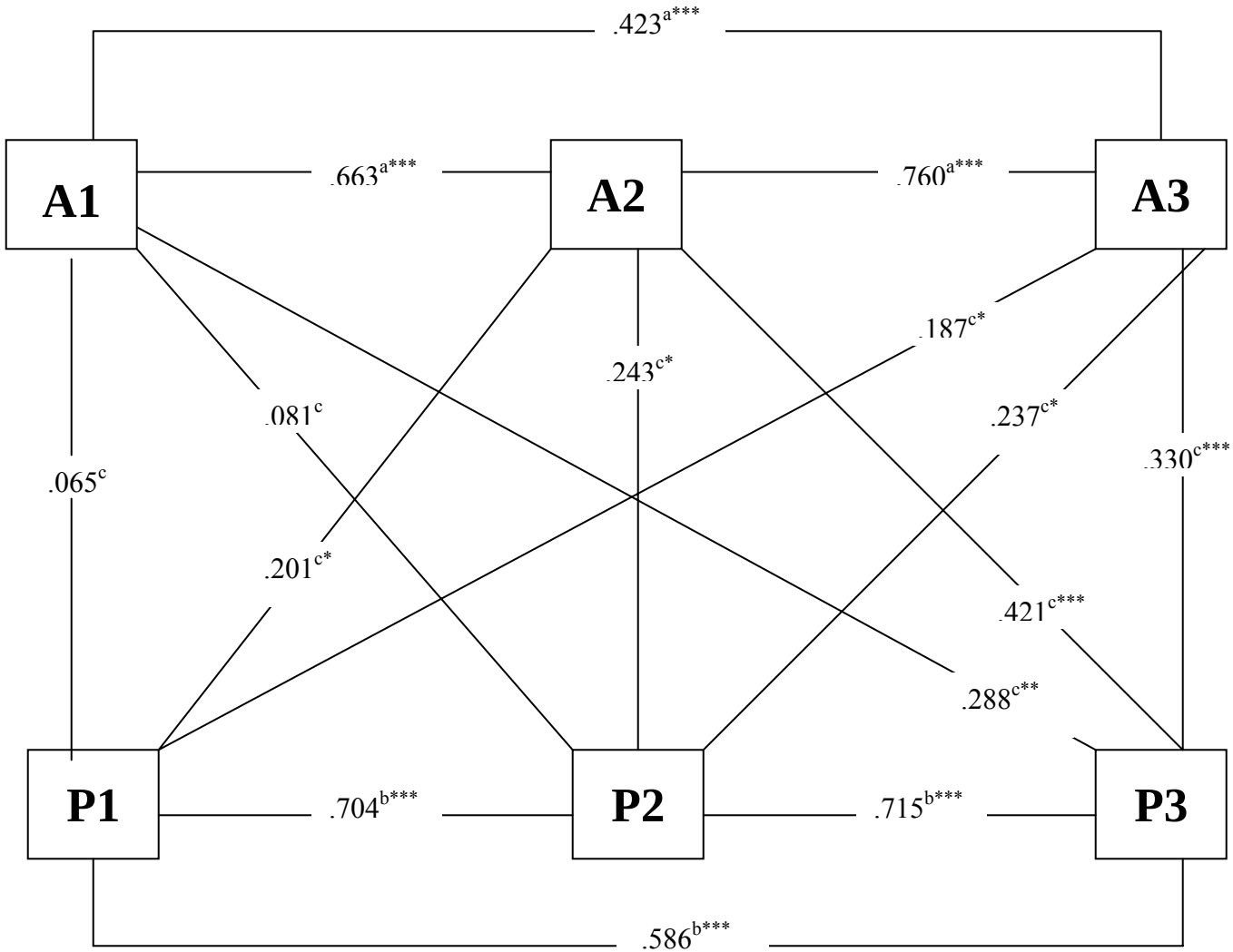

Figure 2

Cross-Lagged panel design involving three 30-day medication adherence periods and corresponding point-prevalence smoking abstinence rates.

Note. N = 112. Two-tailed tests. A1 = % of days with the correct number of doses during the first 30-day period, A2 = % of days with the correct number of doses during the second 30-day period, A3 = % of days with the correct number of doses during the third 30-day period, P1 = point-prevalence abstinence at Day 28 (0 = not abstinent, 1 = abstinent), P2 = point-prevalence abstinence at Day 56, P3 = point-prevalence abstinence at Day 84.

[a] Pearson-produce moment correlation.

[b] Phi coefficients (r_{ϕ}).

[c] Point-biserial correlation.

* $p < .05$

** $p < .01$

*** $p < .001$

if cross-lagged correlations A1-P2, A2-P3, and A1-P3 are significantly greater than correlations P1-A2, P2-A3, and P1-A3, respectively.

In order to support the viability of the cross-lagged panel design, the assumptions of synchronicity and stationarity (Kenny, 1975) were considered. The synchronicity assumption necessitates that the predictor and criterion variables are measured contemporaneously over a minimum of two distinct points in time for the same individuals. The stationarity assumption requires that the underlying structural relationship between the predictor and criterion variables do not vary between the two or more measurement time points. Violations of stationarity are assumed to have occurred if the synchronous correlations (i.e., correlations between the predictor and criterion variables at the same time point, such as A1-P1, A2-P2, and A3-P3) are significantly different over time.

Autocorrelations (i.e., correlations of the same variable at two or more points in time), synchronous correlations, and cross-lagged correlations were calculated in order to evaluate the cross-lagged panel design. Since medication adherence was indexed continuously, Pearson-product moment correlations were computed for the A1-A2, A2-A3, and A1-A3 autocorrelations. Since point-prevalence smoking abstinence was indexed dichotomously, phi coefficients ($\underline{r}_{\phi}$) were computed for the P1-P2, P2-P3, and P1-P3 autocorrelations. Point-biserial correlations ($\underline{r}_{pb}$) were computed for the A1-P2, A2-P3, A1-P3, P1-A2, P2-A3, and P1-A3 cross-lagged correlations.[10] Differences between correlations were tested with the Pearson-Filon $\underline{z}$-test (as cited by Kenny, 1975). Since Pearson and point-biserial correlations are subject to the univariate normality assumption, medication adherence indices were transformed in order that

[10] SPSS for Windows 8.5 calculates point-biserial correlations using the eta statistic. Hand-calculated point-biserial correlations were identical to the eta statistic.

resulting skewness and kurtosis values were within conventional levels (Tabachnick & Fidell, 1996). Specifically, the cube of A1 and the square of A2 and A3 were used in these cross-lagged panel design analyses.

