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Smoking and panic attacks, panic disorder, and agoraphobia: A review of the empirical literature

Michael J. Zvolensky*, Matthew T. Feldner, Ellen W. Leen-Feldner, Alison C. McLeish

*Department of Psychology, The University of Vermont, 2 Colchester Avenue, John Dewey Hall, Burlington,
VT 05405-0134, United States*

Abstract

The empirical literature regarding panic-spectrum problems (i.e., panic attacks, panic disorder, and agoraphobia) and cigarette smoking is reviewed. In the first section of the paper, empirical studies that document the prevalence of smoking and panic-related problems are presented and discussed. In the second section of the paper, studies pertaining to the role cigarette smoking may play in the onset and maintenance of panic-related problems are critically reviewed. In the third section of the paper, studies related to the association between panic vulnerability factors and the nature of smoking behavior are presented. In the fourth section of the paper, specific areas not otherwise covered in the review are presented to stimulate further development in these areas (e.g., specialized treatment development).

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1. Introduction

For at least the past two decades, there has been a broad-based acknowledgement among practitioners working with individuals suffering from anxiety disorders that substance use disorders frequently co-occur with many of these disabling emotional conditions (e.g., Barlow, 2002). At the same time, clinicians working with drug-related problems have observed strong associations between negative affect states, including anxiety, and substance use and related problems (e.g., Gilbert, 1995). Although many

* Corresponding author. Tel.: +1 802 656 8994; fax: +1 802 656 8783.

E-mail address: Michael.Zvolensky@uvm.edu (M.J. Zvolensky).

researchers and clinicians have recognized that comorbidity among psychiatric disorders is a clinically important matter (Brown, Antony, & Barlow, 1995; Glassman, 1993; Pomerleau, 1997; Regier, Burke, & Burke, 1990), there have been few systematic attempts to better understand the nature of the associations that exist between specific types of anxiety psychopathology and substance use disorders (Zvolensky & Schmidt, 2004). Of work that has been completed, the vast majority has focused on alcohol abuse and dependence in the onset and maintenance of anxiety-related problems (e.g., Bowen, Cipywnyk, D'Arcy, & Keegan, 1984; Chambless, Cherney, Caputo, & Rheinstein, 1987; Cox, Norton, Dorward, & Fergusson, 1989; Hesselbrock, Meyer, & Keener, 1985; see Kushner, Abrams, & Borchardt, 2000, for a review). There has been strikingly less empirical work on the role of other substance use (e.g., cigarette smoking) that occurs frequently among individuals with, or at risk for, anxiety psychopathology.

There are a number of reasons to better understand the associations that exist between tobacco use and anxiety disorders. First, although cigarette smoking in the United States has stabilized in the recent past, the prevalence of this behavioral problem remains high and is a leading contributor to premature death and disability (Breslau, Johnson, Hiripi, & Kessler, 2001; United States Department of Health and Human Services, 2000). Indeed, over 45 million American adults currently smoke cigarettes and available evidence suggests that cessation attempts typically meet with a lack of success (Centers for Disease Control and Prevention [CDC], 2002). Moreover, smoking problems are not limited to adults. Empirical work suggests cigarette use among youth (e.g., adolescents in high school) is substantial, with almost 21% of high school seniors smoking on a daily basis (Johnson et al., 2000) and typically smoking for many years thereafter (i.e., greater than 15 years, on average, for both males and females; Pierce & Gilpin, 1996). Second, although the dangers of smoking are well-publicized in the United States, the formal recognition that many individuals with anxiety disorders smoke cigarettes has only garnered scientific attention in recent years (Pohl, Yeragani, Balon, Lycaki, & McBride, 1992) and most of this work has been focused on panic disorder. In fact, up through the early 1990s, much of the panic-smoking work was restricted to a small number of anecdotal reports (e.g., Brodsky, 1985; Dilsaver, 1987; Maany, Woody, & Foulks, 1987; Yeragani, Pohl, Balon, & Jankowski, 1988). Thus, relatively little has been known about the nature of the panic-smoking relation, including how these variables relate to one another across particular developmental stages (e.g., onset, maintenance, and relapse). Drawing from extant empirical work and conceptual models, there is reason to suspect that these behavioral conditions may negatively impact one another in a variety of ways (e.g., bi-directional negative effects; Zvolensky, Schmidt, & Stewart, 2003). Third, to the extent that smoking and anxiety problems negatively impact one another, intervention strategies (prevention and treatment) for these conditions should address these factors. That is, there may be a need for specialized intervention programs to target anxiety-related processes among tobacco smokers and vice versa. Finally, by better understanding the nature of the association between smoking and anxiety problems, advances will be made in understanding the processes underlying comorbidity between anxiety disorders and substance use disorders more generally. Specifically, theory and research from this domain of study could guide work on other drug-related problems (e.g., marijuana, heroin) that have not received an appreciable degree of scientific attention in relation to anxiety psychopathology.

Given this backdrop, the purpose of the present paper is to review the empirical literature on the relation between panic-spectrum problems (i.e., panic attacks, panic disorder, and agoraphobia) and cigarette smoking. Whereas earlier conceptual work suggested possible meaningful associations between panic disorder and smoking (Zvolensky, Schmidt, & McCreary, 2003; Zvolensky, Schmidt, & Stewart, 2003), the present paper explicitly reviews empirical work related to such a conceptualization and

highlights major findings of this literature not previously addressed. In the first section, we review empirical studies that document the comorbidity of smoking and panic-related problems. In the second section, we critically review studies pertaining to the role cigarette smoking may play in the onset and maintenance of panic-related problems. Third, we review studies of the role that panic vulnerability factors play in smoking initiation, maintenance, and relapse. In the final section, we highlight specific relevant areas not previously covered in other sections that should be addressed in future work.

1.1. Study selection criteria

We conducted a literature search utilizing electronic search engines (i.e., PsycINFO and MEDLINE) to examine data bases using the following key word algorithms: smoking OR nicotine OR cigarettes AND panic disorder OR panic attacks OR anxiety OR agoraphobia. These searches yielded approximately 1102 citations. The vast majority of these articles were not relevant to the present review because they were not focused on panic-related problems (i.e., panic attacks, panic disorder, or agoraphobia). As our primary aim was to delineate the nature of the smoking–panic association, we focused on the remaining articles in the present review.

1.2. Defining key variables

1.2.1. Panic-spectrum problems

Given anxiety disorders vary greatly in presentation and nature, it is important for reasons of clarity and specificity to focus on panic-related problems rather than anxiety states or disorders in general. We use the term “panic spectrum” to denote panic attacks, panic disorder, and agoraphobia (with or without panic disorder). This approach implicitly considers the developmental history of panic problems such that individuals typically first develop panic attacks, then panic disorder, followed by agoraphobia (see Barlow, 2002). Although all persons naturally do not proceed through this exact developmental sequence, it provides a useful heuristic for organizing a review on panic-related problems. In this paper, we define panic attacks as a subjective sense of extreme fear or impending doom accompanied by an autonomic surge and strong flight-or-fight action tendency (Barlow, Brown, & Craske, 1994). It is noteworthy that many people experience panic attacks without necessarily developing panic disorder (Norton, Cox, & Malan, 1992). Typically, individuals who experience “nonclinical panic attacks” do not experience these attacks as “spontaneous” or “uncued” as is generally the case in panic disorder, but rather in certain contexts such as stressful or threatening social situations (Norton, 1989). Panic disorder involves recurrent unexpected panic attacks and anxious apprehension about the possibility of experiencing future panic episodes (American Psychiatric Association [APA], 2000). This condition is generally regarded as a disorder of adulthood with a median age of onset of 24 (Burke, Burke, Regier, & Rae, 1990). The distribution of the age of onset for panic disorder, however, is bimodal with peaks at 15–24 years of age and 45–54 years (APA, 2000). As individuals with panic disorder often avoid situations perceived as personally threatening (e.g., anxiety-eliciting situations such as open spaces; see Feldner, Zvolensky, & Leen-Feldner, 2004, for a review), many individuals will limit social involvement and/or personal mobility. In these instances, persons may be said to be suffering from agoraphobia. Although agoraphobia does not necessarily need to be accompanied by the presence of panic attacks (Fava, Grandi, & Canestrari, 1988), most researchers conceptualize agoraphobia as a complication of (severe) panic disorder (Barlow, 2002).

1.2.2. Cigarette smoking

Various developmental stages of smoking are reviewed to enhance the specificity of any observed panic–smoking relation. This approach is based on Flay’s (1993) stage model of smoking, which suggests smokers follow a generally well-specified sequence of smoking behavior that includes the following stages: initiation, maintenance, and relapse. In this model, the initiation stage reflects trying smoking on the initial few trials and further experimentation (irregular use over time). The maintenance stage includes regular use of cigarettes (ranging from weekly to daily use); it is in this stage that individuals are most apt to develop nicotine dependence. The term nicotine dependence is typically used to denote the display of (1) regular or compulsive use and (2) the presence of specific withdrawal symptom profiles upon abstinence (APA, 2000). In general, nicotine dependent individuals will be more apt to smoke heavier amounts than those not classified as nicotine dependent, yet importantly regular smoking does not necessarily indicate nicotine dependence (Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994). In the relapse stage, individuals who have attempted to stop smoking return to their smoking behavior after a period of tobacco abstinence. It is important to consider these developmental stages from the onset of the paper because the nature of an observed smoking–psychopathology association may be qualified by the developmental level of smoking. For example, panic attacks may be more likely during smoking quit attempts made during the maintenance versus initiation stage of smoking.

