Cigarette Smoking and Panic: A Critical Review of the Literature

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Objective: Cigarette smoking increases the risk of panic disorder with or without agoraphobia's emerging. Although the cause of this comorbidity remains controversial, the main explanations are that (1) cigarette smoking promotes panic by inducing respiratory abnormalities/lung disease or by increasing potentially fear-producing bodily sensations, (2) nicotine produces physiologic effects characteristic of panic by releasing norepinephrine, (3) panic disorder promotes cigarette smoking as self-medication, and (4) a shared vulnerability promotes both conditions. The aim of this review was to survey the literature in order to determine the validity of these explanatory models.

Data sources: Studies were identified by searching English language articles published from 1960 to November 27, 2008, in MEDLINE using the key words: *nicotine* AND *panic*, *tobacco* AND *panic*, and *smoking* AND *panic*.

Study selection: Twenty-four studies were reviewed and selected according to the following criteria: panic disorder with or without agoraphobia and nicotine dependence, when used, diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised, Fourth Edition, or Fourth Edition, Text Revision; no additional comorbidity or, if present, adjustment for it in the statistical analyses; use of adult or adolescent samples; comparison with a nonclinical control group or application of a crossover design.

Data extraction: Non-significant results or trends only were reported as *no difference*. Data on *anxiety disorders* or *substance abuse* in general were not included.

Data synthesis: Panic and cigarette smoking each appear to have the capacity to serve as a causal factor/facilitator in the development of the other. Although the temporal pattern and the pathogenetic explanations of such a co-occurrence are still being discussed, cigarette smoking tends to precede the onset of panic and to promote panic itself.

Conclusions: Additional studies are strongly recommended.

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A disproportionate number of people with panic, in the form of either panic attacks or panic disorder, smoke cigarettes compared to those in the general population[1,2] and to individuals with other anxiety disorders.[3] The temporal pattern underlying such a co-occurrence is still a matter of debate. Indeed, although panic can been associated with smoking and nicotine dependence[4–8] according to a bidirectional temporal pattern (going from smoking to panic or from panic to smoking),[7] clinical and experimental data have suggested that cigarette smoking increases the risk of panic disorder's emerging.[9] Similarly, longitudinal studies[3–10] have supported the more common pattern of primary smoking and secondary panic occurrence.

Several explanations have been proposed for this relationship: (1) cigarette smoking may lead to the onset of panic by inducing respiratory abnormalities[11–13] or lung disease. Thus, smoking may increase the risk of panic because, according to the false suffocation alarm theory,[10,14] it induces an overreaction to suffocation signals; (2) nicotine may produce physiologic effects characteristic of panic attacks by promoting the release of norepinephrine into the brainstem[15]; (3) smoking may modify the expression of panic disorder by increasing potentially fear-producing bodily sensations.[16] Thus, individuals with panic disorder who usually perceive themselves as being physically unhealthy would more likely react with exaggerated anxiety.

A different, less frequent, reverse pathway of primary panic and secondary nicotine dependence cannot be excluded.[7] One hypothesis for this pathway is that panic disorder patients smoke as a means of self-medicating their symptoms,[1,17] because of the anxiolytic (pharmacologic) effects of nicotine[18] or because of cognitive mechanisms (smoking narrows the focus of attention and diverts one from stressful cognitions).[19]

A shared vulnerability has been also advanced suggesting that personality, and in particular neuroticism, may be responsible for such a co-occurrence.[20]

Finally, according to Berkson's bias (ie, a type of selection bias that may occur in case-control studies when controls are selected within the hospital instead of from the

general population), the illusion of relationship due to an overrepresentation of patients with both disorders can be hypothesized. However, this potential for bias applies only to clinical studies and not to those conducted in community samples.

Since matters may not be that clear-cut, the present article reviews the existing data on comorbidity between cigarette smoking/nicotine dependence and panic (either panic attacks or panic disorder with or without agoraphobia). The aim is to get a broader perspective on the relationship between panic and cigarette smoking and to identify the possible underlying etiologic mechanisms.

METHOD

A computerized search was carried out (PUBMED 1960–2008) using the key words *nicotine* AND *panic*, *tobacco* AND *panic*, and *smoking* AND *panic*. In addition, the reference lists from existing reviews and from the articles retrieved were inspected. Only English language articles published in peer-reviewed journals were included.

We included studies in the general population, in panic disorder with or without agoraphobia/panic attacks patients, and studies adopting experimental models for panic disorder, as these latter are particularly suited to elucidate possible underlying mechanisms of the co-occurrence between smoking and panic.

In epidemiologic surveys, statistical analyses had to be adjusted for comorbid psychiatric disorders different from nicotine dependence, if present.

In the general and clinical population studies, the diagnosis of panic disorder with or without agoraphobia had to be made according to the *Diagnostic and Statistical Manual of Mental Disorders* Third Edition, Revised (*DSM-III-R)*,[21] Fourth Edition (*DSM-IV),*[22] or Fourth Edition, Text Revision (*DSM-IV-TR*).[23] The definition of panic attacks had to conform to those proposed by the *DSM-III-R*, *DSM-IV,* or *DSM-IV-TR*.

A control group or a crossover design was required, except in epidemiologic surveys.

Studies were excluded when the data referred to *anxiety disorders* or *substance use disorders* in general.

