

Anxiety diagnoses in smokers seeking cessation treatment: relations with tobacco dependence, withdrawal, outcome and response to treatment

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ABSTRACT

Aims To understand the relations among anxiety disorders and tobacco dependence, withdrawal symptoms, response to smoking cessation pharmacotherapy and ability to quit smoking. **Design** Randomized placebo-controlled clinical trial. Participants received six 10-minute individual counseling sessions and either: placebo, bupropion SR, nicotine patch, nicotine lozenge, bupropion SR + nicotine lozenge or nicotine patch + nicotine lozenge. **Setting** Two urban research sites. **Participants** Data were collected from 1504 daily smokers (>9 cigarettes per day) who were motivated to quit smoking and did not report current diagnoses of schizophrenia or psychosis or bupropion use. **Measurements** Participants completed baseline assessments, the Composite International Diagnostic Interview and ecological momentary assessments for 2 weeks. **Findings** A structured clinical interview identified participants who ever met criteria for a panic attack ($n = 455$), social anxiety ($n = 199$) or generalized anxiety disorder ($n = 99$), and those who qualified for no anxiety diagnosis ($n = 891$). Smokers with anxiety disorders reported higher levels of nicotine dependence and pre-quit withdrawal symptoms. Those ever meeting criteria for panic attacks or social anxiety disorder showed greater quit-day negative affect. Smokers ever meeting criteria for anxiety disorders were less likely to be abstinent at 8 weeks and 6 months post-quit and showed no benefit from single-agent or combination-agent pharmacotherapies. **Conclusions** Anxiety diagnoses were common among treatment-seeking smokers and were related to increased motivation to smoke, elevated withdrawal, lack of response to pharmacotherapy and impaired ability to quit smoking. These findings could guide treatment assignment algorithms and treatment development for smokers with anxiety diagnoses.

Keywords Anxiety, cessation, smoking, tobacco dependence, treatment, withdrawal.

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INTRODUCTION

Approximately 55% of smokers have ever met criteria for a psychiatric disorder, and these smokers consume a disproportionately large number of cigarettes [1,2]. Considerable epidemiological research has elucidated connections among psychiatric disorders, smoking initiation, tobacco dependence and smoking cessation likelihood [3–5]. Much of this research has focused upon associations between smoking and either schizophrenia or depression [3,6,7].

Relatively little research has focused upon the relationship of anxiety disorders with tobacco dependence and smoking cessation. This inattention is surprising, given that 15–25% [8] of the more than 60 million smokers in the United States have had at least one anxiety disorder in their life-time. Similar to depression and schizophrenia, epidemiological research shows that anxiety disorders are more common among smokers than non-smokers. In fact, anxiety disorders may be as prevalent among smokers as is depression [9,10]. Moreover, anxiety may be associated more strongly with

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smoking than depression [11], and anxiety disorders may promote the transition from smoking to nicotine dependence [12] (cf. [9]). Finally, some research suggests that anxiety disorders may reduce quitting success [2,13], although the evidence is mixed on this point [9,12].

While both theory and epidemiological data suggest links between smoking and anxiety disorders, few smoking cessation clinical trials have explored this relation [14,15]. Existing theory suggests that anxiety disorders should be related to smoking outcomes and also suggests mechanisms that might explain the linkages. For instance, all anxiety disorders are associated with increased negative affect [16], and substantial evidence links negative affect to smoking motivation [17,18]. To the extent that negative affect either inflates the incentive value of smoking [19] or sets the stage for negative reinforcement [17], anxiety disorders should predict outcomes such as withdrawal severity and relapse (e.g. [20,21]). Other factors associated with anxiety disorders, such as coping deficits, may also influence smoking outcomes [22].

A large, recent clinical trial showed that smokers who ever met criteria for an anxiety disorder (assessed via clinical interview) had higher scores on some nicotine dependence measures and were less likely than other smokers to be abstinent at 8 weeks and 6 months post-quit [23]. However, that paper [23] examined anxiety disorders as an undifferentiated entity and did not examine relations of specific anxiety disorders with smoking measures, nor did it assess the relations of anxiety disorder with withdrawal symptomatology or treatment response.