Assumptions were evaluated initially. Since A1-P1, A2-P2, and A3-P3 correlations were measured at roughly the same respective time periods over three consecutive intervals, the synchronicity assumption was supported. Inequality of the synchronous correlations A1-P1 ($\underline{r}_{pb}$ = .065, $\underline{p} > .10$) versus A2-P2 ($\underline{r}_{pb}$ = .243, $\underline{p} < .02$), $\underline{z}$ = -1.67, $\underline{p}$ = .048, and A1-P1 ($\underline{r}_{pb}$ = .065) versus A3-P3 ($\underline{r}_{pb}$ = .330, $\underline{p} < .001$), $\underline{z}$ = -1.99, $\underline{p}$ = .023, suggested that the stationarity assumption was violated for the Time 1 panel. The synchronous correlations A2-P2 ($\underline{r}_{pb}$ = .243) and A3-P3 ($\underline{r}_{pb}$ = .330) were not significantly different, $\underline{z}$ = -1.16, $\underline{p}$ = .123, thereby validating the stationarity assumption for the Time 2 and 3 panels. Autocorrelations for medication adherence were moderate (A1-A3, $\underline{r}$ = .423, $\underline{p}$ = .000) to strong (A1-A2: $\underline{r}$ = .663, $\underline{p}$ = .000; A2-A3: $\underline{r}$ = .760, $\underline{p}$ = .000). Autocorrelations for point-prevalence abstinence were moderately strong (P1-P3: $\underline{r}_{\phi}$ = .586, $\underline{p}$ = .000) to very strong (P1-P2: $\underline{r}_{\phi}$ = .704, $\underline{p}$ = .000; P2-P3: $\underline{r}_{\phi}$ = .715, $\underline{p}$ = .000). The cross-lagged correlation between A2 and P3 was moderate ($\underline{r}_{pb}$ = .421) and significant ($\underline{p} < .001$), whereas the corresponding cross-lagged correlation between P2 and A3 was smaller ($\underline{r}_{pb}$ = .237), although still significant ($\underline{p} < .02$). The Pearson-Filon $\underline{z}$-test revealed that these cross-lagged correlations were significantly different, $\underline{z}$ = 2.25, $\underline{p}$ = .01. To recapitulate, these results indicate that medication adherence during the second 30-day period was associated with subsequent increased risk of being abstinent from smoking during the final week of the study period. At the same time, these results also suggest that being abstinent from smoking during the mid-point of the study period increased the likelihood of maintaining adherence to the medication regimen during the final 30-day period. When comparing whether the temporal precedence of medication

adherence versus point-prevalence abstinence, results suggested that medication adherence was the stronger antecedent of the two.

4 DISCUSSION

The purpose of this investigation was to examine the rates, predictors, and sequelae of adherence to a 90-day medication regimen among weight-concerned female smokers participating in a smoking cessation trial. Primary and secondary analyses yielded several significant results, including:

1. Ninety-day medication adherence operationalized with a variety of summary indices was suboptimal, with the rates varying from 26% (i.e., via a conservative measure of percentage of days with correct number of doses and timing between doses) to 73% (i.e., via a liberal measure of percentage of total doses taken over 90 days). Moreover, each index showed substantial decrements in medication adherence over each successive 30-day period.
2. Increased levels of conscientiousness were significantly associated with successful completion of a minimum duration of the medication regimen. Caucasian participants were also more likely to complete the minimum medication regimen than non-Caucasian participants. Increased levels of conscientiousness, openness to experience, and Week 6 social support were associated with more favorable 90-day medication adherence.
3. Medication adherence was significantly associated with successful smoking cessation, such that individuals manifesting more favorable adherence were more likely to maintain prolonged smoking abstinence. Increased levels of openness to experience, Week 6 social

support, Week 6 medication outcome expectancies, and agreeableness were also associated with an increased likelihood of maintaining smoking abstinence.

4. Post-hoc analyses revealed that medication adherence significantly mediated the associations between openness to experience and smoking abstinence, and between Week 6 social support and smoking abstinence. Week 6 medication outcome expectancies also mediated the association between openness to experience and smoking abstinence.

5. Cross-lagged panel correlations between the three 30-day periods of medication adherence and three measures of point-prevalence smoking abstinence suggested that medication adherence and abstinence were significant antecedents on one another. Follow-up tests indicated that adherence was the stronger precursor of the two.

6. In a comparison of six summary measures of medication adherence, the index of drug holidays was the best predictor of smoking abstinence.

4.1 Rates of Medication Adherence

To my knowledge, this is the first full-length report of adherence rates in a double-blind, placebo-controlled trial using bupropion for the treatment of tobacco dependence. Six summary measures of medication adherence were computed, but only one index, the percentage of days with correct intake, was used in the primary inferential analyses due to two reasons: (1) its balanced operationalization of quantity and timing of dose administrations, and (2) the minimization of Type I error. Among individuals with complete baseline data and no medication-related adverse events, initial analyses indicated that only six participants failed to complete a minimum number of days with correct intake. For the sub-sample of medication completers, the mean percentage of days with the correct medication intake was 58% for the 90-day period, 79% for the first 30-day period, 56% for the second 30-day period, and 40% for the

last 30-day period. As anticipated, the initial 30-day period was a relative "honeymoon" with the highest level of adherence for the sample, but these rates progressively fell throughout the 90-day period. Descriptive statistics with the other five summary measures corroborated this pattern of findings, as well.

Given the lack of empirical data on bupropion adherence, there are no established guidelines for defining a therapeutically adequate level of adherence. However, Insull (1997) reviewed studies of EEM-measured medication-taking behavior for seizure disorders, glaucoma, asthma, cardiology disorders, and hypertension and recommended three clinically-relevant categories of adherence: (1) adherent ($\geq$ 80%), partially adherent (20%-79%), and non-adherent (< 20%). Insull (1997) also reported the typical distribution frequencies for these categories: adherent—50% to 60%, partially adherent—30% to 40%, and non- adherent—5% to 10%. As done by Sereika and Dunbar-Jacob (2001), applying these categorical thresholds to the present study's adherence data resulted in the following frequency distribution: adherent—25%, partially adherent—70%, and non- adherent—5%. Thus, the percentage of individuals in the non-adherent category was similar to Insull's (1997), but the distribution of the adherent and partially-adherent categories were reversed in the present study. It is somewhat surprising that medication adherence was relatively inferior in this smoking cessation trial, given the relatively short duration of the medication regimen and the substantial hurdles individuals overcame to participate in the project (e.g., the intensive screening process included a physical exam, a SCID, multiple questionnaires, etc.). One possible explanation for the differences in distribution frequencies is the immediacy of the health threats posed by cigarette smoking versus existing chronic medical conditions. That is, quitting smoking is a preventive health behavior with potentially long-term benefits, whereas adhering to a medication regimen designed to ameliorate

an existing chronic disorder may have more immediate payoffs, such as reducing the possibility of experiencing a seizure or myocardial infarction. Methodologically, an important benefit of a larger partially adherent group in the present study was a sample distribution approximating normality. This observed adherence distribution was inconsistent with the J-shaped distribution[11] commonly reported for adherence behaviors across a wide array of assessment methods and disease regimens (Dunbar-Jacob et al., 1998b). Whereas the adherence literature is largely characterized by dichotomizing adherence (e.g., $\geq$ 80% = good adherence, < 80% = poor adherence), the present study's distribution allowed for the operationalization of medication adherence data continuously, the use of parametric statistics, and the concomitant maximization of statistical power.