In order to work with the most conservative approach possible, non-significant results or trends were reported as *no difference*.

RESULTS

Twenty-four studies, of the 61 screened, met our inclusion criteria. First, we present an overview of studies estimating the prevalence of the co-occurrence of cigarette smoking/nicotine dependence and panic attacks/panic disorder with or without agoraphobia. Second, we offer an overview of studies that examined the 3 causal models (from panic to smoking, from smoking to panic, and shared vulnerability) in turn. Finally, experimental studies using laboratory panic provocation procedures will be considered. These studies focus on the underlying mechanisms of the panic/smoking link.

To assist the reader, we report, in Table 1, the samples under study and the definitions of smoking status used and, in Table 2, the parameters measured and the primary results obtained in the studies included in the present review.

Co-Occurrence of Panic and Smoking

In an epidemiologic survey,[24] the lifetime frequency of panic disorder was higher among smokers than nonsmokers for women, while no difference was found for men. Moreover, in a subsample of the National Comorbidity Survey (NCS),[25,26] current and lifetime smokers had significantly higher rates of panic disorder with or without agoraphobia than respondents from the general population, when either lifetime or past-month occurrence was evaluated. Thus, subjects exposed to smoking, either currently or throughout their lifetimes, are at a higher risk of experiencing panic than the general population.

Studies conducted in clinical samples seem to confirm such a co-occurrence. Zvolensky et al[16] found that smokers who had panic disorder with or without agoraphobia reported a higher level of anxiety than nonsmokers who had panic disorder with or without agoraphobia. The authors proposed that smoking modifies the expression of panic disorder with or without agoraphobia by promoting more severe emotional disturbances. Indeed, smoking may confer a negative effect for specific anxiety-related symptoms, enhancing anxiety symptoms and worry about them. From this perspective, Zvolensky and coworkers suggested that smokers with panic disorder would not be more likely to have panic attacks than nonsmokers with panic disorder but would experience more frequent anxiety symptoms.

Four studies have compared the specificity of smoking and panic disorder versus other anxiety disorders. In a national household survey in Great Britain,[27] the prevalence of panic disorder in the nicotine-dependent population was significantly higher than in the nonnicotine–dependent population. Similar results were found for generalized anxiety and phobias.

With regard to the clinical samples, the prevalence of cigarette smoking was investigated in 5 groups of outpatients (ie, depressive disorder, panic disorder, social anxiety disorder, other anxiety disorders, and comorbidity disorders).[28] No significant differences were found.

McCabe et al[29] found different results when examining smoking behaviors among patients who had panic disorder with or without agoraphobia, social phobia, and obsessive-compulsive disorder (OCD). A significantly greater proportion of the panic disorder with or without agoraphobia group reported being a current smoker or a heavy smoker than the social phobia group and the OCD group.

Table 1. Study Populations and Definitions of Smoking Status in Studies of Cigarette Smoking and Panic Selected for Review