It is important to examine associations of specific anxiety disorders because such disorders differ from one another on multiple dimensions, including electrophysiological correlates [24], genetic underpinnings [25] and natural history [26]. Therefore, it is possible that anxiety disorders differ from one another in terms of their relationship with smoking outcomes. In fact, recent epidemiological research has shown that they may be related differentially to smoking behavior [27]. Structural models based upon substantial evidence (e.g. genetic, developmental and covariance structure analyses) suggest that anxiety disorders differ in their causal influences, symptom covariation and comorbidities. One prominent model [16] categorizes anxiety disorders into 'distress' disorders (e.g. generalized anxiety disorder; GAD) which are characterized, in part, by especially strong associations with mood disorders and personality traits [28]; and 'fear' disorders (e.g. panic disorder, social

phobia) characterized, in part, by their exaggerated startle reactions to stressors [29]. However, both types are influenced by a general negative affectivity factor [30].

Despite theoretical support for an association between anxiety disorders and smoking outcomes, little research implicates specific mechanisms in that association. However, some recent research [27,31] suggests that GAD and social anxiety disorder (SAD) in particular may be related to smoking relapse due to especially intense negative affect and affective regulation difficulties. Also, consistent with anxiety sensitivity theory [32], fear of anxiety symptoms has been linked with smoking and an inability to tolerate withdrawal symptoms [15] (cf [9]).

The current paper uses the same large clinical trial sample referred to above [23,33], and extends the previous findings by investigating how specific anxiety diagnoses relate to a broader range of tobacco-related outcomes: dependence, withdrawal symptoms, treatment response and cessation success. If anxiety-smoking linkages are due to features shared across the disorders (negative affect), we would expect to see similar relations across all the tested disorders. However, if anxiety-smoking linkages are due to features that differ meaningfully across disorders (e.g. trait neuroticism, anxiety sensitivity), we might expect to see highly configural patterns. In this secondary data analysis, we analyze three specific anxiety diagnoses: panic attacks, SAD and GAD, all of which are relatively common in the United States¹ and have higher smoking rates than occur in people with no psychiatric diagnoses [2]. To the best of our knowledge, this is the first clinical trial to use structured clinical interviews to diagnose specific anxiety disorders prospectively among smokers, and then to follow these smokers through the course of a cessation attempt, including collecting real-time measures of withdrawal symptoms.

METHODS

Recruitment and inclusion/exclusion criteria

Participants were recruited via TV, radio and newspaper advertisements, community flyers and earned media (e.g. radio and TV interviews, press releases) in the greater Madison and Milwaukee, WI, areas. Primary inclusion criteria included: smoking at least 10 cigarettes per day for the past 6 months and being motivated to quit smoking. Exclusion criteria included: certain medications [including monoamine oxidase (MAO) inhibitors,

¹These anxiety diagnoses were selected based on theoretical and empirical considerations regarding their relations with tobacco dependence and cessation. Other anxiety diagnoses (e.g. specific phobias, obsessive compulsive disorder, post-traumatic stress disorder) were not assessed in an attempt to alleviate participant burden and to minimize participant distress (e.g. as with PTSD assessment).

bupropion, lithium, anticonvulsants and antipsychotics]; any history of psychosis, bipolar disorder or an eating disorder; consuming six or more alcoholic beverages daily 6 or 7 days a week; pregnancy or breast-feeding; and a serious health condition that might prevent study completion. This study was approved by the University of Wisconsin Health Sciences Institutional Review Board.

Procedure

Participants who passed a telephone screen were invited to an information session; a study description was provided and written informed consent was obtained. Next, participants completed multiple baseline screenings, including a medical history screening, vital signs measurements and a carbon monoxide (CO) breath test. Participants also completed demographic, smoking history and tobacco dependence questionnaires and the World Mental Health Survey Initiative version of the Composite International Diagnostic Interview (CIDI [34]).

Eligible participants were randomized to one of six treatment conditions: bupropion SR ($n = 264$); nicotine lozenge ($n = 260$); nicotine patch ($n = 262$); nicotine patch + nicotine lozenge ($n = 267$); bupropion SR + nicotine lozenge ($n = 262$) or placebo (five placebo conditions that matched the five active conditions; $n = 189$). All medications were provided for 8 weeks post-quit except the nicotine lozenge which was provided for 12 weeks post-quit (consistent with prescribing instructions). Randomization was conducted in a double-blind fashion using a blocked randomization scheme blocking on gender and race (white versus non-white). All participants received six individual counseling sessions (each lasting 10–20 minutes), designed to provide social support and training in problem-solving and coping skills. Bachelor-level case managers provided manualized counseling and were supervised by a licensed clinical psychologist.