1.3. Methodological issues

1.3.1. Assessment of psychiatric diagnosis

Across studies, the assessment of psychiatric status varies considerably. To ease interpretation, whenever possible (i.e., if diagnostic method is reported), the diagnostic methodology employed will be included. However, investigators often fail to provide information regarding training and reliability estimates for diagnostic procedures; rather than repeat this issue numerous times in the review, we simply note it from the outset.

1.3.2. Comorbidity

There also is great variability in the consideration of the role of comorbid substance use (e.g., alcohol) and psychological conditions (e.g., depression) when examining the panic–smoking association. Given co-occurring conditions can markedly affect interpretation of panic–smoking relations (e.g., it may be unclear whether a given finding is due to non-tobacco related substance use), care will be taken to delineate this methodological characteristic for each study reviewed. For instance, if alcohol use also was examined in a given study, the relation between such problems and panic-related phenomena will briefly be reviewed.

2. Smoking and panic-spectrum problem comorbidity

When addressing the co-occurrence of smoking and panic-spectrum problems, it is important to recognize at least two key issues. First, prevalence rates will vary as a function of the referenced population. For example, prevalence rates will differ depending on whether one is examining lifetime prevalence rates of smoking among individuals with panic disorder or lifetime prevalence rates of panic

disorder among cigarette smokers. Thus, it is necessary to explicate the target population when discussing prevalence rates for two conditions and understand their rate of co-occurrence within this context. Second, a number of studies have examined smoking–anxiety comorbidity, but have focused on anxiety disorders in general rather than panic-related problems specifically. In particular, researchers have not divided anxiety disorder diagnoses into specific anxiety conditions (e.g., Breslau, 1995; Brown, Lewinsohn, Seeley, & Wagner, 1996; Costello, Erkanli, Federman, & Angold, 1999; Degenhardt, Hall, & Lynskey, 2001; Dierker, Avenevoli, Merikangas, Flaherty, & Stolar, 2001; Hughes, Hatsukami, Mitchell, & Dalgren, 1986; Jorm et al., 1999; Kandel, Huang, & Davies, 2001; Kandel et al., 1997; Merikangas et al., 1998; Tilley, 1987). Given the marked structural and functional differences in the nature of various anxiety conditions and anxiety-related emotional states (Lang, 1984, 1993), these studies, although useful in providing a general context for understanding anxiety disorder–smoking associations, are not helpful in explicating the nature of the smoking–panic co-occurrence. For this reason, we focus only on those studies that have examined panic-related problems (cf., anxiety disorders generally).

2.1. Prevalence of smoking among individuals with panic-spectrum problems

The vast majority of studies examining the co-occurrence of smoking and panic have focused on the extent to which smoking is present among individuals diagnosed with panic-spectrum problems. We divided these studies conceptually into community-based and epidemiologically based investigations to ease interpretation and underscore methodological differences in employed sampling methods.

2.2. Community-based studies

Researchers often utilize samples drawn from psychological or medical treatment centers to document the prevalence of smoking among individuals with panic attacks and panic disorder. In one of the first investigations to examine smoking rates among individuals with specific anxiety disorders, Himle, Thyer, and Fischer (1988) completed a chart review study using records from an outpatient psychiatric center. Participants were randomly selected from the charts of individuals diagnosed and treated at the anxiety disorders treatment program at the University of Michigan Medical Center from 1978 through 1986. Results indicated that individuals with a principal diagnosis of panic disorder or agoraphobia, 47% and 57% reported current smoking, respectively. These rates of smoking were similar to those reported for individuals with specific phobias (47%) and greater than that found among persons with generalized anxiety disorder (29%), social phobia (27%), and obsessive–compulsive disorder (OCD; 9%). Smokers with anxiety disorders also reported significantly greater alcohol use compared to nonsmokers; importantly, this variable was covaried in the smoking comparisons. Because diagnostic and Statistical Manual [DSM] criteria for anxiety disorders changed from 1978 through 1986, it is not clear what criteria were used in making diagnoses.

In a study focused on youth, Hayward, Killen, and Taylor (1989) examined factors associated with panic attacks among adolescents (i.e., 9th graders in public schools). Interviews and health-oriented measures were administered to youth participating in physical education classes in public schools in California. One questionnaire employed assessed cigarette use using a three response option system—“never used,” “experimental,” (i.e., use of the substance less than once a week) and “regular use” (i.e., use of the substance weekly or daily). The panic attack section of the Structured Clinical Interview for DSM

III-Revised (SCID-III-R) was administered by doctoral-level raters to index panic attack history. Among the 95 adolescents who completed the study, 11.6% had a lifetime history of panic attacks. Of those with a lifetime history of panic attacks, 77% had engaged in “experimental” or “regular” cigarette use (i.e., collapsed across these two categories); for those adolescents without a lifetime history of panic attacks, 48% had engaged in “experimental” or “regular cigarette use.” No significant differences between those with panic and those without were evident for alcohol use, although there was a (nonsignificant) trend for marijuana use (with panickers reporting greater “experimental” or “regular” use). As other sections of the SCID-III-R were not administered, it is not clear how psychiatric comorbidity may have affected the results.

Pohl et al. (1992) examined smoking behavior among consecutive adult patients at two sites in Detroit. One site was a research treatment center and offered free psychological treatment; the other was a private practice and offered service for a fee. Participants were screened via an unstructured interview by psychiatrists and excluded from the investigation if they had concomitant diagnoses of mood or eating disorders. Participants also completed a measure of smoking history. In total, 217 participants had a panic disorder diagnosis, with the average duration of the condition of 10.6 (S.D.=10.0) years. The comparison group was 217 age and gender-matched participants recruited through a telephone survey. Results indicated that 51.6% of the persons with panic disorder reported being a smoker at the onset of their condition compared to a rate of 38.3% reported by the control participants (retrospectively reporting smoking status 10 years ago). Although not meeting traditional levels of statistical significance ($p=.07$), 36.9% of the panic disorder patients reported being a current smoker compared to 28.6% of control participants. When examined as a function of gender, women (39.7%) but not men (30.3%) with panic disorder reported significantly greater current rates of smoking compared to female (24.5%) and male (37.9%) control participants.

Using an approach similar to Pohl et al. (1992), Amering et al. (1999) examined 102 consecutive panic disorder patients with or without agoraphobia attending an academic treatment clinic in Austria. Participants were diagnosed using the SCID-III-R and interviewed about their smoking status. Individuals presenting with “severe somatic illness” and comorbid depression and other psychiatric illnesses were excluded from the study. Rates of smoking were benchmarked to population-based statistics from what was a recent general population census. Results indicated that 56% of the panic disorder patients were current smokers compared to the 27.5% found in the general population; this difference was statistically significant. Additionally, 72% of panic disorder patients reported smoking at the onset of their illness.

Lopes et al. (2002) examined the prevalence of cigarette smoking among 277 consecutive psychiatric outpatients in Brazil. Sixty-eight adults with no current or lifetime psychiatric problems were used as a comparison sample. Psychiatric diagnoses were made using the SCID for DSM-IV. Participants were assigned one diagnosis according to the following categories: major depressive disorder, panic disorder, social anxiety disorder, other anxiety disorders, and comorbid disorders. Individuals with more than one disorder were assigned to a “comorbidity category” rather than a principal diagnosis category. In addition to the structured interview, participants completed a self-report measure pertaining to basic smoking history characteristics (e.g., number of cigarettes smoked per day). Results indicated that among current smokers, 30% received a panic disorder diagnosis, 28% received a major depressive disorder diagnosis, 29% a social anxiety disorder diagnosis, 21% another anxiety disorder diagnosis, and 21% received a comorbidity diagnosis.

McCabe et al. (2004) examined rates of smoking among outpatients from the Anxiety Treatment and Research Centre in Hamilton, Ontario. A total of 155 participants were included in the study. To enter

the study, participants had to have a primary diagnosis of panic disorder, social phobia, or OCD, as determined by the SCID-IV. In addition, participants were excluded if criteria were met for one of the other two disorders. Results indicated that a significantly greater proportion of the panic disorder group (40.4%) reported being a current smoker compared to the social phobia group (19.6%) and the OCD group (22.4%). There was no significant difference among anxiety disordered groups in the proportion of participants who reported smoking in the past. Also, a significantly greater proportion of the panic disorder participants reported a heavier maximum smoking history (lifetime) compared to the OCD and social phobia groups.

In another recent study, Baker-Morissette, Gulliver, Wiegel, and Barlow (2004) retrospectively examined point prevalence rates of smoking in 581 patients with anxiety disorders seeking treatment at an anxiety research and treatment center. Participants were screened for alcohol or substance use disorders by a brief telephone survey prior to attending the treatment center. Participants were diagnosed using the Anxiety Disorders Interview Schedule-IV (ADIS-IV; Brown, Di Nardo, Lehman, & Campbell, 2001) and asked whether or not they were a smoker as well as the amount smoked (if applicable). Using this retrospective chart review, 19.2% of persons diagnosed with panic disorder with or without agoraphobia were current smokers. The point prevalence of smoking among those with panic disorder were generally comparable to those found for persons with generalized anxiety disorder (17.2%) and major depressive disorder (25.0%), and greater than those with other anxiety disorder diagnoses. Additionally, rate of smoking did not vary as a function of anxiety disorder, but those with multiple diagnoses were significantly more apt to be heavier smokers than those with a single disorder.