Study	Study Population	Definition of Smoking Status
Black et al[24]	First-degree relatives of psychiatric patients (n = 697) and normal controls (n = 360)	Nonsmoker = never smoked; smoker = all others
Lasser et al[25]	General population (n = 4,411)	Current smoker = smoked in the past month; lifetime smoker = smoked daily for at least 1 month
Zvolensky et al[16]	PD(A) patients (n = 140)	Smoker = smoked > 10 cigarettes/d; nonsmoker = smoked 0 cigarettes/d
Farrell M et al[27]	General population (n = 10,018)	Nicotine dependent = according to the *ICD-10*[44]
Lopes et al[28]	Outpatients (n = 262) and controls (n = 68)	Regular smoker = smoked for at least 4 weeks and still smoking at the time of the interview; exposed subject = smoked in lifetime; nonsmoker = all others
McCabe et al[29]	PD(A), social phobia, and OCD (n = 155)	Current smoker = consumed at least 1 cigarette/d for at least 6 months; past smoker = smoked in the past and was abstinent for at least the last 3 months
Goodwin et al[30]	Pregnant women reporting pregnancy in the past year (n = 1,516)	Nicotine dependent = according to the *DSM-IV*
Isensee et al[7]	General population (n = 3,021)	Nonsmoker = never used tobacco products lifetime; occasional smoker = used at least 1 tobacco product in lifetime but never on a daily basis for a period of at least 4 weeks; nondependent regular smoker = smoked cigarettes daily for at least 4 weeks but never met *DSM-IV* criteria for nicotine dependence, dependent regular smoker = smoked cigarettes daily for a period of at least 4 weeks and met *DSM-IV* criteria for nicotine dependence
Breslau et al[1]	General population (n = 1,007)	Nicotine dependent = according to the *DSM III-R*
Breslau et al[10]	General population (n = 4,411 in one sample; n = 1,007 in the other sample)	Daily smoker = smoked daily for 1 month or longer
Bernstein et al[31]	General population (n = 4,409)	Lifetime regular smoker = smoked in lifetime for at least 1 month; current regular smoker = smoked for at least the past month
Johnson et al[3]	General population (n = 688)	Sample stratified using a cutoff of 1 pack of cigarettes smoked/d during adolescence (< 1 pack/d n = 649; ≥ 1 pack/d n = 39)
Breslau et al[8]	General population (n = 4,411)	Pre-existing daily smoker = smoked 1 year or more before the year of onset of PD; past smoker = smoked 1 year or more before the onset of PD; current smoker = continued to smoke in the year of the onset of the disorder
Leen-Feldner et al[33]	General population (n = 249)	Current smoker = smoked in the previous 30 days
Pohl et al[17]	217 patients with PD(A) and 217 age- and sex-matched controls	Smoker = has used cigarettes daily regularly
Amering et al[2]	PD patients (n = 102)	Assessment of smoking status at the onset of panic: onset, duration, daily number of cigarettes, and changes in cigarette consumption over time
Reichborn-Kjennerud et al[34]	Female-female twin sample (n = 3,172)	Lifetime daily smoker = has used cigarettes daily regularly
Agrawal et al[35]	Monozygotic and dizygotic twin pairs, including opposite sex twins (n = 6,257)	Regular cigarette smoker = has smoked between 20 and 100 times in lifetime and as often as 1 or 2 days a week (or daily) for a period of 3 weeks or longer
Goodwin et al[36]	General population (n = 940)	Daily lifetime smoker and ever lifetime smoker on the basis of lifetime cigarette use, current frequency of cigarette smoking, and highest previous frequency of cigarette smoking
Zvolensky et al[37]	General population (n = 924)	Current regular smoker = has regularly self-reported smoking during the past month
Brooks et al[38]	17 PD(A) smokers and 22 PD(A) nonsmokers matched for age and sex	Nonsmoker = has been abstinent for at least 2 years; smoker = has had a regular habit of smoking more than 10 cigarettes/d for at least 6 months
Zvolensky et al[39]	Who regularly daily has used cigarettes PD regular smokers, 20 PD nonsmokers, 20 regular smokers without PD	Regular smoker = has smoked at least 10 cigarettes/d
Cosci et al[42]	Healthy nonsmokers (n = 33)	Nonsmoker = has smoked fewer than 10 cigarettes in lifetime and none in the last 5 years
Abrams et al[43]	24 heavy smokers in 12-hour nicotine withdrawal and 24 nonsmokers	Smoker = has smoked at least 20 cigarettes/d for at least 2 years, was nicotine dependent as indicated by a score of 5 or greater on the Fagerstrom Test of Nicotine Dependence, and has not attempted to cut back or quit smoking in the previous month; nonsmoker = has used fewer than 10 nicotine products in lifetime and none in the past 5 years

Abbreviations: *DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised, *DSM-IV = Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, ICD-10 = *International Statistical Classification of Diseases and Related Health Problems,* Tenth Revision, PD = panic disorder, PD(A) = panic disorder with or without agoraphobia.

Table 2. Parameters Measured and Primary Results in Studies of Cigarette Smoking and Panic Selected for Review