It is noteworthy that medication adherence rates were measured in this study with MEMS Smart Caps, which provided real-time information on quantity and timing of dose administrations to participants in their daily lives. The importance of self-monitoring is underscored by previously reported findings that electronic monitors elicit participant reactivity and may actually enhance adherence behavior. For example, McKenney, Munroe, and Wright (1992) demonstrated that adherence was significantly elevated ($p = .002$) in the group using an electronic pill monitor (80%) with those using the standard pill bottle and cap (78%). Moreover, informing participants of the importance of using an electronic pill cap for clinical or research purposes may encourage them to be more adherent. For example, Kruse and Weber (1990) reported that 91% of individuals informed about the electronic medication monitor were adherent

[11] The J-shaped distribution usually consists of a majority of individuals being highly adherent (> 90%), a smaller proportion ranging from 10% to 90% adherent, and a small increase in the less than 10% range (Dunbar-Jacob et al., 1998b).

whereas 78% of uninformed individuals were adherent. In the present study, all participants were informed about the research purpose of the MEMS caps and were encouraged to use the caps' digital displays to facilitate adherence. Indeed, the correlation between the participants' self-reported usage of the MEMS cap to keep track of medication consumption and actual EEM-measured adherence was statistically significant. Although the MEMS Smart Caps' digital display may have enhanced overall rates of adherence, the relatively suboptimal 90-day adherence rate argues against the possibility that the present findings were substantively biased in a positive direction and therefore invalid. In fact, it is debatable whether the widespread availability of inexpensive pill organizers in commercial pharmacies makes the present study's findings more externally valid than medication studies not using self-monitoring devices. In the end, the only way to reach definitive conclusions regarding the effects of dosing administration information on medication-taking behavior would be to randomize participants to use caps with or without digital displays in a true experimental design.

4.2 Prediction of Medication Adherence

One of the strengths of this study was the examination of several psychosocial variables that are commonly explored in a univariate manner, but in fact are empirically and conceptually interrelated. This multivariate approach allowed for the examination of the independent contributions of psychosocial parameters along with potentially overlapping or redundant constructs, in addition to permitting exploration of mediational and moderational effects. Importantly, preliminary analyses revealed that several potentially confounding variables, including levels of medication treatments (bupropion vs. placebo) and counseling treatments (CBT for weight concerns vs. standard behavior therapy), were unrelated with medication adherence. This evidence suggested that the interventions were not a confounding influence on

medication adherence, and as such, subsequent regression analyses were conducted by collapsing across levels of medication. It is also suggests that the effects of psychosocial variables on medication adherence were independent of any active treatments.

Although not the focus of the present study, the failure to detect a main effect of medication status (bupropion versus placebo) on smoking cessation rates is an important deviation from previous findings (Hurt et al., 1997; Jorenby et al., 1999; Hays et al., 2001) and thus warrants some discussion. The most likely explanation for this null finding was the lack of statistical power. Regression analyses in the present study relied on 112 participants, whereas previous studies reporting positive findings utilized samples well over 600 participants (Hurt et al., 1997; Jorenby et al., 1999; Hays et al., 2001). Another major difference was the intensive nature of group counseling in the present study. That is, participants attended twelve ninety-minute cognitive-behavioral group therapy sessions and five nurse visits over the course of the 90 days of treatment. In contrast, Hurt et al. (1999) provided self-help materials, a physician-based message, and brief (10-15 minutes) weekly individual counseling sessions over seven weeks, and similarly, Jorenby et al. (1999) provided brief (less than or equal to 15 minutes) weekly individual counseling sessions over nine weeks. It is possible that the relative thoroughness of counseling in the present study diluted potential differences between medication groups. Moreover, although differences in smoking cessation rates between bupropion and placebo groups were observed in the aforementioned studies at the 12 week point (Hurt et al., 1997; Jorenby et al., 1999; Hays et al., 2001), it is also possible is that the relatively short-term duration of the present study was insufficient to detect medication effects with this particular sample of weight-concerned women. That is, it may be that bupropion's effects are delayed until weight gain secondary to prolonged abstinence is perceived as problematic enough to justify re-

initiating smoking as a weight control aid. Thus, it is possible that greater weight gains associated with longer periods of prolonged abstinence (i.e., in excess of 11 weeks) are necessary for bupropion to decrease the probability of relapsing among women who report being worried about post-cessation weight gain prior to treatment (e.g., either by reducing weight gain itself or by decreasing concerns about weight gain). These explanations are admittedly speculative, and answering this question will ultimately require a larger sample size, a longer-term follow-up assessment, and a careful examination of changes in concerns about post-cessation weight gain and actual changes in body weight.

Although the percentage of racial/ethnic minorities was relatively small in this study (11%), initial results indicated that non-Caucasian participants tended to withdraw from the study within the first two weeks, and therefore were presumed to be nonadherent and relapsed. Of the six participants who failed to complete a minimum threshold of the medication regimen, two were African-American and one was Native Hawaiian/Pacific Islander. This finding is consistent with a body of research showing that racial and ethnic minorities commonly manifest poorer adherence rates in comparison to the majority of the population. These racial/ethnic disparities in adherence may be attributable to several impediments, including financial constraints, logistical barriers, cultural barriers, and environmental stressors (National Institutes of Health, 1/25/01). Although this study was not designed to assess factors influencing racial/ethnic differences in adherence, it is plausible that any of these factors were related with medication non-completion among these three individuals. For example, the counseling groups were composed primarily of Caucasian participants and the research staff was composed entirely of Caucasian individuals, and this may have inadvertently created cultural barriers for engagement and retention in the trial. However, it is important to note that the number of

minority non-completers was quite small, so this statistically significant effect may have been due to chance, as well.

The present findings suggest that personality constructs may improve the prediction of adherence. As expected, results demonstrated that individuals with lower levels of conscientiousness were less likely to complete the minimum duration of the medication regimen, and among medication completers, lower conscientious levels predicted poorer adherence throughout the 90-day period. The notion that conscientiousness is associated with adherence is intrinsically appealing in that this trait is defined largely by self-control, which involves active planning, organizing, and executing tasks, as well as a lack of impulsiveness (Costa and McCrae, 1992). The conscientiousness factor of the full-scale NEO-PI-R (Costa and McCrae, 1992) includes six facets: competence, order, dutifulness, achievement striving, self-discipline, and deliberation. These facets are negatively related to characteristics typical of individuals who are impulsive, unsocialized, and sensation seeking (Gilbert, 1995). Thus, it may be that individuals with low levels of conscientiousness tend to choose behaviors that promise immediate rewards rather than behaviors that may have potential long-term benefits (e.g., adhering to a pharmacotherapy regimen). Unfortunately, the short-form NEO-FFI does not include personality facets and therefore does not allow for the examination of specific aspects of conscientiousness that may be responsible the factor's association with mediation adherence.