Finally, Valentiner, Mounts, and Deacon (2004) evaluated associations between drug and alcohol use, including tobacco, in relation to panic attacks among college students. Participants were screened for panic attacks as indexed by their responses to the Panic Attack Questionnaire (PAQ; Norton, 1989). Of the 47 students meeting panic attack criteria, 66% reported a lifetime history of tobacco use and 23.4% reported daily tobacco use. These rates were not significantly different from individuals not meeting panic attack criteria ($n=290$), whereby 53.4% and 16.3% tobacco use reported for lifetime and daily use, respectively. Similar findings were apparent for other substances (e.g., opioid, alcohol, and cocaine) in that persons with panic attacks reported greater, but not necessarily statistically significant, rates of use compared to those without such a history. The relatively small sample size (i.e., $n=47$) and associated limited statistical power as well as the questionnaire identification of panic attacks, which may not be as accurate as structured interviews (Brown & Deagle, 1992), may account for these findings which differ from the generally consistent differences documented between panic and non-panic attack groups.

2.2.1. *Epidemiologic studies*

Whereas the previously reviewed studies used community or treatment clinic samples, Covey, Hughes, Glassman, Blazer, and George (1994) employed epidemiological sampling methods as part of the National Institute of Mental Health-Epidemiologic Catchment Area study in Durham, North Carolina.¹ Participants were 2980 individuals in the community who were selected based upon stratified

¹ We do not review a study by Glassman and his colleagues (1990) in detail, as this study was focused on smoking and major depressive disorder. It should be noted, however, that this investigation included secondary analyses for individuals with panic disorder and agoraphobia. Results suggested that participants with panic disorder or agoraphobia compared to those without such psychopathology were 1.23 to 2.13 times more likely (odds ratios) to endorse “ever smoking” in their lifetime (regardless of history of major depressive disorder). No actual percentage rates were reported.

multistage sampling. Interviews were completed by trained raters used the Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan, & Ratcliff, 1981) to assess for psychiatric disorders. The DIS included a single-item question of “ever smoking,” asking if participants had ever smoked cigarettes for a month or more at some point in their life. Results indicated that for females, 2.8% with a lifetime diagnosis of panic disorder and 4.7% with a lifetime diagnosis of agoraphobia endorsed “ever smoking.” In regard to males, 2.8% with a lifetime diagnosis of panic disorder and 10.1% with a lifetime diagnosis of agoraphobia reported “ever smoking.” Rates of lifetime smoking also were low for other psychiatric conditions; for instance, approximately 1% of individuals diagnosed with schizophrenia (collapsed across gender) and 11.6% diagnosed with alcohol abuse/dependence (collapsed across gender) reported “every smoking.” These low overall rates of smoking endorsement across psychiatric conditions suggest that the study results may be limited by the nature of the smoking assessment employed.

In a more recent epidemiologic study, Lasser et al. (2000) examined smoking status according to psychiatric diagnoses using data from the National Comorbidity Survey (NCS), a nationally representative study that used a structured clinical interview to document mental illness (Kessler et al., 1994). Participants were 4411 individuals, ranging in age from 15 to 54 years old. Trained raters used the Composite International Diagnostic Interview (CIDI; World Health Organization Version 1.0) to document mental illness and health behaviors such as smoking. Smoking status was assessed by a question asking participants “if they are a daily smoker.” Among individuals diagnosed with panic attacks, panic disorder, and agoraphobia in their lifetime, 38.1%, 35.9%, and 38.4% were current smokers, respectively. These rates were significantly greater than rates of current smoking among individuals without mental illness. By comparison, 36.6% of individuals with a lifetime history of major depression and 49.0% of individuals with a lifetime diagnosis of drug abuse or dependence were current smokers. Rates of lifetime smoking among persons with a lifetime history of panic-related problems (i.e., panic attacks, panic disorder, or agoraphobia) ranged from 58.9% to 61.3%. When diagnostic status in the past month was used as the defining variable, the rates of smoking were greater than that observed for lifetime diagnosis; 46.4% of persons with panic attacks, 42.6% of persons with panic disorder, and 48.1% of persons with agoraphobia were current smokers. Although not specific to panic-related problems, it is noteworthy that as number of mental diagnoses increased (ranging from 0 to 4 or more), the percentage of heavy (i.e., peak consumption exceeding 24 cigarettes a day) compared to light (i.e., peak consumption less than 24 cigarettes per day) smokers increased.

Finally, Farrell et al. (2001) evaluated associations between drug-related problems, including tobacco, and psychiatric conditions using a national household survey in Great Britain. Participants included individuals drawn from representative (private) households in Great Britain with the exception of the Highlands and Islands of Scotland. Of the 12,370 adults between ages 16 and 64 years who were eligible for the study, 10,018 were interviewed. Assessment of psychiatric conditions was determined by trained raters using the Clinical Interview Schedule-Revised (CIS-R). The ICD-10 criteria for dependence were employed for all types of drugs. Results indicated that of individuals diagnosed with panic disorder, 1.5% were nicotine dependent compared to .5% who were not nicotine dependent on any drug; this rates were significantly different from one another. Generally similar rates of elevated dependence were apparent for persons with panic disorder for alcohol (2.7%) and other (illicit) drug use (2.5%). These data, again, suggest that individuals with panic disorder may be more apt to become dependent on a wide variety of drugs.

2.3. Prevalence of panic-spectrum problems among smokers

Researchers also have sought to document the prevalence of panic-related problems among cigarette smokers, although this literature is modest in terms of overall number of studies. Due to the small number of studies in this domain, we do not break them down into specific categories (e.g., community-based versus epidemiologic-based).

Whereas extant work thus far reviewed has focused on the presence versus absence of smoking behavior, Breslau, Kilbey, and Andreski (1991) were the first to evaluate whether *nicotine dependence* was associated with panic and other psychiatric disorders.² In this study, dependence was defined in the following manner: (1) “no dependence” was operationalized as abstinence or the use of cigarettes without nicotine withdrawal symptoms; (2) “mild dependence” was operationalized as the presence of three or four withdrawal symptoms, but not including interference in social, occupational, or recreational functioning; and (3) “moderate dependence” was operationalized as five or six withdrawal symptoms, or three symptoms when one is interfering with life functioning. Participants were 1007 young adults (21 to 30 years of age) in Detroit, Michigan. They were drawn randomly from a 400,000 person health maintenance organization. Thus, the participants were representative of the health maintenance organization but not necessarily the population at large. For instance, this sample was primarily Caucasian (i.e., 80.7%) and highly educated (i.e., over 75% having some college education). Participants were interviewed in their homes by trained raters using the National Institute of Mental Health Diagnostic Interview Schedule (Robins, Helzer, Cottler, & Golding, 1989). Results indicated that 6.6% of persons meeting criteria for moderate dependence, 4.8% of those with mild dependence, and 2.4% of those with no dependence had a lifetime diagnosis of panic disorder. Both mild and moderate dependence were significantly greater than no dependence, although they did not significantly differ from one another.

Nelson and Wittchen (1998) examined associations between nicotine dependence, smoking status, and psychiatric disorders in a large sample ($n=3021$) from Munich, Germany. Participants were drawn from 1994 government registries of residents in metropolitan Munich and oversampled for youth (ages 14–15 years old) due to the higher rates of substance use problems in this age bracket; the range in age of the sample was between 14 and 24 years of age. Trained raters administered the CIDI to assess for both psychiatric disorders and substance use disorders, including nicotine dependence. In this study, the DSM-IV criteria for nicotine dependence were used to diagnose dependence (i.e., three of seven of the dependence criteria within a single 12-month time frame; APA, 1994). Of participants endorsing a lifetime history of smoking (yes/no), 7.6% met lifetime diagnostic criteria for panic attacks, 2% for panic disorder, and 4.4% for agoraphobia. These rates of panic-spectrum problems were greater than those reported among nonsmokers; 2.4% had a panic attack history, .7% had panic disorder, and 1.6% had agoraphobia. Smokers with a lifetime nicotine dependence diagnosis compared to smokers without such a diagnosis evidenced greater rates of panic attacks (11.3% versus 4.0%), panic disorder (2.2% versus 1.8%), and agoraphobia (6.4% versus 2.5%); these were significant differences for panic attacks and agoraphobia, but not panic disorder. It should be noted that a similar, albeit not uniform, pattern of findings was apparent for individuals with other psychiatric disorders (e.g., alcohol dependence, drug dependence, generalized anxiety disorder).

² It should be noted that there are difference conceptualizations of nicotine dependence and there is no current consensus as to the best way to define it (see Piper et al., 2004, for an expanded discussion of the issue).

More recently, Black, Zimmerman, and Coryell (1999) examined lifetime prevalence rates of psychiatric disorders among cigarette smokers and nonsmokers in a community sample from Iowa. Participants included 1057 individuals; 360 were first-degree relatives of persons with no psychiatric history, 131 were first-degree relatives of persons with schizophrenia, 482 were first-degree relatives of persons with major depressive disorder, 74 were first-degree relatives of persons with OCD, and 10 had first-degree relatives with some “other type” of psychiatric condition. Participants were interviewed by trained raters using the Diagnostic Interview Schedule (DIS; Robins et al., 1981) for axis I disorders and the Structured Interview for DSM-III Personality Disorders (SIDP; Stangl, Pfohl, Zimmerman, Bowers, & Corenthal, 1985); approximately 25% of the interviews were conducted in person and the other 75% were completed via the telephone. In this study, cigarette smoking was indexed by a DIS item pertaining to whether one was a “daily smoker for a month or more.” Results indicated that lifetime frequency of panic disorder was significantly greater among female smokers (5.6%) compared to nonsmokers (2.1%); no significant effect was found for males. Additionally, there was an overall greater risk for smokers (6.2%) compared to nonsmokers (3.2%) to be diagnosed with agoraphobia. After controlling for comorbidity among the disorders, however, only alcohol and drug dependence were independently related to smoking status.