Study	Parameters Measured	Primary Results
Black et al[24]	Lifetime prevalence of PD smokers vs nonsmokers	Women: 5.6% vs 2.1%; OR = 2.8; 95% CI, 1.1–7.0
Lasser et al[25]	Lifetime prevalence of PD current smokers vs US population	35.9% vs 3.4%, $P < .001$
	Lifetime smokers vs US population	61.3% vs 3.4%, $P \leq .0001$
	Prevalence of PD in the past month	
	Current smokers vs US population	42.6% vs 4%, $P < .001$
	Lifetime smokers vs US population	63.5% vs 4%, $P < .0001$
Zvolensky et al[16]	Comparison of means	
	PD(A) smokers vs PD(A) nonsmokers	Beck Anxiety Index: 22.54 ± 13.23 vs 33.06 ± 16.49, $P < .01$
		Sheehan Patient Rated Anxiety Scale: 51.97 ± 27.81 vs 71.63 ± 33.79, $P < .05$
		Panic Disorder Severity Scale anticipatory anxiety about panic: 2.19 ± 1.17 vs 3.00 ± 1.20, $P < .05$
		Panic Disorder Severity Scale composite: 1.94 ± 0.78 vs 2.39 ± 0.96, $P < .05$
		Disability Scale social: 4.66 ± 2.83 vs 6.31 ± 3.18, $P < .05$
		Panic Disorder Severity Scale social interference: 1.57 ± 1.18 vs 2.47 ± 1.36, $P < .01$
		Days for gastrointestinal illness: 0 vs 0.65, $P < .01$
		Days for cardiovascular illness: 0 vs 0.37, $P < .05$
Farrell et al[27]	Prevalence of different anxiety disorders	
	Nonnicotine dependents vs nicotine dependents	PD: 0.5% vs 1.5%, $P < .001$
		GAD: 2.4% vs 4.1%, $P < .001$
		Phobias: 0.8% vs 1.5%, $P < .001$
Lopes et al[28]	Prevalence of cigarette smoking	
	Depressive disorder vs PD vs social anxiety disorder vs other anxiety disorders vs comorbidity disorders	Difference NS
McCabe et al[29]	Prevalence of current cigarette smoking	
	PD(A) vs SP	40.4% vs 19.6%, $P < .05$
	PD(A) vs OCD	40.4% vs 22.4%, $P < .05$
	Prevalence of heavy cigarette smoking	
	PD(A) vs SP	30.8% vs 14.3%, $P < .05$
	PD(A) vs OCD	30.8% vs 10.2%, $P < .05$
Goodwin et al[30]	Prevalence of PD(A)	
	Nicotine dependents vs nonnicotine dependents	3.0% vs 0.4%; OR = 3.1; 95% CI, 1.58–6.09
Isensee et al[7]	Baseline association between smoking status and PAs	
	Occasional smokers vs nonsmokers	2.0% vs 0.7%; OR = 3.0; 95% CI, 1.2–7.1
	Nonnicotine dependents vs nonsmokers	1.9% vs 0.7%; OR = 3.0; 95% CI, 1.1–8.0
	Nicotine dependents vs nonsmokers	7.6% vs 0.7%; OR = 12.8; 95% CI, 5.6–28.9
	Baseline association between smoking status and PD	
	Occasional smokers vs nonsmokers	1.3% vs 0.2%; OR = 9.8; 95% CI, 1.2–74.7
	Nonnicotine dependents vs nonsmokers	2.1% vs 0.2%; OR = 13.8; 95% CI, 1.7–108.6
	Nicotine dependents vs nonsmokers	3.8% vs 0.2%; OR = 28.0; 95% CI, 3.7–208.4
	Association between smoking status at baseline and new onset of PAs	
	Nonnicotine dependents vs nonsmokers	3.6% vs 1.4%; OR = 2.9; 95% CI, 1.0–8.9
	Nicotine dependents vs nonsmokers	4.4% vs 1.4%; OR = 3.6; 95% CI, 1.2–10.5
	Nicotine dependents vs occasional smokers	4.4% vs 2.0%; OR = 2.4; 95% CI, 1.0–5.2
	Association between panic and the subsequent onset of nicotine dependence	
	Cox regression with time-dependent covariates	PAs: HR 3.3, 95% CI, 2.5–4.5
		PD: HR = 3.3; 95% CI, 2.1–5.1
	Association between pre-existing panic and the risk of subsequent onset of smoking	
	Cox regression with time-dependent covariates	HR = 2.7; 95% CI, 1.7–4.2
	Association between nicotine dependence and the risk of subsequent onset of PAs	
	Nicotine dependents vs nonsmokers	HR = 2.7; 95% CI, 1.7–4.2
Breslau et al[1]	Risk of PD occurrence	
	Moderately dependent vs nondependents	OR = 2.86; 95% CI, 1.04–7.90
Breslau and Klein[10]	NCS	NCS
	Risk of lifetime association of PAs	Men: OR = 1.64; 95% CI, 1.10–2.50
		Women: OR = 1.69; 95% CI, 1.26–2.25
	Daily smokers vs nonsmokers	HR = 2.02; 95% CI, 1.47–2.77
	Smokers who had quit	HR=1.85; (95% CI, 0.98–3.50
	Persistent smokers vs nonsmokers	HR = 2.07; 95% CI, 1.49–2.87
	Risk of lifetime association of PD	
	Daily smokers vs nonsmokers	OR = 1.60; 95% CI, 1.27–2.18
	Prior daily smokers vs nonsmokers	HR = 2.93; 95% CI, 1.84–4.66
	Persistent daily smokers vs nonsmokers	HR = 3.18; 95% CI, 1.99–5.10
	Epidemiologic Study of Young Adults	Epidemiologic Study of Young Adults
	Risk of lifetime association of PAs	Men: OR = 3.13; 95% CI, 1.30–7.50
		Women: OR = 2.61, 95% CI, 1.66–4.09
	Daily smokers vs nonsmokers	HR = 3.96; 95% CI, 2.28–6.89
	Smokers who had quit	HR=0.21; (95% CI, 0.05–0.88
	Persistent smokers vs nonsmokers	HR = 4.71; 95% CI, 2.70–8.21
	Risk of lifetime association of PD	
	Daily smokers vs nonsmokers	OR = 4.24; 95% CI, 2.23–8.06
	Prior daily smokers vs nonsmokers	HR = 13.13; 95% CI, 4.41–39.10
	Persistent smokers vs nonsmokers	HR = 14.46; 95% CI, 4.81–43.50

(continued)

Table 2. (continued) Parameters Measured and Primary Results in Studies of Cigarette Smoking and Panic Selected for Review