Secondary analyses revealed that openness to experience was positively associated with medication adherence. This effect was not hypothesized a priori since the other Big Five dimensions of have received the majority of attention in health behavior research, and in fact, no published findings exist on openness to experience and treatment adherence. Still, there are a few published studies on the association between openness to experience and various health-related

phenomena. Booth-Kewly and Vickers (1994) reported that openness to experience was positively associated with substance use and associated high-risk behaviors (e.g., driving while intoxicated). Shadel et al. (2000) found in a sample of 37 smokers that openness to experience was positively associated with nicotine dependence, but was unrelated to duration of recent cessation attempt and recent exposure to cigarette smoke. In another recent study, Duberstein et al. (2003) reported that older primary care patients scoring higher on openness to experience tended to report better perceived physical functioning.

Closer examination of the openness to experience dimension provides some insight into possible processes underlying the openness to experience/medication adherence relationship found in the present study. The openness to experience dimension is characterized by curiosity and receptiveness to new ideas and experiences, in addition to diverse interests, mindfulness, and resourcefulness (Costa & McCrae, 1992). Individuals scoring high on this factor also tend to be cognitively flexible and intelligent (McCrae & John, 1992). Thus, it is possible that individuals who are open to experience are more willing to try out new behaviors, such as experimenting with nicotine in the first place and then taking a psychotropic medication to facilitate smoking cessation. It is also conceivable that, given the positive association between the openness to experience and intelligence quotient (e.g., Holland, Dollinger, Holland, & MacDonald, 1995), individuals scoring high on this personality dimension may be better able to problem-solve when obstacles to adherence arise and may be more apt to remember to take their medication as prescribed. Indeed, medication adherence has been characterized as a memory task that may require substantial cognitive demands (Gould, McDonald-Miszczak, & King, 1997) and adherence rates decrease as the complexity of a medication regimen increases (e.g., Trotta et al., 2002).

Secondary analyses also showed that perceived social support and medication outcome expectancies measured at Week 6 were positively associated with 90-day medication adherence. However, the same psychosocial constructs measured at baseline were not significantly associated with medication adherence. The discrepant effects of social support on adherence are somewhat difficult to explain given the evidence that perceived social support functions somewhat like a trait. For instance, the six-week test-retest reliability of ISEL scores was .76 in the present study, and other researchers have reported an equally high test-retest reliability of ISEL scores over six months (e.g., $\underline{r}$ = .74, Cohen et al., 1985). Moreover, a recent quantitative genetic study demonstrated that genetic factors account for a significant proportion of the variance in ISEL scores (Raynor et al., 2002). One possible explanation for the discrepant social support findings is that the salutary effects of perceived support may occur while engaging in the stressful quit process and during the early maintenance phase rather than the relatively quiescent time prior to quitting. This conceptualization of social support is commonly referred to as the buffering hypothesis (Cohen & Wills, 1985) and previous smoking cessation (Cohen et al., 1988) and chronic disease adherence-related research (e.g., Christensen, Turner, Slaughter, & Holman, 1989; Littlefield, Rodin, Murray, & Craven, 1990) is consistent with this explanation. Thus, it is possible that the generally mixed findings in the social support/adherence literature may be due to the failure to examine the predictive utility of repeated measures of social support, particularly during times of high stress. Another possibility is that favorable adherence during the first six weeks of treatment was positively reinforced by social support from participants' family, friends, and others support network members, which in turn contributed to more favorable adherence (Czajkowski et al., 1998). Finally, the inconsistency of the present social support findings also

raises the possibility that various aspects of social support (e.g., information, tangible, etc.) may affect adherence differentially.

The discrepant associations between baseline and Week 6 medication outcome expectancies[12] and medication adherence may be attributable to the influence of adhering to several weeks of the medication regimen and group smoking cessation therapy (Czajkowski et al., 1998). Participants taking the medication as prescribed during the early phases of changing their smoking behavior may have developed the expectation that the medication would facilitate prolonged smoking abstinence. These positive beliefs may have subsequently contributed to the maintenance of favorable adherence. Those who manifested less favorable regimen adherence, on the other hand, may not have developed the expectation that the medication would be of much assistance in quitting smoking and therefore did not adhere as well.

Some discussion of unsupported links between the other psychosocial variables and medication adherence is warranted. The influence of agreeableness on medication adherence was suggested by the broader health-behavior change literature but was not observed in the present study. It is possible that only certain aspects of the agreeableness versus antagonism dimension are deleterious to medication adherence. According to the five-factor model, two forms of hostility exist: (1) neurotic hostility, exemplified by frequent and intense experience of anger, frustration, and rage, and (2) antagonistic hostility, exemplified by cynicism, rudeness, and condescension (Costa & McCrae, 1992). As previously discussed, in one of the only studies examining the effect of hostility on medication adherence, Christensen et al. (1997) found that an

[12] It is interesting to note that there was no difference ($p = .27$) in medication outcome expectancies between individuals taking bupropion ($M = 48.06$) and placebo ($M = 45.04$) at the 6-week assessment, indicating that double-blinding procedure was successful and medication expectancies were a nonspecific aspect of the medication regimen.

index of antagonistic hostility, the Cook-Medley Hostility scale (Cook & Medley, 1954), was linked to less favorable medication and dietary adherence among hemodialysis patients. Thus, it is conceivable that differentiating agreeableness into its two forms would have shown that antagonistic hostility is predictive of medication adherence in the present study. Although the full-scale NEO-PI-R indexes antagonistic hostility via the trust and compliance facets of agreeableness factor, its short-form NEO-FFI does not permit an examination of these facets.

The medication self-efficacy expectancies subscale measured at baseline was unrelated to adherence. Although this experimenter-developed measure demonstrated adequate internal consistency, it is possible that the restricted variability reduced its predictive utility. Specifically, the possible range of the medication self-efficacy subscale was from 11 to 77, the sample mean was quite high, M = 66.8 (SD = 7.8), and the distribution was highly negatively skewed, skewness = -.92 (SE = .23). By comparison, although the possible range of the medication outcome expectancies subscale was similar (13 to 91), the sample mean was lower (M = 58.5), the standard deviation was larger (SD = 11.5), and the distribution approximated normality, skewness = .22 (SE = .23). Moreover, this null finding is consistent with the previously mentioned postulation that the relative ease of the present study's two pills per day regimen would reduce the predictive power of self-efficacy expectancies, particularly in comparison to medication outcome expectancies.

The hypothesized influence of side effects (alone or in combination with depressive symptoms) on medication adherence was not confirmed, as well. Since the levels of pretreatment physical symptoms and Week 5 side effects were not unusual per se, it is unlikely that ceiling or floor effects were problematic. One possibility is that specific side effects have a deleterious effect on medication adherence, whereas others have either no effect or even a positive effect on

adherence. For instance, it is conceivable that newly developed insomnia would have a greater prognostic significance than other side effects, such as decreased appetite. Since a composite index of 38 side effects was computed without respect to particular symptoms in the present study, this possibility is speculative.