2.4. Conclusions

Our review of studies focused on the co-occurrence of smoking and panic-related problems suggests a number of specific conclusions and areas for future research. First, studies have found associations between (1) daily smoking among those with panic-related problems (average current smoking rate of approximately 40% among those diagnosed with a panic-spectrum problem across studies) and (2) panic-related problems among those who are daily smokers (approximately 5% of smokers compared to 2% among nonsmokers). Yet, the strength of the associations is attenuated when psychiatric comorbidity, particularly substance use disorders, is statistically controlled. This finding is not surprising given smoking is highly correlated with other types of drug/alcohol use and problems (Amos, Wiltshire, Bostock, Haw, & McNeill, 2004) and individuals with anxiety psychopathology may use multiple types of psychoactive substances (Zvolensky & Schmidt, 2004). For example, Grant et al. (2004) using data from the National Institute on Alcohol Abuse and Related Conditions (NESARC), a nationally representative survey of 43,093 respondents in the U.S., found that the 12-month prevalence of substance use disorders among individuals with panic disorder with or without agoraphobia was 20.5%. These data suggest that smoking and panic may co-occur within a context of drug abuse and potentially dependence. Here, it should be noted that to the extent that other substance use and related problems co-occur with smoking, it may not be useful to statistically covary for the effects of these other substances, as doing so may threaten the integrity of the dependent variable (e.g., it is unlikely that smokers with panic-related problems will be using only this psychoactive substance; see Miller & Chapman, 2001, for an expanded discussion). Rather, it may prove most clinically helpful to understand the role of polysubstance using individuals (e.g., smoking and alcohol) in relation to panic vulnerability, rather than focus on one type of drug problem. Given the frequent absence of assessment of other drug use in the above reviewed studies, future research would increase our understanding of this issue by assessing and reporting rates of polysubstance use and how such use relates to panic spectrum problems.

Second, there are a number of issues central to the generalizability of the results of the reviewed investigations. With the exception of Lasser et al. (2000), Covey et al. (1994), and Farrell et al. (2001),

none of the studies have employed an empirically derived representative sample. Thus, it is not possible to rule out the role of systematic sampling biases across this body of work. For example, the vast majority of studies documenting smoking among persons with panic disorder have been conducted in psychologically oriented treatment facilities. These sites may increase the probability of self-selection biases (e.g., more severe psychopathology, high degree of self-focused mental health knowledge) and therefore should not be considered uniformly applicable to all persons with the condition. It also is noteworthy that only [Hayward et al. \(1989\)](#) focused exclusively on youth. Therefore, it is not possible to generalize the present smoking–panic relations to other segments of the lifespan (e.g., adolescents) and the various stages of smoking (e.g., initiation, maintenance) that would presumably be operative across different age ranges. Future work could be usefully directed toward developing a better understanding of the linkages between smoking stages and panic-spectrum problems across the lifespan. Prospective tests, rather than solely cross-sectional designs, would be particularly informative in this capacity. Additionally, it is striking that the vast majority of studies have been comprised of individuals with a Caucasian background and little systematic attention has been focused on ensuring ethnically representative backgrounds. As factors that govern smoking behavior may vary across ethnic communities, in conjunction with the worldwide impact of smoking and panic psychopathology, it is important to extend work in this area across diverse populations.

Third, existing work has largely utilized a narrow assessment of smoking and panic problems. To improve upon the smoking assessment, it would be important to verify self-report findings with biochemical verification assessment technologies. Perhaps more importantly, due to the focus on the “presence or absence of daily smoking,” little is known about the nature or topography of smoking behavior in terms of its association with panic-related problems (e.g., age of onset, amount used when smoking the heaviest). On the one hand, this work could be improved by broadening smoking assessments to include a more detailed account of smoking history. It would be particularly useful for future work to distinguish daily smoking and nicotine dependence, as only [Breslau et al. \(1991\)](#), [Farrell et al. \(2001\)](#), and [Nelson and Wittchen \(1998\)](#) examined dependence criteria, and there is some evidence to suggest panic disordered individuals smoke heavier amounts ([McCabe et al., 2004](#)). On the other hand, it may be fruitful to move away from unidimensional models of smoking altogether and toward a multidimensional approach that takes into consideration theoretically relevant motivational processes guiding compulsive cigarette use ([Piper et al., 2004](#)). This type of approach could be particularly valuable when examining linkages between smoking and panic psychopathology, whereby motivation to smoke to avoid negative affect might be a formative psychological process ([Zvolensky, Schmidt et al., 2005](#)). In regard to the assessment of panic-spectrum problems, future work should assess for and distinguish between panic attacks, panic disorder, and agoraphobia. As it stands, there is a paucity of available work that has uniformly made these distinctions, leaving unclear the extent to which smoking is specific to a particular type of panic-related problem.

3. Associations between smoking and panic-spectrum problems: prospective and cross-sectional empirical evidence

Given the documented smoking–panic association, a next task is to explicate the extent these conditions may influence one another. In this context, it is important to remember that multiple bi-directional processes are potentially applicable across various stages of disorder development. For

example, smoking may increase the risk for developing panic attacks. At the same time, panic disorder may decrease the chance of successfully quitting among active smokers. To best represent these potentially complex associations, we have organized our review by work that speaks to these bi-directional influences.

3.1. Smoking behavior: association with panic-spectrum problems

3.1.1. Prospective associations

A number of studies focus on documenting prospective relations between smoking and vulnerability for developing panic-related problems. These studies are oriented toward better understanding the etiology of panic-spectrum problems. From the outset, it is important to remember that the onset of daily smoking typically occurs between the ages of 15 and 20 and rarely after age 25 (Breslau et al., 2001). The median age of onset for panic disorder is approximately 24 years of age (Burke et al., 1990), yet panic attacks often first occur during adolescence (Hayward et al., 1992). For example, the median age for the onset of panic attacks (cf., panic disorder) is 13 years of age (Warren & Zgourides, 1988) and the majority of persons with panic disorder report having their first panic attack as an adolescent (Von Korff, Eaton, & Keyl, 1985). These data suggest that while smoking initiation may typically precede the onset of panic disorder, the temporal relation between smoking and panic attack onset may be much closer in proximity. With this background, researchers have evaluated the association between smoking and risk of panic-related problems in a number of studies.

In one of the earliest empirical evaluations, Breslau and Klein (1999) tested the association between daily smoking and risk for panic attacks and panic disorder. Participants were drawn from two separate epidemiologic data sets: prospective data from 1007 participants in the Epidemiological Study of Young Adults in southeast Michigan (see Breslau et al., 1991) and cross-sectional data from 4411 individuals in the NCS investigation (see Lasser et al., 2000). In regard to the Epidemiological Study of Young Adults, participants were assessed in 1989 with a structured clinical interview (see Breslau et al., 1991 for details) and then again in 1990, 1992, and 1994. Results indicated that there was a significant lifetime association between daily smoking and onset of panic attacks and panic disorder; daily smokers were almost 4 times more apt to experience panic attacks and 13 times more likely to develop panic disorder after controlling for major depression and gender. Additionally, among those individuals who continued to smoke compared to those who had quit, there was a significant increased risk for experiencing a panic attack and panic disorder. Interestingly, there was no increased risk of daily smoking (covarying for major depression) among those with a pre-existing history of panic attacks or panic disorder. In terms of the NCS data, daily smoking was similarly associated with an increased risk of panic attacks after controlling for major depression and gender. There was no significant difference, however, in regard to having a panic attack among those smokers who had quit and those who had not. There were similar results in regard to panic disorder; daily smoking increased risk for developing the disorder, but did not significantly differ between individuals who had and had not quit smoking. Additionally, there was a modest increased risk for panic attacks and panic disorder to lead to smoking (hazards ratios were 1.37 and 1.06, respectively). In exploratory analyses aiming to determine if smoking may lead to panic problems via respiratory disease, the sex-adjusted odds ratios for reporting a lifetime history of panic attacks were greater for persons with lung disease (regardless of smoking status) than for smokers alone or persons who neither smoked nor reported lung disease. Furthermore, this pattern of findings was replicated by examining incidence of first panic attack; persons with lung disease, regardless of smoking

status, were most likely to report their first panic attack during the 5-year follow-up period relative to smokers with no lung disease and healthy nonsmokers.

In a separate investigation, 688 participants were randomly drawn from a large-scale prospective investigation and interviewed in their homes (Johnson et al., 2000). At the first assessment, participants were an average of 14 (S.D.=3) years of age. They were assessed again when they were an average of 16 (S.D.=3) and 22 years old (S.D.=3). Participants were largely Caucasian (91%) and from New York State. Trained raters administered the DIS for children at the time 1 assessment and then at each of the follow-up assessments. After controlling for a variety of theoretically relevant covariates (i.e., “difficult temperament,” gender, parents’ educational level, parental smoking status and psychopathology, as well as adolescent alcohol and drug use and anxiety and depressive disorders), participants who smoked 20 or more cigarettes per day at the time 1 assessment were at significantly greater risk for panic disorder, agoraphobia, and generalized anxiety disorder as young adults. As in the Breslau and Klein (1999) study, anxiety psychopathology at time 1 was not associated with increased risk of smoking as a young adult.