Study	Parameters Measured	Primary Results
Bernstein et al[31]	Association between age at onset of daily smoking and risk of PD subsequent occurrence	OR = 0.92; 95% CI, 0.86–0.97
Johnson et al[3]	Risk of PD(A) occurrence	
	Subjects smoking > 20 cigarettes/d vs subjects smoking < 20 cigarettes/d	OR = 15.58; 95% CI, 2.31–105.14
	Risk of different anxiety disorders	
	Subjects smoking > 20 cigarettes/d in adolescence and early adulthood vs subjects smoking < 20 cigarettes/d	PD: OR = 7.55; 95% CI, 1.55–36.86 GAD: OR = 3.28; 95% CI, 1.42–7.61
	Risk in early adulthood	
	Subjects smoking > 20 cigarettes/d during adolescence vs subjects smoking < 20 cigarettes/d	PD: OR = 15.58; 95% CI, 2.31–105.14 Agoraphobia: OR = 6.79; 95% CI, 1.53–30.17 GAD: OR = 5.53; 95% CI, 1.84–16.66
Breslau et al[8]	Risk of subsequent onset of different anxiety disorders	
	Pre-existing daily smokers vs nondaily smokers	PD: OR = 2.6; 95% CI, 1.2–5.4 Agoraphobia: OR = 4.4; 95% CI, 2.3–8.0
	Risk of PD	
	Nicotine-dependent current smokers vs nondaily smokers	OR = 2.7; 95% CI, 1.2–6.0
	Elapsed time since quitting and risk of the first onset of psychiatric disorders	PD: OR = 0.5; 95% CI, 0.4–0.7
	Past daily smokers vs nondaily smokers	Agoraphobia: OR = 0.5; 95% CI, 0.5–0.8
Leen-Feldner et al[33]	Factors predicting an increased frequency of panic symptoms	Elevated fear: $\beta = .22$, $sr^2 = 0.02$, $t = 3.90$, $P < .01$ Being a smoker: $\beta = .10$, $sr^2 = 0.008$, $t = 2.19$, $P < .05$
Pohl et al[17]	Prevalence of smoking	
	PD(A) patients at the onset of the illness vs controls	51.6% vs 38.3%, $P = .005$ In women: 53.6% vs 35.1%, $P = .001$
	PD(A) patients at the time of the assessment vs controls	39.7% vs 24.5%, $P = .005$
	Mean age at onset of PD(A)	
	PD(A) patients at the time of the assessment vs controls	In men: PD(A) smokers 29.7 ± 10.1 y vs PD(A) nonsmokers 23.7 ± 12.9 y, $P < .0005$
Amering et al[2]	Mean age at onset of PD(A)	PD(A) smokers had lower age at PD(A) onset than PD(A) nonsmokers, $t = .63$, $P < .05$
Reichborn-Kjennerud et al[34]	Shared factors accounting for the covariance between cigarette smoking and panic	Best-fitting model Environmental factors that affect lifetime daily smoking vs those affecting lifetime panic (rc = 1) Common environmental factors accounted for 75% of the covariance Genetic factors affecting smoking and panic were distinct, ie, specific to each phenotype (ra = 0) Individual specific environmental factors affecting the 2 phenotypes overlap to a small degree (re = 0.25; 95% CI, 0.07–0.44) In the full model Environment factors were perfectly correlated and accounted for 61% of the covariance Genetic factors accounted for 18% of the covariance (ra = 0.17; 95% CI, 0.00–1.00)
Agrawal et al[35]	Correlates of regular smoking	History of PAs: HR = 1.45; 95% CI, 1.11–1.89
Goodwin et al[36]	Risk factors of PAs at the 24th birthday	Parental anxiety and parental smoking: OR = 3.3; 95% CI, 1.0–10.8
Zvolensky et al[37]	Risk factors of PD	Neuroticism and smoking: $\chi^2 = 4.73$, Wald = 4.15, $\beta = .00$, $P < .05$
Brooks et al[38]	Ipaspirone-induced increases in cortisol concentrations PD(A) smokers vs PD(A) nonsmokers	Data not shown, $P < .05$
Zvolensky et al[39]	Anxiety after the challenge and during recovery	
	Smokers with PD vs smokers without PD	B = 15.9, SE = 4.6, $P = .001$
	Smokers with PD vs nonsmokers with PD	B = 13.6, SE = 3.9, $P = .001$
	Bodily distress after the challenge and during recovery	
	Smokers with PD vs smokers without PD	B = 11.3, SE = 4.9, $P = .02$
	Smokers with PD vs nonsmokers with PD	B = 11.0, SE = 4.3, $P = .01$
Cosci et al[42]	Postpatch minus baseline values	Heart rate (beats/min): 6.242 ± 7.168 vs −3.515 ± 11.364, $P = .000$
	Healthy nonsmokers under nicotine vs healthy nonsmokers under placebo	Mean ± SD PSL score: 1.393 ± 2.249 vs −0.030 ± 3.450, $P = .003$
Abrams et al[43]	Over challenge values Smokers vs nonsmokers	Subjective breathlessness: $F_{1,44} = 69.95$, $P < .02$ Acute Panic Inventory: $t_{45} = 2.11$, $P < .04$

Abbreviations: GAD = generalized anxiety disorder, HR = hazard ratio, NS = not significant, NCS = National Comorbidity Survey, OCD = obsessive-compulsive disorder, OR = odds ratio, PAs = panic attacks, PD = panic disorder, PD(A) = panic disorder with or without agoraphobia, PSL = Panic Symptom List, ra = genetic correlation, rc = shared environmental effects, SP = social phobia, sr^2 = squared semipartial correlation.

Finally, Goodwin and coworkers[30] investigated the association between mental disorders and nicotine dependence among pregnant women. With regard to anxiety disorders, nicotine dependence significantly predicted the occurrence of panic disorder with or without agoraphobia, social phobia, specific phobia, and generalized anxiety disorder. However, after adjustments for demographic differences and comorbid Axis I and Axis II mental disorders were made, the only association that remained significant was between nicotine dependence and panic disorder with or without agoraphobia.

In brief, a specific relationship between panic disorder with or without agoraphobia (vs other anxiety disorders) and cigarette smoking/nicotine dependence seems to be still a matter of debate. Only 2 studies of the 4 described above supported a unique relationship between panic disorder with or without agoraphobia and cigarette smoking/nicotine dependence.