4.3 Prediction of Smoking Cessation

The hypothesized association between medication adherence and prolonged smoking abstinence was supported. Importantly, this association was statistically significant despite a lack of evidence that level of medication (bupropion versus placebo) influenced smoking cessation. Since regression analysis does not provide information regarding direction of causality, a cross-lagged panel design was used to test hypotheses regarding the temporal nature of the medication adherence/smoking abstinence relationship. Cross-lagged panel correlations showed that both adherence and point-prevalence smoking abstinence were significant antecedents of one another. That is, medication adherence during the second 30-day period significantly predicted subsequent point-prevalence abstinence at Day 84 of the study period, and point-prevalence abstinence at Day 56 significantly predicted medication adherence during the third 30-day period. The former effect may be interpreted as support for the main effect of adherence hypothesis; the latter effect may be interpreted as failure to quit smoking or maintain early abstinence resulted in women considering the medication to be inefficacious and therefore deciding to discontinue adhering to the prescribed regimen. Although results showed that adherence was the stronger antecedent of the two behaviors, it is important to note that these two directional effects are not mutually exclusive. In other words, both of these processes may have been functioning within the same time frame.

The effect of smoking relapse on subsequent regimen adherence has clinically relevance in that continued use of pharmacotherapies after initially failing to quit smoking may contribute to successful long-term cessation. Specifically, in a post-hoc examination of a large-scale smoking cessation RCT (viz., Jorenby et al., 1999), Jamerson and her colleagues (2001) found that, among patients who failed to quit smoking within the first three weeks of treatment, those taking SR bupropion alone or in combination with nicotine patch were more successful in long-term smoking cessation (through 52 weeks) than those taking placebo. Thus, the positive correlation between point-prevalence abstinence at Day 56 and subsequent medication adherence during the third 30-day period observed in the present study, together with findings reported by Jamerson et al. (2001), suggests that individuals failing to quit smoking early in treatment should be urged to continue adhering to their pharmacotherapy regimen because this may lead to successful behavior change in the long run.

The positive correlation between medication adherence during the second 30-day period and subsequent smoking status at Day 84 is consistent with a similar effect found by Killen et al. (1997) in a nicotine patch intervention study as well as a growing body of research involving a variety of health-related behaviors and outcomes. In designing this study, it was believed advantageous to include several psychosocial variables that, heretofore, had not been used to examine pathways underlying the main effect of adherence. However, adjustment for these psychosocial variables did not attenuate the main effect of adherence on smoking abstinence. Notwithstanding these null findings, it remains possible that favorable medication adherence was representative behavior of a subset of "good patients" who also were making a thoroughly determined effort to quit smoking (Hitsman et al., 2001). Although differing aspects of multicomponent treatment regimens are typically thought to be unrelated (e.g., Orme & Binik,

1989), a moderately strong correlation (r = .46, p = .000) between participants' medication adherence and attendance with behavioral treatment sessions in the present study is consistent with this explanation.

The search for psychosocial processes underlying the main effect of adherence was disappointing, but the exploration of mediational effects between psychosocial variables and smoking abstinence was more fruitful. Post-hoc analyses demonstrated that two mediators—medication adherence and Week 6 medication outcome expectancies—together accounted for 72.5% of the variance shared between openness to experience and prolonged smoking abstinence. Stated differently, individuals scoring high on openness to experience tended to maintain smoking abstinence more readily than individuals scoring low on this factor in part because they adhered to the medication regimen more closely and also because they believed the medication was helping to ameliorate factors associated with maintaining smoking abstinence. That medication outcome expectancies functioned as a mediator may be interpreted as high-openness to experience individuals may be more amenable to believing in the efficacy of the study medication in a double-blind medication trial. Post-hoc analyses also revealed that medication adherence accounted for 37.2% of the variance shared between Week 6 social support and prolonged smoking abstinence. Although research has shown that social support is one of the most reliable predictors of successful smoking cessation (Mermelstein, Cohen, Lichtenstein, Baer, & Kamarck, 1986), this is the first study to demonstrate that pharmacotherapy adherence is a behavioral pathway for this association. Interestingly, post-hoc analyses also revealed that, if Week 6 social support had not been examined concurrently, medication adherence would have mediated the association between Week 6 depressive symptoms and prolonged smoking abstinence. Thus, previous research on depressive symptoms

and treatment adherence in the absence of relevant correlates, such as social support, should be interpreted with caution. Finally, although agreeableness was associated with increased likelihood of maintaining smoking abstinence, the mechanisms underlying this association remain unclear given that this personality factor was uncorrelated with medication adherence.

Since it is common practice to operationalize medication adherence with one index, the examination of the relative prognostic significance of the six summary measures of adherence yielded unique information. It was particularly interesting to find that the index of drug holidays was the strongest predictor of smoking abstinence. It suggests that failing to take a medication for one or more days may increase the likelihood of experiencing a smoking relapse to a greater extent than other forms of nonadherence, such as regularly underdosing (e.g., taking one instead of two pills per day). Indeed, there is a growing appreciation for the effects of drug holidays on health outcomes (c.f., Heynen, 1999). For instance, a study on HIV medication adherence showed that drug holidays from protease inhibitors were significantly associated with the onset of drug-resistant HIV mutations (Vanhove, Schapiro, Winters, Merigan, & Blaschke, 1996). However, this research has focused singularly on the effects of non-adherence to active medication regimens, and as such, it provides minimal insight into pathways underlying the consequences of holidays from both bupropion and placebo regimens that were observed in the present study.

4.4 Limitations

The interpretations of this study's results should be qualified for several reasons. Foremost, in comparison to the broader population of smokers, the present sample was relatively homogenous and restricted in composition. In addition to being concerned about post-cessation weight-gain, participants were exclusively women, primarily Caucasian, and well educated. These volunteers

were highly motivated to quit smoking and were willing to travel to an urban medical center for extensive screening and attend 18 counseling sessions over a year. They were also willing to take a study medication for six months, even though the possibility of being randomized to bupropion or placebo was entirely dependent on chance. The limited generalizability of the present findings is underscored by meta-analytic findings showing that nicotine replacement therapy interventions are more effective when participants are self-referred rather than invited (Tang, Law, & Wald, 1994). Alternatively, one could consider that these highly-selected participants might represent a group of refractory smokers, given the well-replicated finding that treatment seekers in a variety of clinical and research settings have more severe and complicated behavioral and psychological problems (e.g., Wilfley, Pike, Dohm, Striegel-Moore, & Fairburn, 2001; Kessler et al., 1999; Strohmetz, Alterman, & Walter, 1990).

Like most prospective intervention trials, a potential limitation of this study was the existence of missing data. Roughly 21% of participants (who were not withdrawn from the medication regimen due to adverse effects) were missing one or more psychosocial variables at baseline or measures of side effects at Weeks 2, 3, or 5. Although careful exploratory analyses did not reveal any patterns to the missingness, it is possible that the use of non-missing data only in primary analyses biased the findings in some unidentified manner. Also, secondary analyses included psychosocial indices measured at Week 6 that involved additional missing data. In order to maintain a sample size comparable to the one used in primary analyses, missing data for these indices were imputed from their respective non-missing means. Although results involving these measures were comparable with and without imputation, caution should be used when interpreting these findings due to the possibility that results were biased toward significance (Harrell, 2001).