In a prospective study completed in Germany, 2500 participants (age range: 14–24 years at baseline) were evaluated over a 4-year period (Isensee, Wittchen, Stein, Höfler, & Lieb, 2003). Participants were selected to represent the population and completed an initial baseline assessment and two follow-up assessments. The CIDI was used to document psychiatric disorders and assess for smoking behavior. This study included a detailed smoking assessment: nonsmokers indicated no lifetime use of tobacco products; occasional users used a tobacco product at least once in their lifetime but never on a daily basis; nondependent smokers smoked cigarettes daily for at least 4 weeks but never met nicotine dependence criteria; and dependent regular smokers smoked daily for at least 4 weeks and met DSM-IV criteria for nicotine dependence. At baseline, dependent smokers reported the highest lifetime rates of panic attacks (7.6%) and panic disorder (3.8%) compared to the other smoking categories (i.e., range: .7% to 2.0% for panic attacks and .2% to 2.1% for panic disorder across other smoking categories). A similar pattern of results was apparent for agoraphobia at baseline, with 4.9% of dependent smokers meeting lifetime criteria for the disorder (range: 1.5% to 2.2% for other smoking categories). The prospective analyses indicated that dependent regular smokers at baseline were significantly more likely to develop panic attacks and panic disorder in the future. The panic disorder effect, however, failed to reach statistical significance after controlling for comorbid psychopathology at baseline. Interestingly, respondents with pre-existing panic attacks and panic disorder at baseline were at increased risk for smoking at the follow-up assessment. The authors note that this effect may be due to the retrospective nature of age of onset data before the baseline interview.

3.1.2. *Concurrent associations*

Whereas prospective data is useful in guiding an understanding of temporal sequencing of risk, cross-sectional studies provide a “snap shot” of associations at one point in time. Thus, these investigations could potentially be applicable to maintenance-related effects. They also are helpful in testing theoretical predictions derived from specific models and therefore can distill the merit of particular conceptualizations in a cost-efficient manner. In fact, a number of cross-sectional studies have tested associations between smoking and panic-relevant *processes* (e.g., bodily vigilance), as well as vulnerability variables, rather than the presence or absence of disorder status. For instance, several studies have examined fearful responding to bodily sensations induced by biological challenge in an effort to obtain a “real-time” picture of panic-relevant processes. Others have examined panic-relevant risk factors, such as anxiety sensitivity, a commonly studied cognitive risk factor for panic problems that reflects a tendency to

respond fearfully to bodily sensations. Indeed, this body of work has been useful in helping identify how processes may unfold and in guiding an understanding of possible mechanisms of action.

Goodwin and Hamilton (2002) evaluated the role of neuroticism in the association between smoking and panic attacks. Data were drawn from the Midlife Development in United States Survey, which is a representative household survey of the adult population ($n=3032$); participants ranged in age from 25 to 74 years. Participants completed a 30-min telephone interview and mailed in written responses for relevant questionnaires. Twelve-month diagnostic status was evaluated over the telephone using the CIDI short-form scales. Personality was measured with an unpublished self-report instrument, entitled the Midlife Development Inventory, which assesses five personality traits: agreeableness, openness to experience, conscientiousness, extroversion, and neuroticism.³ Results indicated that 12-month panic attack diagnoses were associated with a higher likelihood of smoking (odds ratio=1.9); this relation remained statistically significant after controlling for comorbid psychiatric disorders, but not neuroticism. Follow-up analyses indicated that neuroticism was associated with the co-occurrence of smoking and panic attacks, but not panic attacks without smoking or smoking without panic attacks; this effect was above and beyond variance accounted for by psychiatric comorbidity and demographic characteristics. Other personality characteristics did not relate to the co-occurrence of smoking and panic attacks in a similar way.

In another study focused on smoking and panic attacks, Zvolensky, Forsyth, Fuse, Feldner, and Leen-Feldner (2002) evaluated panic-relevant cognitive processes in a sample of persons ($n=70$) who met criteria for either (1) a positive panic attack history and regular smoking (smoking at least 10 cigarettes per day for ≥ 12 months), (2) a positive panic attack history but no history of smoking, or (3) regular smoking history alone (smoking at least 10 cigarettes per day for ≥ 12 months). The average age of the sample was 21.7 years (S.D.=6.8). Panic attack history was determined using a conservative definition of panic and indexed by the Panic Attack Questionnaire-Revised (PAQ-R; Norton, Dorward, & Cox, 1986). Specifically, persons who reported: (a) having more than one panic attack in the past 3 months, (b) having at least 5 out of the 13 DSM-IV panic symptoms, (c) gave intensity ratings greater than 2 (moderate) for the symptoms endorsed, and (d) reported that their attacks occurred in the absence of identifiable threat (uncued) were classified as having a “positive” panic attack history. In contrast, participants who did not meet all of these same symptom criteria were classified as not having had a panic attack. In addition, participants completed a battery of theoretically relevant self-report measures tapping various panic-relevant fears. Results indicated smokers with panic attacks reported significantly greater bodily vigilance and anxiety sensitivity Mental Incapacitation Concerns compared to persons with either panic attacks or smoking histories alone. Effects involving other dimensions of anxiety sensitivity, suffocation fear, and trait anxiety did not differ between groups.

In a follow-up investigation, Zvolensky, Schmidt, and McCreary (2003) evaluated concurrent associations between current smoking and a wide variety of panic-related indices of impairment among treatment-seeking panic disorder patients. The sample consisted of 140 consecutive patients meeting the following criteria: (a) principal DSM-IV (APA, 1994) diagnosis of panic disorder with or without agoraphobia, (b) no change in medication type or dose during the 8 weeks prior to treatment, (c) no

³ Numerous temperamental variables have been studied as indices of a “propensity to experience negative affect” (e.g., neuroticism, negative affectivity). Although there are theoretical nuances in terms of the conceptual underpinnings of these constructs, they all converge on the idea of a broad-based disposition to experience negative affect. Thus, for the purposes of the present paper, we use the terms neuroticism and negative affectivity interchangeably.

evidence of serious suicide intent, (d) no evidence of current substance abuse (other than smoking), and (e) no evidence of current or past schizophrenia, bipolar disorder, or organic mental disorder. Diagnostic status was determined by SCID-IV interviews and participants' mean age was 37.6 years (S.D. = 11.5). Results indicated that smokers with panic disorder compared to those who were not smokers reported significantly more severe and intense anxiety symptoms, greater interview-based overall severity ratings of panic symptoms, and more social impairment. No differences in physical health status or depressive symptoms were apparent between groups.

Zvolensky, Kotov, Antipova, and Schmidt (2003) evaluated the interactive effects of level of smoking (cigarettes per day) and anxiety sensitivity (fear of anxiety and anxiety-related sensations) in predicting self-reported panic attacks in the past week and agoraphobic avoidance among an epidemiologically defined sample from Moscow, Russia. In contrast to previous work focused on “main effects” of smoking (i.e., between subjects) in regard to panic vulnerability, this investigation tested a moderating hypothesis among current daily smokers (i.e., within subjects). The 95 smokers in the study were 82% male, 69% college educated, and had an average age of 42 years (S.D. = 13.5 years). After controlling for negative affectivity, alcohol abuse, and the main effects of cigarettes per day and anxiety sensitivity, results indicated that the combination of high levels of anxiety sensitivity and smoking predicted agoraphobic avoidance, but not frequency of panic attacks during the past week. These findings suggest individual differences in anxiety sensitivity may moderate the relation between level of smoking and certain panic psychopathology processes even after controlling for the variance accounted for by the other theoretically relevant variables. The lack of an interaction for panic attacks is potentially due to the fact that the researchers restricted measurement to a 1 week (most recent) time frame to enhance the validity of the self-report measures (i.e., an attempt to reduce recall biases), but may have truncated variability and thereby reduced statistical power. Indeed, there was a trend in the expected direction for the interaction term.

In a recent report, Breslau, Novak, and Kessler (2004) evaluated daily smoking and subsequent onset of psychiatric disorders, including panic disorder, using the NCS data. Indices were operationalized in relation to “pre-existing” smoking status and psychiatric diagnoses. Specifically, daily smoking was defined as “pre-existing” if it first occurred 1 year or more before the onset of a given psychiatric disorder. In addition, pre-existing smoking status was classified as current versus past according to the year in which the respondent smoked last, compared to the year of onset of the disorder of interest. “Past smokers” were individuals who reported that they last smoked 1 year or more before the onset of disorder and “current smokers” were persons who smoked in the year of onset of the psychiatric disorder. Both current and past smokers also were classified as nicotine dependent or non-dependent. Results indicated that the onset of panic disorder (odds ratio=2.6) and agoraphobia (odds ratio 4.4) were associated with pre-existing daily smoking after controlling for age, gender, ethnicity, and educational level. Additionally, after controlling for pre-existing psychiatric disorders and sociodemographic characteristics, current nicotine dependent smokers were significantly more likely to have panic disorder compared to current non dependent smokers and former smokers. In regard to agoraphobia, both nicotine dependent and nondependent current smokers were significantly at greater risk for the onset of the disorder compared to former smokers. Interestingly, the likelihood of panic disorder and agoraphobia was significantly reduced as time since quitting increased; these effects were specific to these conditions and not other psychiatric disorders (e.g., major depressive disorder). Although the results from this investigation are striking in many respects, it is important to remember recall biases and other memory distortions cannot be ruled out as alternative explanations. Moreover, although the authors assumed that

daily smoking (and nicotine dependence) continued in all of the intervening years from the year it began until it last occurred, there are no data that speak to this issue. Thus, it is unclear how patterns and fluctuations in smoking behavior may have affected the observed findings.