From Panic to Smoking

Isensee and coworkers[7] prospectively evaluated adolescents and young adults. This is, to our knowledge, the only study showing that subjects with pre-existing baseline panic attacks or panic disorder have an increased risk for onset of nicotine dependence.

From Smoking to Panic

Breslau and coworkers[1] evaluated a random sample of young adults and found that nicotine-dependent smokers are at a higher risk of developing panic than nonsmokers. Moreover, the higher the level of nicotine dependence, the higher the risk of panic.

When the NCS[23] and the Epidemiologic Study of Young Adults datasets[10] were analyzed, a significantly higher risk of panic occurrence (either panic attacks or panic disorder) was found in subjects with pre-existing smoking if compared to nonsmokers and in subjects who persist in smoking after panic onset compared to nonsmokers.

Examining subjects with a history of panic and a history of daily smoking, Bernstein et al[31] found that the earlier the age at onset of daily smoking, the greater the risk of developing panic disorder.

Longitudinal studies have found similar results. In one study, adolescents who smoked 20 cigarettes or more per day were at elevated risk of panic disorder with agoraphobia during both adolescence and early adulthood when compared with those who smoked fewer than 20 cigarettes per day.[3]

Nondependent regular smokers and dependent smokers were at higher risk of panic attacks than nonsmokers, and an elevated risk was maintained in dependent smokers when compared to occasional smokers.[7]

Current smokers, with or without nicotine dependence, were at higher risk of panic disorder occurrence than nonsmokers, while being a former smoker seemed to reduce such a risk. Examining the relationship between time elapsed since quitting and the risk of the first onset of panic disorder in past daily smokers, using a standardized variable that counts the number of years passed beginning with the year after quitting, researchers found that the likelihood of panic was reduced by one-half with each standard deviation unit of time elapsed since quitting.[8] Thus, the authors showed some evidence that smoking cessation might reduce the risk of subsequent panic.

Some hypotheses explaining the co-occurrence of smoking and panic have been proposed. Breslau and Klein[10] suggested that lung disease might be one of the mechanisms linking smoking to panic. By increasing the risk of lung disease, smoking might indirectly increase the risk of panic attacks. In addition, they found that, according to the false suffocation alarm theory,[14] cigarette smoking, by leading to chronic bronchitis and emphysema as well as to subclinical respiratory impairment, may favor panic attacks in subjects predisposed to overreaction to suffocation signals. Alternatively, they proposed that the carbon monoxide in cigarette smoke might affect the suffocation alarm threshold via inhibition of the carotid body.[32]

Another interesting hypothesis was put forth by Leen-Feldner et al.[33] Observing that smoking status was related to elevations in panic frequency among adolescents who were high in health fear, they suggested that, if a smoker experiences disease or illness, she or he may develop health fear, and exposure to smoke may increase attention to, and catastrophic misinterpretation of, bodily cues. Over time, the repeated pairing of fear with bodily cues may result in a learned association, such that somatic events ultimately elicit a panic-type response.

Examining clinical samples, Pohl et al[17] showed a rate of smoking in patients with panic disorder with or without agoraphobia at its onset significantly higher than the one observed in healthy controls. They also found a strong gender effect. Indeed, in women, smoking may promote panic disorder onset and persistence; in men, smoking may protect against panic disorder occurrence, since it delays its onset.

These results seem inconsistent with most of the findings presented here. Indeed, Pohl et al[17] suggested that smoking might be a risk factor for the development of panic disorder in women, while the relationship between cigarette smoking and panic disorder might not be a causal one in men. Thus, we argue that gender should be carefully considered in data analyses and interpretation of results.

In Amering et al,[2] smokers with panic disorder with or without agoraphobia were significantly younger at the onset of panic disorder with or without agoraphobia than nonsmokers with panic disorder with or without agoraphobia. Thus, age at panic onset should be taken into account in clinical population studies as well as in clinical practice.

Two studies have compared the specificity of smoking in promoting panic disorder among anxiety disorders. Johnson et al[3] found that adolescents who smoked 20 cigarettes or

more per day were at elevated risk for generalized anxiety disorder, during both adolescence and early adulthood, and at elevated risk for agoraphobia and generalized anxiety disorder during early adulthood. Breslau et al[8] showed a 4 times greater risk of onset of agoraphobia when associated with pre-existing smoking relative to nonsmoking. These results, consistent with other studies,[27,29] suggest that smoking is linked uniquely to panic among anxiety disorders.

Common Etiology of Shared Vulnerability

Reichborn-Kjennerud et al[34] investigated the hypothesis that a shared vulnerability can account for the relationship between cigarette smoking and panic. They examined shared genetic and environmental liability factors. The results suggest that genetic factors that influence panic and daily smoking appear to be distinct or weakly correlated, while shared environmental factors influencing the 2 phenotypes were highly similar.

Finding consistent results, Agrawal et al[35] examined monozygotic and dizygotic twin pairs and found that a history of panic attacks, together with other environmental factors (ie, parental education, parental smoking, early family influences, early life events, and conduct problems), was a significant predictor of regular cigarette smoking.