Although the use of electronic monitors to measure medication adherence has several benefits, this methodology incurred some problems in the present study. One of the primary benefits of the EEM methodology is to capture continuous medication-taking behavior in real-time for subsequent computer upload, but small minority of participants encountered events of daily living[13] that resulted in loss of varying degrees of data. Also, a minority of participants in the present study anecdotally reported that the pill container was bulky and inconvenient and therefore transferred the medication to another pill container. Some of these women reported that they continued to open their MEMS cap routinely to portray proper adherence, whereas others indicated that they were perfectly adherent but did not bother to feign adherent behavior. Another weakness of using of MEMS as the sole measure of adherence in this study is that it did not provide any information regarding purpose of nonadherence. Two different types of nonadherence are thought to exist: intentional and inadvertent (Bauman, 2000). Intentional nonadherence is characterized by deliberately deciding not to adhere, whereas inadvertent nonadherence is characterized by forgetting about the regimen or experiencing barriers to adherence. As psychosocial predictors may vary across purpose of nonadherence, it is unfortunate that this type of information was not measured in this study.

The research design of this study was non-experimental, so any causal inferences about relationships among the psychosocial variables, medication adherence, and smoking abstinence would be unsubstantiated. The limited causal information derived from the mediational analyses exemplifies this interpretive limitation. If an association between two variables attenuates or

[13] For example, one participant's MEMS cap was confiscated at an airport-screening checkpoint due to its perceived security risk. Another instance of lost data occurred when a participant fell into a lake and lost her purse, which was carrying the MEMS cap.

disappears when the variability of a third variable is removed, it is tempting to conclude that the third variable caused the relationship between the other two. However, this reasoning is flawed in that it is not known whether the particular third variable examined is responsible for the relationship between the two variables or whether the relationship is due to yet another variable correlated with the third variable. Similarly, caution should be exercised when interpreting results from the cross-lagged panel design analyses, which were based on correlational analyses. Path analyses would have strengthened inferences from this passive-observational study (Kazdin, 1992), but statistical power considerations would have necessitated a much larger sample size (Bentler & Chou, 1987). Another design limitation of this study was the limited duration of smoking cessation follow-up. That is, given that life-long abstinence is the ultimate goal of smoking cessation interventions, the SRNT subcommittee on abstinence measures recently recommended that follow-up assessments be at least 6 or 12 months post-cessation (Hughes et al., 2003).

Finally, this research was exploratory in nature and therefore results should be considered tentative. The preliminary state of knowledge on adherence to smoking cessation pharmacotherapies dictated that the primary goal of this study was to identify plausible predictors and consequences of adherence, rather than to test an existing theory. One consequence of not using an overarching theoretical model to guide selection and integration of psychosocial parameters is that conclusions are restricted to only those variables deemed worthy of inclusion. Although the putative predictors of medication adherence were carefully chosen, potentially important variables were not examined, and as a result, the processes underlying the main effect of adherence on smoking cessation were not elucidated. In particular, a potentially important omission was the failure to measure motivation to adhere to the treatment regimen.

Given the growing body of research supporting the application of the stages of change model to smoking behavior (Prochaska, 1996), as well as the time-varying effects of psychosocial characteristics observed in the present study, it may have been fruitful to repeatedly measure fluctuations in readiness to adhere to the medication regimen and to maintain smoking behavior changes throughout this study.

4.5 Future Research

Notwithstanding the aforementioned limitations, the findings from the present study point to several directions for future research. The most conspicuous need is to replicate these results with samples more representative of the broader population of smokers. This would involve studying adherence to smoking cessation pharmacotherapy, for instance, among men, racial/ethnic minorities, and individuals in community settings. Importantly, many of the present study's inferential limitations could be addressed with methodological adjustments. To begin with, a longer-term follow-up assessment of smoking status at 6 or 12 months would provide more convincing information about the long-term consequences of adhering to the medication regimen. Secondly, recently developed multilevel modeling techniques (c.f., Bock, 1989; Longford, 1993) could be used to incorporate all participants' data, thereby maximizing statistical power and minimizing potential bias associated with casewise deletion or imputation characteristic of traditional regression analysis. Thirdly, a substantially larger sample size would allow for the utilization of other advanced statistical techniques, such as structural equation modeling, which add flexibility for testing a wider array of hypotheses as well as increasing confidence in causal inferences. In particular, path analysis is the preferred choice to conduct a cross-lagged panel design because it allows for multiple, simultaneous statistical tests of partial correlations among measured variables (Finkel, 1995). Another advantage of testing a cross-

lagged panel design with path analysis is that several nested models could be compared with inferential statistics (i.e., χ^2 tests; see Nauta, Kahn, Angell, & Cantarelli, 2002). For example, several of the following hypothesizes could have been tested via path analysis: (1) no relation between medication adherence and smoking abstinence (baseline model), (2) adherence is an antecedent in the adherence/smoking abstinence relationship, (3) smoking abstinence is an antecedent, (4) both adherence and smoking abstinence are antecedents (i.e., a reciprocal relationship), and (5) adherence and smoking abstinence as equally strong antecedents of one another (i.e., comparing the model fit of hypotheses 4 and 5 would inform on whether one direction is more robust than the other). Moreover, a larger sample size would allow for the examination of the main effect of adherence in the placebo condition alone. This would provide a relatively pure test of this non-specific effect given that individuals taking sugar pills would not be affected pharmacologically. Fourthly, the facets of the higher order domains comprising the Five-Factor Model of Personality should be measured with the full-scale NEO-PI-R (Costa & McCrae, 1992) in order to characterize potentially specific pathways among personality, medication adherence, and smoking cessation. Finally, future research should also include multiple measures of medication adherence in order to triangulate on "true" medication adherence and minimize error variance. For example, blood assays would provide important biological verification of EEM-measured medication adherence, and if unannounced, would minimize "white coat adherence" characteristic of scheduled tests.

Another direction for future research would be to utilize an assessment methodology that could potentially enhance the predictive power of psychosocial variables on medication adherence. As evidenced by the discrepant results from Baseline versus Week 6 measures of social support and medication outcome expectancies in the present study, repeatedly measuring

putative psychosocial predictors of medication adherence may be particularly advantageous. Since standard paper-and-pencil measures are notoriously unreliable (e.g., Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002), a recently developed approach for assessing psychosocial and behavioral processes in natural settings, called Ecological Momentary Assessment (EMA; Stone & Shiffman, 1994), could be utilized to measure psychosocial characteristics and smoking behavior in near real-time. EMA approaches utilize repeated self-report diary assessments, often via hand-held computers, to examine phenomena as they occur in real life, therapy minimizing cognitive recall biasing and maximizing ecological validity (Stone & Shiffman, 1994). The EMA-based self-report diary would yield information on within-subject fluctuations of psychosocial states that could be linked with adjacent within-subject changes in EEM-measured medication adherence by means of within-subjects repeated measures analyses. Also, individual differences in psychosocial characteristics, such as personality factors, could be used to predict within-subject changes in medication adherence on a daily basis rather than with global summary measures. In a similar vein, a time-varying covariate survival analysis with EEM-measured medication adherence and EMA-measured smoking behavior would also yield fine-tuned information on the temporal precedence of these two behaviors. For example, this approach would provide a careful test of whether drug holidays pose an acute risk for subsequent smoking relapses or vice versa.