Whereas previously reviewed work focused on studies conducted in non-laboratory environments, Zvolensky, Leen-Feldner et al. (2004) employed a well-established voluntary hyperventilation paradigm to examine associations between smoking and fearful responding to bodily sensations. Participants were 61 (40 females; M_{age} was 24.8 [S.D.=7.8]) individuals from the greater Burlington, Vermont community. Psychiatric history was evaluated by trained doctoral-level raters using the ADIS-IV. Regular smoking was defined as (current) smoking of at least 10 cigarettes per day for at least 1 year. One-third of the sample met diagnostic criteria for current panic disorder (primary diagnosis) and were regular smokers, one-third met only the diagnostic criteria for current panic disorder (primary diagnosis) and were not smokers, and the final third were regular smokers who did not have panic disorder or any other psychopathology. None of the participants had current or past cardiopulmonary illness (e.g., heart disease, chronic obstructive pulmonary disease). Results indicated that smokers with panic disorder reported greater levels of anxiety than smokers without panic disorder at baseline and showed greater increases in anxiety during the post-challenge assessment and recovery period. Although smokers with panic disorder did not differ from nonsmokers with panic disorder on baseline or post-challenge anxiety, in terms of rate of recovery, there was a significant time by group interaction for the panic groups; specifically, the linear decrease in anxiety during recovery was significantly steeper for nonsmokers with panic disorder than for smokers with panic disorder. This finding suggests that there is a slower affective recovery in terms of anxiety for smokers with panic disorder compared to nonsmokers with the disorder. The observed difference for anxiety ratings between the smoking and non-smoking panic disorder groups is interesting given the lack of group differences in physiological responding during all phases of the study, highlighting a marked degree of response discordance. It is important that the observed findings cannot be attributed to a variety of theoretically relevant baseline variables such as anticipatory anxiety or depressive symptoms.

3.2. Conclusions

There is a recent, albeit rapidly growing, empirical literature focused on better understanding associations between smoking and the expression of panic-spectrum problems. Inspection of this literature suggests a number of conclusions. First, three large-scale independently replicated prospective studies indicate daily smoking increases the risk for panic attacks, panic disorder, and agoraphobia. These smoking-related effects are most robust when the smoker is currently smoking heavier amounts. At the same time, there is less compelling evidence of the opposite relation, that is, panic-spectrum problems conferring increased risk for smoking initiation. Thus, these studies imply a temporal sequence from smoking to panic-related problems rather than vice versa. Additionally, although each of these studies covaried for a variety of theoretically relevant factors (i.e., mostly other types of psychopathology), it is possible other “third variables” may account for these effects. As one illustrative example, none of the investigations tested the incremental validity of smoking relative to volume of alcohol consumed (cf. alcohol use disorders), which is particularly important as smoking and alcohol use covary at high rates (see above section on Prevalence of smoking among individuals with panic-spectrum problems). As a second example, none of the studies ruled out pre-existing medical illness (e.g., frequency of respiratory disease), perceptions of health, or fitness levels (e.g., level of aerobic

activity) as possible third factors. Again, these health-related variables are theoretically and empirically related to both smoking and panic and may be responsible for the observed smoking–panic effects. Furthermore, although it is tempting to interpret the prospective data from these studies as “causal,” these are not experimental designs and therefore stronger evidence is necessary to bolster such an inference. Here, randomized prevention programs may prove to be a fruitful next step (see Feldner, Zvolensky, & Schmidt, 2004, for further discussion of this issue). Indeed, as Breslau et al. (2004) documented, there is initial evidence that quitting smoking may decrease the risk of experiencing panic-related problems in the future.

A second key conclusion is that all prospective and cross-sectional work with the exception of the Zvolensky, Kotov et al. (2003) study have focused exclusively on the “main effect” of smoking in relation to panic problems. This focus on the main effect of smoking is in line with the developmental stage of the research (i.e., it is a relatively young literature). Yet, the literature is now poised to move from tests of main effects to tests of moderating and mediating processes. In regard to moderating factors, there is little doubt that individual differences and contextual factors help to specify which smokers will go on to develop panic-spectrum problems. Indeed, although smoking is consistently associated with panic-related vulnerability, not all daily smokers are developing such problems. By working to understand moderators of panic-related outcomes, researchers will be in a better position to increase power in their tests of panic-related factors and offer clear clinically relevant suggestions regarding which individuals might be most responsive to specialized prevention or treatment programs. In a related fashion, there has been very little scientific attention to mediators of smoking–panic associations and therefore almost no empirical knowledge exists pertaining to the causal mechanisms. Intensifying the focus on mediators of smoking–panic relations is a clinically relevant and timely task. Specifically, clarification of key mechanisms through which smoking achieves its panic-relevant effects will (1) stimulate the development of targeted interventions focused on key therapeutic processes, and (2) help to establish such processes (e.g., emotional reactivity) as important in the etiology and/or maintenance of panic-related problems. Only Breslau and Klein (1999) conducted exploratory analyses of possible mediators by evaluating the role of lung disease. Although medical illness is one useful process to better understand, other factors such as perceived health, distress tolerance, various trajectories of affective distress (e.g., delayed recovery), withdrawal symptoms, and avoidance-oriented smoking patterns are examples of other theoretically relevant factors to study in the future (see Zvolensky, Schmidt, & McCreary, 2003; Zvolensky, Schmidt, & Stewart, 2003, for a further discussion).

Third, our review of the literature has indicated that there is a limited amount of work on panic-relevant *processes*. That is, the majority of studies have used dichotomous classification to index panic-related problems (i.e., diagnostic ratings) and employed self-report assessment devices to index such problems. Thus, there is an overarching emphasis on a limited methodological approach to the study of smoking–panic associations. For example, there has only been one laboratory study of smoking and panic vulnerability (Zvolensky, Leen-Feldner et al., 2004). Accordingly, almost no data are available that speak to how smoking at various stages of development relates to anxious and fearful responding in “real time.” Without broadening the methodological approaches used in this area of study to tap theoretically relevant processes, it will be difficult to document the nature of vulnerability processes across and between levels of analysis (e.g., cognitive, physiological, and affective systems) and remove concern that the associations documented to date are not attributable, at least in part, to recall biases or memory distortions.

3.3. Panic-spectrum problems: association with smoking behavior

Although most work on smoking and panic-spectrum problems pertains to the potential role of smoking in the onset or maintenance of panic-related problems, panic vulnerability characteristics also may impact smoking behavior in a variety of ways. Thus, there is reason to better understand the extent to which panic-related factors are related to the nature of smoking. In this section, we review available studies dealing with panic characteristics and their association with (1) smoking cessation outcome, (2) withdrawal symptoms, and (3) motivation to smoke and related cognitive processes. Although there are other possible ways panic characteristics might relate to smoking (e.g., reasons for quitting, the acute panic alleviating effects of smoking, motivation to quit), we only review areas where there is existing empirical work. Additionally, we do not review studies dealing with smoking initiation, as this work has been presented earlier (see Smoking behavior: association with panic vulnerability).

3.3.1. Smoking cessation

Given empirical evidence that smoking increases the risk for panic-psychopathology, individuals with, or at risk for, panic-spectrum problems might be especially motivated to quit smoking. In fact, at least one study has found panic-relevant cognitive dispositions are positively related to *increased* motivation to quit smoking (Zvolensky, Baker et al., 2004; Zvolensky et al., *in press*). Yet, given that the process of quitting also elicits a wide variety of aversive interoceptive cues (Hughes, Higgins, & Hatsukami, 1990; Piasecki, Fiore, & Baker, 1998; Piasecki, Kenford, Smith, Fiore, & Baker, 1997), periods of smoking abstinence may trigger escalating anxiety reactions such as panic attacks and thereby impair successful quitting (see Zvolensky, Schmidt, & McCreary, 2003; Zvolensky, Schmidt, & Stewart, 2003, for an expanded conceptual analysis). To better understand these issues, a number of studies have evaluated success in quitting as a function of panic-spectrum problems or risk factors for such problems.

There have been two epidemiologic studies that have evaluated quit rates as a function of panic spectrum problems (Covey et al., 1994; Lasser et al., 2000); the details of the design of these studies have been reviewed above and therefore will not be repeated here. Using the NCS data, Lasser et al. (2000) reported quit rates (i.e., proportion of lifetime smokers who were not current smokers) in relation to psychiatric diagnosis. In their study, quit rates among individuals with a lifetime diagnosis of panic attacks, panic disorder, and agoraphobia were 36.9%, 41.4%, and 34.5%, respectively. None of these quit rate percentages differed from individuals with no mental illness, although there was a trend for agoraphobia in the expected direction. Covey et al. (1994) reported similar results. When 1-month rather than lifetime diagnostic status was used, the quit rate was 29.8% for persons with panic attacks, 32.9% for those with panic disorder, and 23.2% for persons with agoraphobia. Individuals with both panic attacks and agoraphobia in the past month were significantly less successful in quitting smoking compared to individuals with no mental illness (42.5%).