Measures

Baseline assessments

Participants completed questionnaires that assessed characteristics including gender, ethnicity, age, marital status, education level, employment and smoking history features such as number of cigarettes smoked per day, age at smoking initiation and number of prior quit attempts. They also completed the Fagerström Test of Nicotine Dependence (FTND; $\alpha = 0.61$) [35] and the Wisconsin Inventory of Smoking Dependence Motives (WISDM) [36] to assess tobacco dependence. The WISDM yields primary dependence motives (PDM; $\alpha = 0.82$) and secondary dependence motives (SDM; $\alpha = 0.85$) [37].

The PDM assesses the degree to which smoking is heavy, automatic, out of control and related to significant craving—factors that may represent the core of dependence [37]. The SDM assesses auxiliary motives such as smoking because of environmental influences, or smoking to control mood or hunger.

Ecological momentary assessment (EMA) reports

Participants completed EMA reports twice a day (just after waking and prior to going to bed) for 1 week pre-quit and 1 week post-quit. EMA reports assessed smoking, withdrawal symptoms and affect in the last 15 minutes, number of alcoholic drinks consumed that day, stress and temptation events since the last prompt, self-efficacy, motivation and cessation fatigue (i.e. 'I'm tired of trying to quit smoking') in the last 15 minutes.

World Mental Health Survey initiative version of the Composite International Diagnostic Interview (CIDI)

The CIDI [34], a structured clinical interview with good to excellent reliability [38], was administered by certified study personnel using computer-assisted personal interviews (CAPI), version 20. The CIDI provided both past-year diagnoses (i.e. within the last 12 months) as well as ever diagnoses (i.e. ever in the participant's life-time, including in the past year) for various disorders, including: panic disorder, SAD, GAD, substance use disorders and depression. The analyses presented in this paper are based on 'ever diagnoses' except where noted.

Cessation outcomes

The cessation outcomes were: initial cessation (defined as 24 hours of abstinence in the first week of the quit attempt), and CO-confirmed 7-day point-prevalence abstinence at 8 weeks and 6 months post-quit. Alveolar CO was assessed using a Bedfont Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) and smokers with a CO < 10 parts per million (p.p.m.) were considered abstinent.

Analytical plan

Analyses were conducted using Predictive Analytics Software (PASW) Statistics version 17.0 (SPSS Inc, Chicago, IL, USA) unless noted otherwise. Unless specified, smokers with specific anxiety diagnoses were compared to smokers who had never met criteria for an anxiety diagnosis, although they may have met criteria for other psychiatric diagnoses—e.g. substance use disorder. We conducted independent-samples *t*-tests to compare dependence indices for each anxiety diagnosis group versus the no anxiety diagnosis group and

one-way analyses of variance (ANOVAs) with *post-hoc* Tukey tests using anxiety diagnosis as a categorical variable (i.e. panic attacks, SAD, GAD, more than one anxiety diagnosis and no anxiety diagnosis) to assess differences in dependence among the anxiety diagnoses. We analyzed the EMA withdrawal data using hierarchical linear modeling to estimate four withdrawal parameters: (i) mean pre-quit level, (ii) pre-quit slope, (iii) increase on the quit day and (iv) post-quit slope. We conducted independent-samples *t*-tests to determine the differences in empirical Bayes' estimates of these withdrawal parameters for each of the three anxiety diagnosis groups versus the no anxiety diagnosis group. Logistic regression was used to determine the relation of ever meeting criteria for an anxiety diagnosis to cessation outcome with treatment, gender, race and age as covariates. We also conducted logistic regression analyses with all three anxiety diagnoses included in the model to assess orthogonal variance in cessation due to the different specific diagnoses.

RESULTS

Of the 1504 participants, 579 (38.5%) ever met criteria for at least one anxiety diagnosis (Table 1) and 205 (13.6%) participants met criteria for an anxiety diagnosis within the last 12 months. It should be noted that no participants met criteria for panic disorder, which requires a month or more of either concern about having more panic attacks or worry about the implications of the attacks or making a significant change in behavior related to the attacks [26]. With respect to comorbidity, GAD had the most frequent co-occurrence with another anxiety disorder (only 30% had a life-time history of GAD only), and smokers with a life-time history of GAD had substantially higher rates of life-time depression than did smokers with life-time panic attacks or SAD. The rates of

life-time substance use disorders were similar across the three anxiety diagnoses (Table 1). Women were more likely than men to have ever met criteria for an anxiety diagnosis ($P < 0.01$), but there were no racial differences across the diagnostic groups (Table 2).