Like the present study, every previous attempt to ascertain processes underlying the main effect of adherence on health outcomes has yielded null findings. These attempts have consisted of statistically controlling for a variety of psychosocial and biomedical variables only to have the main effect of adherence remain significant. In future studies of this phenomenon, a different approach would be to explore whether latent factors explain phenotypic covariation among

relevant parameters. Specifically, confirmatory factor analysis could be used to examine whether one or more latent variables would satisfactorily explain covariation among various indices of treatment adherence. Although the significant correlation between medication adherence and group therapy attendance was the only adherence-related covariation reported in the present study, it is plausible that adherence to other treatment recommendations overlapped, as well. For instance, participants who manifested favorable medication adherence and group therapy attendance may also have followed recommendations from the behavior therapist to reduce exposure to caffeine and alcohol (i.e., due to their conditioned associations with smoking behavior, as well as the latter substance's deleterious influence on cognitive processes associated with problem-solving and overcoming high-risk situations). It is also possible that this hypothetical subset of adherent participants made other self-initiated health-related lifestyle changes, such as increasing physical activity or improving dietary intake behaviors. Likewise, in addition to examining latent factors underlying potential covariation among adherence-related behaviors, it is possible that phenotypic covariation among parameters involved in the mediational effects observed in the present study (e.g., openness to experience/medication adherence/smoking abstinence) could be accounted for by one or more common factors. Indeed, a common latent factor underlying medication adherence and smoking cessation would shed light on why adjusting for psychosocial variables has had no impact on this correlation.

If phenotypic structural equation modeling supported the existence of one or more common latent factors, the exploration of the relative contributions of genetic and environmental influences on variation and covariation of medication adherence, its psychosocial correlates, and smoking cessation may also be a fruitful area for future research. Since almost all behavioral phenotypes are determined in part by genetic factors (Plomin, DeFries, McClearn, & Rutter,

1997), it is surprising that the enormous literature on medication adherence does not include any quantitative genetic studies of this behavior. In the present study, test-retest reliabilities of medication adherence over the three 30-day periods of this study ranged from very strong (r = .76) to moderately strong (r = .42), suggesting that this behavior may be a relatively stable individual difference. Also, previous research has shown that other health-related behaviors, such as physical activity (Maia, Thomis, & Beunen, 2002) and food intake (Heitmann, Harris, Lissner, & Pedersen, 1999), are genetically influenced. Thus, it is plausible to hypothesize the genetic factors may significantly influence adherence to smoking cessation pharmacotherapy. Moreover, behavior genetic studies have shown that several of the psychosocial correlates of medication adherence in the present study are affected by genetic factors. Loehlin (1992) analyzed personality data from family, twin, and adoption studies with structural equal modeling and reported heritability estimates of 38 percent for conscientiousness and 45 percent for openness to experience. Bergeman et al. (1993) conducted a twin/adoption study with the Big Five factors and reported heritability estimates of 29 percent for conscientiousness and 40 percent for openness to experience. With a twin study design, Raynor et al. (2002) reported that genetic factors accounted for 59% of the variance of ISEL scores and other researchers have reported substantial genetic effects on other measures of social support (e.g., Kessler, Kendler, Heath, Neale, & Eaves, 1992; Bergeman, Plomin, Pedersen, & Nesselroade, 1990). Likewise, based on their review of behavior genetic studies, Heath and Madden (1995) concluded that genetic factors account for a significant amount of the variance in risk of initiation and persistence of long-term smoking behavior, and a recent twin study showed that genetic influences accounted for 54% of the variance in risk of smoking cessation failure (Xian et al., 2003). Given the observed phenotypic associations and previously reported genetic etiology, it is plausible to

hypothesize that the covariation between medication adherence and one or more of these psychosocial characteristics may be accounted for by common genetic influences. It is also conceivable that the main effect of adherence on smoking cessation may be explained in part by common etiological factors, possibly genetic in nature. The use of multivariate structural equation modeling within a genetically informative family study would permit testing of such hypotheses.

Heretofore, all of the suggestions for future research have involved variations of passive-observational, or correlational, designs. Given the inferential limitations of such designs, it would be imperative to conduct experimental research in order yield causal information related to pharmacotherapy adherence and smoking behavior. One such possibility is the utilization of a balanced placebo design (Marlatt & Rohsenow, 1980), which involves experimentally manipulating instructions (Told Active versus Told Placebo) and pharmacological content of a drug (Received Active versus Received Placebo) in a 2 x 2 factorial design. This approach would allow for the examination of main and interaction effects of the actual drug and participants' expectations about its effects on medication adherence and smoking behavior.

Future experimental research should also focus on developing effective interventions to enhance adherence and maximize health-related outcomes. Unfortunately, a recent literature review showed that the relatively few interventions designed to help patients follow medication prescriptions were poorly designed and generally ineffective (Haynes et al., 2000). Based on the present study's findings, two general approaches for developing more effective interventions are indicated. One approach would be to develop interventions that would modify factors associated with medication adherence. For instance, the positive associations between Week 6 social support, medication adherence, and smoking cessation suggest that interventions designed to

enhance social support may be efficacious, particularly in the first few weeks following medication initiation and smoking cessation. Although none of the treatment studies reviewed by Haynes et al. (2000) demonstrated the effectiveness of social support interventions per se, previous research has shown that such treatments are effective in enhancing adherence to other preventive health regimens, such as weight control (e.g., Brownell, Heckerman, Westlake, Hayes, & Monti, 1979; Wing & Jeffery, 1999), diabetes management (e.g., Shenkel et al., 1985-1986), hypertension control (e.g., Morisky et al., 1985), and smoking cessation (e.g., West, Edwards, & Hajek, 1998).

Another approach to developing effective interventions would be to match treatments to individual differences in psychosocial characteristics associated with medication adherence and/or smoking cessation. Based on the present study, low-conscientious individuals would comprise one subset of female smokers at high-risk for medication nonadherence. A variety of empirically-supported techniques exist that may be particularly beneficial to such individuals, including directly observed medication consumption (Chaisson et al., 2001), tailoring the regimen to daily habits (Haynes et al., 1976), and appointment and prescription refill reminders (Peterson et al., 1984). Importantly, the usage of such techniques among high-conscientiousness individuals may be superfluous and cost-ineffective. By the same token, high-openness to experience smokers may be more receptive to alternative forms of therapy (e.g., meditation, imagery), whereas low-openness to experience smokers may favor more straightforward approaches (e.g., informational support, practical advice; Miller, 1991). Indeed, the provision of treatments based on individualized reasons for nonadherence and smoking relapse may be particularly efficacious in utilizing limited resources on a public health scale.