To avoid retrospective reporting errors, two other research strategies have been employed in the study of panic and smoking cessation. One approach has been to monitor success in quitting during a quit attempt as a function of a panic vulnerability. Brown, Kahler, Zvolensky, Lejuez, and Ramsey (2001) examined a subset of data from a randomized clinical trial comparing standard smoking cessation treatment versus standard smoking cessation plus cognitive-behavioral treatment for depression in smokers with past major depressive disorder. In this investigation, researchers tested whether anxiety sensitivity, was predictive of relapse during the early stages of a quit attempt (e.g., first week) when

individuals are most apt to experience symptoms of anxiety (Hughes et al., 1990). Participants in this study were 56.7% female and averaged 45.2 years old. At baseline, participants reported smoking an average of 26.1 (S.D.=9.4) cigarettes per day and had been smoking for an average of 27.3 years (S.D.=8.4). The sample mean on the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) was 6.7 (S.D.=2.1), indicating moderate to heavy levels of nicotine dependence. Results indicated anxiety sensitivity was significantly associated with increased odds of lapsing during the first week after quit day (odds ratio=2.0). In regard to longer term cessation outcome, results indicated that although anxiety sensitivity was associated with reduced probability of abstinence across time (odds ratio=.59), this association was nonsignificant.

A second approach in panic cessation work has been to use laboratory methodologies and correlate smoking history characteristics with panic-relevant processes in “real time.” Using this approach, Zvolensky, Feldner, Eifert, and Brown (2001) evaluated anxiety sensitivity, emotional reactivity to bodily sensations, and distress tolerance in heavy smokers using a biological challenge paradigm. Participants were young adult heavy smokers (≥ 20 cigarettes per day) without pre-existing psychopathology. Individuals were partitioned into those who were able to quit for at least 7 days ($n=10$) and those who were able to quit for less than 7 days ($n=12$). All participants completed measures of anxiety sensitivity, maximum breath-holding duration, and then were exposed to a panic-relevant 20% carbon dioxide-enriched air challenge. Results indicated that heavy smokers who had not been able to remain abstinent from smoking for at least 1 week during a quit attempt demonstrated significantly greater cognitive-affective reactivity to the challenge relative to their counterparts, but did not differ at a physiological level of analysis (e.g., heart rate). Neither anxiety sensitivity scores nor maximum breath-holding duration (i.e., index of distress tolerance) significantly differed between the groups. These data suggest affective reactivity to bodily sensations (a proxy for panic-related responding) may be related to the duration of quit attempts.

3.3.2. *Withdrawal symptoms*

One of the most striking aspects of nicotine use is that withdrawal symptoms (i.e., symptoms emerging from drug reduction in the body) are prominent features during the course of addictive use. Indeed, a large body of work has sought to explicate withdrawal symptoms across specific periods of time (e.g., Pomerleau, Pomerleau, & Marks, 2000) and to clarify the role of withdrawal symptoms in relapse (e.g., Hughes, 1992). Panic-related factors may be relevant to the experience of withdrawal symptoms in a variety of ways. For example, panic-relevant cognitive dispositions may promote catastrophic thinking about the possible negative consequences of withdrawal symptoms and thereby exacerbate affective distress. In an early study in this domain, Breslau, Kilbey, and Andreski (1992) found tobacco withdrawal symptoms in a sample of young adults were significantly elevated among smokers with “any anxiety disorder” compared to individuals without a history of these disorders; however, specific anxiety diagnoses were not provided, rendering unclear the specificity of such results to panic-spectrum problems. Since this study, investigations have examined panic-related factors and the nature of tobacco withdrawal.

Zvolensky, Lejuez, Kahler, and Brown (2004) evaluated the association of nonclinical panic attacks among regular smokers with the type and intensity of DSM-IV smoking withdrawal symptoms. Participants were 40 daily smokers (20 female; $M_{\text{age}}=27.1$ years, S.D.=8.0). Fifty percent of the sample had a positive nonclinical panic attack history and were regular smokers and 50% were regular smokers that did not meet the panic attack criteria, indexed via the ADIS-IV. All participants reported smoking

≥ 10 cigarettes per day for at least 1 year and were screened for psychopathology using the ADIS-IV by a trained doctoral-level clinician; none of the participants had a positive psychiatric or medical history. Specific exclusionary criteria were: (1) a current or past axis I psychiatric disorder (excluding nicotine dependence), including alcohol dependence; (2) current or past cardiopulmonary illness (e.g., heart disease); and (3) current psychotropic medication use. Results indicated that daily smokers with a history of panic attacks reported significantly more intense anxiety-related withdrawal symptoms (anxiety, restlessness, difficulty concentrating, and irritability) compared to smokers without such a history; no differences were evident for the other tobacco withdrawal symptoms (e.g., increased appetite). Also, it is noteworthy that smokers with panic had a significantly shorter average quit attempt history, measured in days, compared to smokers without panic; these data are consistent with those of Lasser et al. (2000).

In another study, Zvolensky, Baker et al. (2004); Zvolensky et al. (in press) tested whether anxiety sensitivity predicted the intensity of withdrawal symptoms during the first week of smokers' most recent quit attempt. Participants were 127 (72 females) daily smokers from the greater Burlington, Vermont community. The mean age of the sample was 20.4 (S.D.=4.6) years and 91% was Caucasian. Participants were excluded if they reported having a history of axis I psychopathology or current psychotropic medication use as determined by answers on the SCID-IV administered by trained researchers. Participants averaged 10.2 (S.D.=5.1) cigarettes per day and had smoked regularly for an average of 4.3 (S.D.=4.1) years. Results indicated that anxiety sensitivity predicted the intensity of nicotine withdrawal symptoms during the first week of smokers' most recent quit attempt. The effect was above and beyond variance accounted for by negative affectivity, panic attack history, gender, cigarettes per day, nicotine dependence, and age of smoking onset; it accounted for 16% of unique variance.

Finally, Zvolensky, Feldner et al. (in press), Zvolensky, Schmidt et al. (2005), evaluated the incremental validity of acute nicotine withdrawal symptoms (elicited by an average of 2 h of nicotine deprivation) relative to negative affectivity, anxiety sensitivity, and nicotine dependence in predicting anxiety responding to 3-min voluntary hyperventilation. The sample consisted of 90 regular smokers (46 females), as defined by smoking ≥ 10 cigarettes per day for at least 1 year, recruited through the general community. In addition, the participants in this study were screened for axis I psychopathology prior to study participation. Consistent with prediction, greater levels of pre-challenge nicotine withdrawal symptoms uniquely predicted post-challenge intensity of panic symptoms and anxiety relative to other established factors. These data suggest that acute nicotine withdrawal offers unique explanatory value in regard to the perceived intensity of panic-relevant physical symptoms and anxiety reactions. As this investigation focused on acute nicotine withdrawal, it will be useful for future work to extend the findings to more severe types of withdrawal symptoms.

3.3.3. *Motivation to smoke and related cognitive processes*

In regard to smoking-related motivational processes, there is a large empirical literature that documents smokers attribute their smoking, at least in part, to its mood-regulating functions and believe that smoking will reduce negative affect states (Parrott, 1999). Due to their affective vulnerability, smokers with panic-spectrum problems may be a subgroup of individuals that is highly motivated to smoke to temporarily escape from negative emotional distress elicited by acute nicotine withdrawal or non-withdrawal states (e.g., anticipatory anxiety; see Zvolensky, Schmidt, & McCreary, 2003; Zvolensky, Schmidt, & Stewart, 2003, for an expanded discussion). In particular, as persons with panic disorder generally believe negative affect-related cues (e.g., restlessness, bodily agitation, and

anxiety) are personally dangerous and experience high levels of anxiety when exposed to interoceptive cues, they would presumably be motivated to smoke in response to anxiety-related distress as a way of coping with such affective disturbances. In other words, self-administration may be aimed principally at terminating or avoiding nicotine withdrawal or related aversive states such as anxiety. At the same time, they may express little confidence in abstaining from smoking due to their affective vulnerability.

In this domain, Zvolensky, Schmidt et al. (2005) examined whether panic disorder would be associated with specific motivations to smoke and confidence ratings for smoking abstinence. Participants were 170 daily smokers (88 females; $M_{\text{age}}=25.2$ years, $S.D.=8.4$), as defined by smoking ≥ 10 cigarettes per day for at least 1 year. Participants were excluded from the study if they evidenced diagnostic criteria for a history (current or lifetime) of alcohol dependence or substance use disorder or current or past schizophrenia or organic mental disorder (determined via structured clinical interviews by trained researchers [e.g., SCID-IV]). Sixty-nine individuals had a principal DSM-IV diagnosis of panic disorder with or without agoraphobia and 101 individuals had no (current or lifetime) axis I psychiatric history. Participants were recruited in approximately equal amounts across four anxiety research centers: University of Vermont, The Ohio State University, State University of New York at Albany, and St. Joseph's Healthcare, Hamilton. In total, participants averaged 15.6 ($S.D.=8.1$) cigarettes per day, began smoking at age 13.5 ($S.D.=2.4$), and considered themselves regular smokers by age 16.2 ($S.D.=2.0$). The average level of nicotine dependence, as indexed by the FTND, was 3.3 ($S.D.=2.0$); this is a relatively low level of nicotine dependence and may be due to the demographic characteristics of the sample (e.g., young adults) and/or the screening criteria employed (e.g., no alcohol use disorders). Results indicated that smokers with panic disorder reported higher levels of smoking to reduce negative affect than their counterparts without such a history (4% of unique variance); this effect was above and beyond the variance collectively accounted for by nicotine dependence, negative affectivity, and gender. Additionally, individuals with panic disorder, relative to those without a psychiatric history, also reported significantly less confidence in remaining abstinent from smoking when emotionally distressed.