Goodwin and colleagues[36] focused more on heritability than environmental factors. They showed evidence of an interaction between parental smoking and parental anxiety's influencing the risk of co-occurrence of cigarette smoking and panic attacks among offspring. The authors propose possible explanations: (1) offspring with higher levels of parental anxiety disorders have an inherited (either genetic or environmental) vulnerability to anxiety, thereby they develop anxiety and subsequently begin smoking as a means of self-medication; (2) other behavioral factors associated with anxiety (eg, alcohol consumption) may increase the risk of cigarette smoking initiation; (3) initiation of cigarette smoking among individuals who are vulnerable to anxiety disorders may lead to development of panic attacks through anxiogenic effects or changes in respiratory functioning, and this risk may be more pronounced among those with a familial vulnerability to anxiety disorders; and (4) the risk of panic related to parental cigarette smoking may be, in part, attributable to changes in respiratory function resulting from exposure to environmental tobacco smoke early in life.

A moderational model studying neuroticism as a possible factor linking smoking and panic disorder was applied to a subsample of the NCS.[37] Current smokers high in neuroticism (ie, a generalized tendency to experience negative affect) smoked greater numbers of cigarettes per day and were the most apt to have a lifetime diagnoses of panic disorder. No such moderating effects were apparent for other anxiety disorders. According to Zvolensky and coworkers,[37] these data suggest that individual differences in theoretically relevant physiologic vulnerability factors (such as neuroticism) may amplify the effects of smoking in terms of panic-related problems.

Mechanisms Underlying the Panic/Smoking Link

The question of whether neurobiologic effects induced by serotoninergic agents are affected by the smoking status of panic disorder with or without agoraphobia patients was examined by Brooks et al.[38] The patients under study underwent a neuropharmacologic challenge with ipaspirone, a selective 5-hydroxytryptamine-1A receptor agonist, and a placebo according to a crossover design. In the group of panic disorder with or without agoraphobia smokers, the ipaspirone-induced increases in cortisol concentrations were about twice as high as in the nonsmoker group. Brooks and coworkers suggested controlling for smoking status in neuroendocrine challenge studies when comparing patients with different psychiatric disorders or patients with healthy controls. According to them, nicotine has to be considered as a psychopharmacological comedication exerting its own effects on certain brain receptors.

Zvolensky et al[39] evaluated anxious and fearful responses to bodily sensations as a function of panic disorder and smoking status. Participants completed a voluntary hyperventilation procedure that elicits panic-relevant bodily sensations. At the postchallenge assessment and recovery period, smokers with panic disorder reported greater levels of anxiety and bodily distress than smokers without panic disorder and nonsmokers with panic disorder. These findings suggested a slower recovery in term of anxiety for smokers with panic disorder than for nonsmokers with panic disorder. Thus, among subjects with panic disorder, a history of regular smoking is related to an increased risk of prolonged anxious responding to bodily sensations.

In recent years, experimental psychiatry has developed different paradigms that allow one to provoke panic in an experimental setting. The CO_2 inhalation procedure has proven to be a specific, valid, reliable, and safe way to produce experimental panic.[40] It appears that healthy individuals display a distinct behavioral vulnerability to increasing levels of acute hypercapnia. This effect is dose dependent, and it shares a striking similarity with the psychiatric condition of panic.[41]

Cosci et al[42] tested whether nicotine has a direct influence on laboratory-elicited panic in healthy nonsmoking volunteers. Subjects underwent a 35% CO_2 challenge after transdermal administration of a nicotine or placebo patch, according to a crossover design. Compared to the placebo condition, nicotine increased heart rate and panic symptoms prior to the CO_2 challenge but did not affect response to the CO_2 challenge itself. The change in physiologic measures before the challenge was attributed to nicotine's impact on autonomic activation.

In a study employing the Read rebreathing method, Abrams and colleagues[43] examined heavy smokers in

withdrawal and nonsmokers on subjective and physiologic reactivity to a 4-minute, 5% CO_2 challenge. Under the challenge condition, smokers experienced greater subjective breathlessness than did nonsmokers. Despite decreased respiration during the challenge, smokers experienced a significantly greater increase in self-reported cognitive and somatic panic symptoms than nonsmokers. The authors suggested that the findings are consistent with the idea that smoking may promote fearful responses to somatic sensations and, hence, may reflect a panic vulnerability factor.

Although Cosci et al[42] and Abrams et al[43] evaluated subjects without a diagnosis of panic disorder with or without agoraphobia, the 2 studies were not excluded since they are, to our knowledge, the only reports in the literature using a CO_2 challenge aimed at clarifying the relationship between smoking and panic.

Experimental studies are strongly heterogeneous in their methods but not in their results. They generally show that regular nicotine use in cigarette smokers or nicotine-dependent individuals leads to exaggerated challenge response, although nicotine use in nicotine-naive individuals does not.[42]

DISCUSSION

Panic and cigarette smoking each appear to have the capacity to serve as a causal factor/facilitator in the development of the other. For example, the bulk of the literature supports a strong relationship between smoking and panic. Few studies are in disagreement. For instance, Black et al[24] found no difference in panic occurrence between smokers and nonsmokers, but when the sample was stratified by gender, they observed such a difference in females. Further studies clarifying the role of gender are warranted.