Dependence indicators

Results revealed no differences between each anxiety group, relative to the no anxiety diagnosis group, in number of cigarettes smoked, baseline CO, pack years, age began daily smoking, age at first cigarette or number of previous quit attempts. The anxiety groups scored higher on the FTND and WISDM PDM and SDM subscales, with the exception of the panic attack diagnosis FTND scores (Table 2). The results were similar after controlling for gender using a one-way analysis of covariance (ANCOVA). Logistic regression revealed that when PDM and SDM were entered simultaneously as predictors of diagnosis (e.g. panic attack versus no anxiety disorder), only the SDM was related significantly to diagnosis for panic attacks and SAD, but both PDM and SDM were related significantly to GAD. Finally, anxiety diagnoses did not differ from one another on any of these dependence indicators.

Withdrawal

Figure 1a,b illustrates the withdrawal and cessation fatigue curves for the different diagnostic groups. Independent-samples *t*-tests were conducted to compare diagnostic groups with regard to mean level of pre-quit symptoms, pre-quit slope, quit-day increase and post-quit slope for craving, negative affect, positive affect, total withdrawal and cessation fatigue. All the parameters were significantly different from zero, with a few exceptions: i.e. pre-quit slope of craving; pre-quit and post-quit slope of positive affect; and post-quit slope and quit-day

Table 1 The number (and %) of smokers within different life-time anxiety diagnostic categories who also received life-time comorbid anxiety, depression or substance use disorder diagnoses.

<i>Comorbid diagnoses</i>	<i>Never met criteria for an anxiety diagnosis (n = 891)</i>	<i>Ever met criteria for a panic attack (n = 455)</i>	<i>Ever met criteria for social anxiety disorder (n = 199)</i>	<i>Ever met criteria for GAD (n = 99)</i>
Never met criteria for an additional anxiety disorder	–	317 (69.7%)	82 (41.2%)	30 (30.3%)
Ever met criteria for panic attacks	–	–	81 (40.7%)	33 (33.3%)
Ever met criteria for social anxiety disorder	–	81 (17.8%)	–	12 (12.1%)
Ever met criteria for GAD	–	33 (7.3%)	12 (6.0%)	–
Ever met criteria for both of the other anxiety disorders	–	24 (5.3%)	24 (12.1%)	24 (24.2%)
Ever met criteria for depression	83 (9.3%)	136 (29.9%)	75 (37.7%)	56 (56.6%)
Ever met criteria for a substance use disorder	456 (51.2%)	282 (62.0%)	135 (67.8%)	65 (65.7%)

Data should be read down columns such that rows represent comorbid diagnoses within a column's diagnostic category. The percentages do not sum to 100% because of the occurrence of more than one comorbid anxiety diagnosis (e.g. three anxiety diagnoses). GAD: generalized anxiety disorder.

Table 2 Demographics and tobacco dependence means (SD) by anxiety category.

Dependence and other variables	Never met criteria for an anxiety diagnosis (n = 891)	Ever met criteria for a panic attack (n = 455)	Ever met criteria for social anxiety disorder (n = 199)	Ever met criteria for GAD (n = 99)	Ever met criteria for >1 anxiety disorder (n = 150)
% Women	54.1	65.9**	63.3*	69.7**	67.3**
% White	84.7	82.8	84.3	77.8	81.3
Cigarettes/day	21.63 (9.17)	20.95 (8.55)	21.03 (8.36)	22.49 (9.34)	20.95 (8.39)
Pack years	30.02 (21.20)	27.88 (18.50)	29.02 (18.36)	31.55 (21.07)	28.45 (18.32)
Age at first cigarette	14.65 (3.71)	14.33 (4.05)	14.13 (4.10)	14.96 (5.91)	14.59 (5.46)
Age began smoking daily	17.45 (4.02)	17.16 (4.32)	17.28 (4.03)	17.74 (5.90)	17.57 (5.37)
Baseline CO	25.55 (11.37)	26.20 (14.06)	25.49 (13.13)	26.86 (14.75)	25.91 (14.40)
FTND	5.31 (2.11)	5.46 (2.21)	5.74** (2.19)	6.01** (2.14)	5.86** (2.24)
WISDM primary dependence motives (PDM)	4.82 (1.19)	5.09** (1.14)	5.15** (1.16)	5.32** (1.15)	5.24** (1.15)
WISDM secondary dependence motives (SDM)	3.65 (1.06)	3.99** (1.04)	4.12** (1.15)	4.12** (1.14)	4.09** (1.11)

GAD: generalized anxiety disorder. * $P < 0.05$ for comparison with the group that never met criteria for an anxiety diagnosis; ** $P < 0.01$ for comparison with the group that never met criteria for an anxiety diagnosis. CO: carbon monoxide; FTND: Fagerström Test of Nicotine Dependence; WISDM: Wisconsin Inventory of Smoking Dependence Motives.