A number of other cross-sectional studies have investigated associations between anxiety sensitivity and smoking motives. This body of work has found that anxiety sensitivity is associated with coping-oriented smoking motives among young adults with no history of psychopathology (Novak, Burgess, Clark, Zvolensky, & Brown, 2003; Stewart, Karp, Pihl, & Peterson, 1997), adolescents (Comeau, Stewart, & Loba, 2001), and individuals with a past history of major depression (Brown, Kahler et al., 2001). The Comeau et al. (2001) investigation, in particular, is noteworthy in that anxiety sensitivity moderated the relation between trait anxiety (frequency of anxiety symptoms) and use of cigarettes to cope with affective distress; specifically, there was a stronger relation between anxiety and use of cigarettes to cope with negative emotions in high anxiety sensitive than in low anxiety sensitive youth.

Individual differences in anxiety sensitivity also may be associated with theoretically relevant smoking outcome expectancies among daily smokers. Zvolensky, Feldner, Leen-Feldner et al. (2004) evaluated the association between the lower-order facets of the anxiety sensitivity construct (Physical, Mental Incapacitation, and Social Concerns) and positive (negative affect reduction) and negative (negative personal consequences) smoking outcome expectancies. Participants were 90 young adult regular smokers (37 females; $M_{\text{age}}=23.4$ years [$S.D.=8.9$]; mean number of cigarettes per day=11.7 [$S.D.=6.1$]) with no history of psychopathology or nonclinical panic attacks (as indexed by the ADIS-IV administered by trained researchers) recruited from the general population. Anxiety sensitivity Physical Concerns and Mental Incapacitation Concerns, as indexed by the Anxiety Sensitivity Index (ASI; Reiss,

Peterson, Gursky, & McNally, 1986), both were significantly and incrementally associated with smoking outcome expectancies, as indexed by the Smoking Consequences Questionnaire (SCQ; Brandon & Baker, 1991), for (1) negative affect reduction as well as (2) negative personal consequences; the observed effects were over and above variance accounted for by theoretically relevant smoking history characteristics, gender, and negative affectivity.

3.4. Conclusions

Albeit small, the literature pertaining to panic-relevant factors and smoking behavior has indicated a number of interesting and significant patterns of findings. First, initial data from epidemiologic (Lasser et al., 2000), prospective (Brown, Kahler et al., 2001), and laboratory (Zvolensky, Feldner et al., 2001) studies suggest panic-related factors may relate to difficulties in quitting smoking. These findings are broadly consistent with the selection hypothesis of smoking prevalence that posits that smokers who are able to quit successfully are not “burdened” by specific characteristics that make it more challenging to quit (Coombs, Kozlowski, & Ferrence, 1989; Hughes & Brandon, 2003). For example, those less successful in quitting smoking may be more likely to suffer from psychiatric vulnerabilities. Despite the general consistency in the documented panic–smoking cessation associations, it is noteworthy that no direct tests involving panic-spectrum problems have been completed. Thus, future work should test the extent to which panic phenotypes relate to latency to first smoking lapse and point prevalence rates over time.

Second, there is empirical evidence to suggest daily smokers with high levels of anxiety sensitivity report more intense withdrawal symptoms for their most recent quit attempt (Zvolensky, Baker et al., 2004; Zvolensky et al., *in press*) and daily smokers with a history of nonclinical panic attacks report anxiety-related withdrawal symptoms as particularly intense (Zvolensky, Lejuez et al., 2004). Although consistent with earlier work (Breslau et al., 1992), there have been no definitive prospective tests. Thus, the possibility of recall biases, memory distortions, or related information processing confounds are leading alternative explanations. The utilization of time sampling methodologies that improve specificity of measures of nicotine withdrawal and anxiety-related states is necessary before more firm conclusions can be drawn. Additionally, it will be important to test withdrawal associations among heavier smokers, as existing work has involved relatively light daily smokers. Another important realm for study in reference to withdrawal pertains to the panicogenic effects of withdrawal symptoms and emotional learning. Specifically, interoceptive cues produced by nicotine withdrawal may act to amplify emotional responding to bodily sensations. In the absence of an opportunity to smoke to cope with withdrawal symptoms, interoceptive cues might be misappraised as personally dangerous (e.g., “I’m losing control,” “I’m going crazy”), leading to further intensification of anxiety symptoms and perhaps culminating in a panic attack. Experimental tests of this issue represent a fecund area for further pursuit.

Finally, cross-sectional studies have identified relations between panic disorder and anxiety sensitivity and (1) motivation to smoke to reduce negative affect (Zvolensky, Schmidt et al., 2005), and (2) outcome expectancies for negative affect reduction as well as negative personal consequences (Zvolensky, Feldner et al., 2004). Some evidence suggest these effects are not attributable to negative affectivity, severity of smoking history or nicotine dependence, or gender. Though promising, these data are all limited by the fact that they are cross-sectional in nature and involve daily but not heavy smokers. One clear recommendation for the future would therefore be to test prospective associations between panic factors and theoretically relevant smoking motivational processes and outcome

expectancies; these tests would be particularly informative when evaluated in relation to a broad sample of smokers (heavy and light daily smokers). Additionally, experimental tests that manipulate outcome expectancies in the context of panic-relevant stimuli also would be an important next step.

4. Future directions

We have heretofore outlined in the conclusion sections many areas for further study. In this final section, we briefly highlight three additional domains of public health relevance not already presented.

4.1. *Relapse processes for panic-spectrum problems*

There is a broad-based recognition that psychological vulnerabilities can negatively affect smoking cessation (Hughes & Brandon, 2003; Horn et al., 2004). Additionally, there is evidence that many anxiety disorders, including panic-spectrum problems, maintain a chronic and fluctuating course (Keller et al., 1992). Even after successful intervention, many anxiety-disordered individuals are at risk for relapse and may suffer “bouts” of excessive anxiety and life impairment related to it. Yet, there is no work evaluating the extent to which drug problems such as smoking, if left untreated, promote relapse to anxiety psychopathology. Future work needs to attend to drug problems among those with panic-related problems and understand its role in relapse processes for panic and related disorders. Research suggesting that successful treatment of general anxiety-related psychopathology (cf., panic-specific) among youth reduces the likelihood of substance use and associated problems at a 7 year follow-up (Kendall, Safford, Flannery-Schroeder, & Webb, 2004) can serve as a useful model for such work. Given the high rates of comorbidity between substance use disorders and panic psychopathology, these tests may prove most fruitful when comparing singular versus polysubstance use problems rather than solely focusing on one type of drug problem (e.g., smoking).

4.2. *Specialized intervention for tobacco dependence and panic psychopathology*

Although researchers have attempted to understand the utility of integrating cognitive-behavioral treatment of depression into standard cessation protocols (e.g., Hall, Muñoz, & Reus, 1994), no research has directly targeted panic vulnerability factors in smoking cessation. At the same time, there is little work addressing smoking in the context of panic-related treatments. Given consistent empirical evidence of bi-directional associations between these behavioral problems, it is important to develop specialized treatments, as broad-based interventions may not target the affective vulnerability processes apparent in this population. For example, it may be useful to integrate interoceptive exposure, cognitive restructuring, and psychoeducation exercises developed for panic prevention and treatment programs with standard smoking cessation strategies and nicotine replacement therapy. These tactics may be most effective when they target theoretically relevant panic risk factors like anxiety sensitivity in order to facilitate cessation. As a second illustration, given many individuals with panic-spectrum problems are smokers (Lasser et al., 2000), it may be useful to target smoking cessation as part of evidence-based panic-problem treatment strategies. There have been some inroads made in this domain, with successful case reports now documented (see Zvolensky, Lejuez, Kahler, & Brown, 2003).

4.3. Knowledge and training about smoking among anxiety disorders practitioners

At the level of training and curriculum, there is little known about the extent of knowledge (1) clinicians focused on treating anxiety disorders have about smoking and (2) clinicians focused on smoking cessation counseling have about anxiety disorders. In one recent study focused on anxiety practitioners, therapists reported assessing smoking behavior in less than 30% of clients, perceived themselves as “definitely unprepared” to deliver smoking cessation treatment, and only a minority (17%) had received formal training in empirically based smoking cessation practices during the past 3 years (Zvolensky, Baker et al., 2004; Zvolensky et al., in press). Moreover, when benchmarked against primary care physicians, anxiety specialists illustrated deficits on “basic” smoking cessation counseling practices (e.g., assessment of smoking behavior). Yet, anxiety specialists who had received formal training in smoking cessation in the past 3 years reported significantly greater levels of perceived preparedness in helping an anxiety disordered patient quit and reported delivering a greater degree of evidence-based smoking cessation treatment. These data illustrate that while there likely are major gaps in evidence-based care for smoking among anxiety specialists, training in cessation counseling is a potentially useful exercise. Similar types of tests could be completed among smoking cessation counselors. Additionally, rigorous experimental tests of the effects of such training on clinical practice within various types of training programs represent important next steps in this domain of work.

4.4. Summary

The present review evaluated extant empirical work focused on associations between smoking and panic-spectrum problems. Overall, empirical evidence suggests (1) smoking and panic spectrum problems co-occur although the extent to which this co-occurrence is similar or different from other substance use problems is unclear; (2) smoking is prospectively and concurrently associated with panic vulnerability; and (3) panic vulnerability factors are prospectively and concurrently related to various aspects of smoking behavior. Future work in this domain of study will not only lead to clinically relevant healthcare advances, but also stimulate work on other drug-psychopathology comorbidity issues.

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