A large body of literature suggests a specific relationship between smoking and panic relative to other anxiety disorders,* while few authors found such a relationship valid between smoking and other anxiety disorders.[3,7,8,27,28] However, it is worth noting that 5 of the 11 epidemiologic studies presented here were conducted within the framework of the NCS.[26] While the studies referring to the NCS sample strongly support the hypothesis of a specific relationship between smoking and panic, the majority of those referring to non-NCS samples also suggest a link with other anxiety disorders. Thus, the results may have been influenced by the sample under study. Further investigations in samples other than that of the NCS, as well as investigations comparing subjects with different affective diagnoses, are warranted.

The pathogenetic explanations of the co-occurrence between cigarette smoking and panic, highlighted in the studies presented here, refer mainly to 3 hypotheses. According to a moderational model, neuroticism is a third factor linking smoking to panic, as it moderates smoking frequency in subjects with a lifetime history of panic.[37] According to a pathoplastic model of dysfunction, smoking is a vulnerability variable that modifies the expression of panic disorder by exacerbating affective disturbances and negative health processes.[16,33,43] Finally, according to the false suffocation alarm theory, smoking, by increasing the risk of lung disease or impacting the carotid body, may induce an overreaction to suffocation signals and indirectly increase the risk of panic.[10] The first 2 hypotheses have been supported by several studies. However, replication studies mainly derive from the research group of Zvolensky and coworkers[16,33,37] or groups in joint venture with them.[43] Independent groups may lend support to the findings obtained.

With regard to the role of neuroticism, studying the personality of smokers versus nonsmokers who have panic disorder with or without agoraphobia would be fruitful. The idea that smoking may promote fearful responses to somatic sensations could be further developed in order to understand the mechanisms by which this process might occur and, hence, help to identify high-risk individuals. For example, it would be interesting to engage comorbid individuals at different levels of nicotine dependence in biologic challenges. Finally, the nature of the respiratory abnormalities in smokers/nonsmokers who have panic disorder with or without agoraphobia and healthy smokers/healthy nonsmokers should be compared to better understand the role of smoking in inducing clinical or subclinical abnormalities that may favor panic occurrence.

Some authors found a unidirectional relationship going from smoking to panic[1,2,8,31] Several causal mechanisms may explain this temporal relationship: (1) the biologic models according to which nicotine influences several neurochemical systems, (2) the cognitive perspective of panic attacks, and (3) the cardiovascular effects of nicotine misinterpreted as signs of danger, thus triggering panic attacks according to the Klein model.[14]

On the other hand, only one study showed a bidirectional relationship between smoking and panic.[7]

Experimental studies have been strongly heterogeneous in their methods but not in results. With the exception of Cosci et al,[42] they have consistently found that cigarette smoking increases fear reactivity to a biologic challenge, both in panic disorder patients and healthy volunteers. Cosci et al[42] found that nicotine causes an autonomic activation before a biologic challenge without affecting the response to the challenge itself. However, they studied nonsmokers, rather than smokers and nonsmokers, acutely exposed to nicotine or placebo.[43] Assuming that higher doses of CO_2 activate the same physiologic chain of events in panic-free individuals, CO_2 challenges may have a strong potential as a substitute for early clinical trials in testing novel pharmacologic compounds.[41]

*References 1, 2, 10, 16, 17, 25, 29, 31, 34–39.

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A few studies evaluated patients with a formal diagnosis of nicotine dependence.[1,7,8,27] Among these studies, consistency was found. Breslau et al[1] and Isensee et al[7] showed that the more severe the level of nicotine dependence, the higher the risk of comorbidity with panic. Farrell et al[27] and Isensee et al[7] found an association not only between nicotine dependence and panic but also between nicotine dependence and generalized anxiety disorder.

It is quite surprising that, although cigarette smoking has been classified among substance use disorders since the 1980s,[23,45] only a minority of studies in the present review referred to this formal diagnosis. Researchers more often defined cigarette smoking according to heterogeneous criteria; less often they assessed nicotine dependence via specific instruments, and only rarely did they use the diagnostic criteria for nicotine dependence. Thus, cigarette smoking seems to be considered a habit of life rather than a disorder. In this framework, it would be desirable to have a larger number of studies assessing nicotine dependence and using the formal diagnosis. This approach would focus on cigarette smoking as a clinically relevant disorder and shed some light on the pathogenetic mechanisms of the co-occurrence between nicotine dependence and panic. Moreover, this approach might have interesting implications for clinical practice and research. In clinical practice, it might encourage health care workers to consider cigarette smoking as a substance use disorder rather than as a habit of life, favor a proper diagnostic assessment, and promote quitting as well as preventive strategies. For research purposes, the use of similar inclusion criteria would very likely improve comparability between studies.

CONCLUSIONS

The above evidence suggests that a lifetime association between daily smoking and panic does exist and might reflect causal mechanisms.

Nicotine is a complicated molecule that promotes turnover of several neurotransmitters (eg, acetylcholine, dopamine, norepinephrine) and upregulates the receptors in critical brain areas (eg, the locus ceruleus, mesolimbic dopaminergic pathway).

The following additional studies are warranted: (1) epidemiologic and clinical studies comparing male and female subjects, (2) epidemiologic surveys utilizing new samples, (3) clinical studies comparing the relationship between smoking and panic with the relationship between smoking and other anxiety disorders, (4) experimental studies conducted in independent laboratories, (5) replication of studies focusing on shared vulnerability, and (6) systematic use of the diagnosis of nicotine dependence.

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