5 SUMMARY AND CONCLUSIONS

The present study assessed rates, predictors, and sequelae of adherence to a medication regimen among women participating in a smoking cessation program. Results supported several hypotheses: (1) overall medication adherence was less than optimal throughout the 90-day study period and adherence rates decreased during each successive 30-day period; (2) conscientiousness predicted medication completion and 90-day medication adherence, and (3) 90-day medication adherence predicted prolonged smoking abstinence. Follow-up analyses indicated that: (1) conscientiousness did not predict prolonged smoking cessation, (2) medication adherence predicted subsequent point-prevalence smoking abstinence, point-prevalence smoking abstinence predicted subsequent medication adherence, and medication adherence was the stronger antecedent of the two behaviors; and (3) among six summary indices of medication adherence, the measure of drug holidays was the strongest predictor of prolonged smoking abstinence. Contrary to expectations, agreeableness, depressive symptoms, medication self-efficacy expectancies, (baseline) medication outcome expectancies, (baseline) social support, and medication side effects did not aid in predicting medication adherence. Secondary analyses indicated that: (1) openness to experience, Week 6 medication outcome expectancies, and Week 6 social support predicted 90-day medication adherence, (2) openness to experience and Week 6 social support predicted prolonged smoking abstinence, and (3) 90-day medication adherence mediated the association between openness to experience and smoking abstinence, and between Week 6 social support and smoking abstinence.

In conclusion, given that medication adherence was less than optimal and was positively associated with smoking cessation outcome in the present study, further research on predictors of pharmacotherapy adherence is warranted. Moreover, the present findings indicate that efforts to enhance adherence by either modifying psychosocial variables that are somewhat amenable to change (e.g., social support or medication outcome expectancies), or by matching treatments to levels of characteristics that are comparatively stable (e.g., conscientiousness and openness to experience) may be particularly efficacious in improving medication adherence rates, and possibly enhancing smoking cessation outcomes.

APPENDICES

APPENDIX A

Study Medication Expectancies Questionnaire

Instructions: Individuals in the process of quitting smoking may experience uncomfortable symptoms. Use the scale below to rate your beliefs about how the Study Medication will affect **YOUR** symptoms and how it will affect **YOUR** quit attempt. For questions 1-13, please circle the number that best describes how much you agree with each question using the following scale:

1 = Not at all agree, 4= Somewhat agree, 7 = Completely agree.

How much do you believe that the Study Medication will…

	Not at all agree			Somewhat agree			Completely agree
1. reduce irritable feelings associated with quitting smoking?	1	2	3	4	5	6	7
2. reduce feelings of hunger?	1	2	3	4	5	6	7
3. decrease worries about gaining weight?	1	2	3	4	5	6	7
4. reduce cravings to smoke?	1	2	3	4	5	6	7
5. help you to quit smoking permanently?	1	2	3	4	5	6	7
6. lead you to experience uncomfortable physical side effects?	1	2	3	4	5	6	7
7. reduce negative mood associated with quitting smoking?	1	2	3	4	5	6	7
8. minimize weight gain after quitting smoking?	1	2	3	4	5	6	7

How much do you believe that the Study Medication will…

	Not at all agree					Somewhat agree	Completely agree
9. reduce sleep problems associated with quitting smoking?	1	2	3	4	5	6	7
10. reduce anxious feelings associated with quitting smoking?	1	2	3	4	5	6	7
11. reduce restlessness associated with quitting smoking?	1	2	3	4	5	6	7
12. reduce concentration difficulties associated with quitting smoking?	1	2	3	4	5	6	7
13. be helpful to you overall?	1	2	3	4	5	6	7

Instructions: The Study requires you to take the Study Medication twice every day, once in the morning and once in the evening, for 6 months. Some situations may make it difficult to stick with the schedule for taking the Study Medication. Use the scale below to rate your confidence in sticking with the Study Medication schedule under a variety of conditions. For questions 14-24, please circle the number to the right of each item that best describes your confidence level using the following scale:

1 = Not at all confident, 4 = Somewhat confident, 7 = Extremely confident.

How confident are you that you will take the Study Medication …

	Not at all confident					Somewhat confident	Extremely confident
14. for the first 3 months?	1	2	3	4	5	6	7
15. if your daily routine changes?	1	2	3	4	5	6	7
16. if you are traveling?	1	2	3	4	5	6	7
17. if you aren't feeling well?	1	2	3	4	5	6	7
18. if it's the weekend?	1	2	3	4	5	6	7

How confident are you that you will take the Study Medication …

	Not at all confident						Somewhat confident						Extremely confident
19. if you are not at home?	1	2	3	4	5	6	7
20. if you are feeling discouraged about your attempt to quit smoking?	1	2	3	4	5	6	7
21. if you think the study medication is not helping you?	1	2	3	4	5	6	7
22. if people close to you tell you they think the study medication is not helping you?	1	2	3	4	5	6	7
23. if you experience minor physical side effects?	1	2	3	4	5	6	7
24. if you gain a significant amount of weight?	1	2	3	4	5	6	7

Appendix B

Diagnostic Analyses

Before formal multiple linear regreession modeling began, data were edited for diagnostic and, if necessary, remedial action. Variables were initially converted to standardized $\underline{z}$-scores and examined for outliers ($|\underline{z}| > 3.29$). Data points over three standard deviations from the mean were excluded from data analysis. Next, scatter plots with fitted Lowess regression lines of the predictor variables against medication adherence were used to examine the linearity of bivariate relationships among predictor variables and medication adherence. These plots did not reveal any non-linear (e.g., quadratic, cubic) relationships. A preliminary regression model with all predictor variables force entered was fitted to examine the multivariate normality assumption. Since residual plots of predictors versus fitted data were uniformly scattered, the multivariate normality assumption was supported and the assessment of univariate normality for the predictors was not necessary (Tabachnick & Fidell, 1996).

Consistent with suggestions of Neter, Kutner, Nachtsheim, and Wasserman (1996), final diagnostics were performed once a model was fitted. A plot of the residuals against the fitted values was obtained in order to assess the appropriateness of the multiple regression function and the constancy of the error variances. Residuals were plotted against each of the predictor variables to check for normality and predicted values were plotted against absolute residuals to check for homoscedasticity. A normal probability plot of the residuals was also assessed for departures from linearity. The variance inflation factor was examined for values greater than 10, which is the typical cutoff for multicollinearity violations. Studentized deleted residuals were examined with the Bonferroni simultaneous procedure to diagnose outlying or extreme criterion

observations, whereas centered leverage values were used to identify outlying predictor observations. Finally, DFITS AND DFBETAS measures were used to determine whether or not the outliers were influential (i.e., a case is influential if its exclusion causes major changes in the fitted regression function).

For multiple logistic regression models, problems with linearity were assessed with the Box-Tidwell transformation test and outlying or overly influential cases were analyzed via studentized residual and DFBETA analysis (Menard, 2002).

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