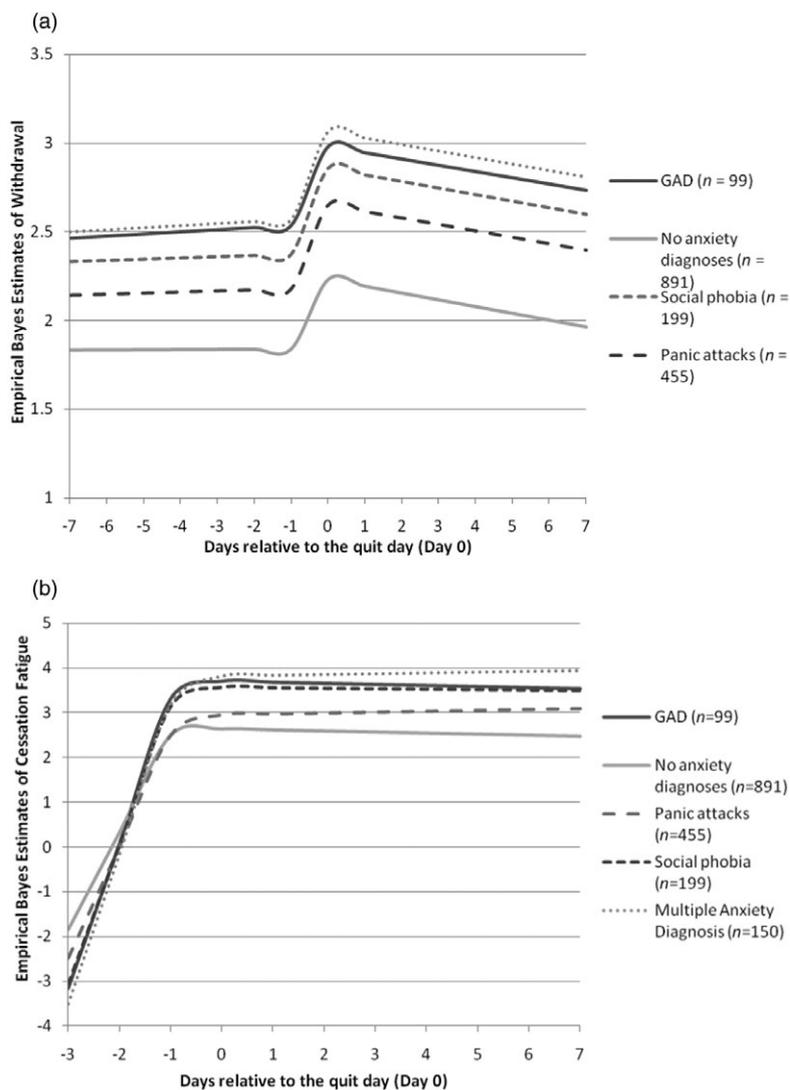


Figure 1 (a) Withdrawal curves for different life-time anxiety diagnoses; (b) cessation fatigue curves for different life-time anxiety diagnoses. GAD: generalized anxiety disorder

increase of cessation fatigue. Relative to smokers with no anxiety diagnosis, smokers who had ever had panic attacks had higher levels of pre-quit negative affect and withdrawal and an increasing post-quit slope of cessation fatigue. Smokers ever diagnosed with GAD had higher pre-quit levels of craving, negative affect, withdrawal and cessation fatigue and steeper pre-quit slopes and quit-day increases in cessation fatigue. Smokers ever diagnosed with SAD had higher pre-quit levels of craving, negative affect, withdrawal and cessation fatigue, greater pre-quit increases in cessation fatigue leading up to the quit day and greater quit-day increases in cessation fatigue.²

Cessation

Smokers who had a panic attack in the past year—but not smokers who had a panic attack prior to the past year—showed a decreased ability to establish initial cessation [odds ratio (OR) = 0.45, $P = 0.003$, 95% confidence interval (CI) = 0.27–0.76]. No other anxiety diagnostic category predicted initial cessation. Analyses of 8-week and 6-month abstinence were conducted with the no anxiety group as the comparison, and controlling for age, race, gender and treatment (Table 3).³ Having ever had a panic attack or multiple anxiety diagnoses was associated with worse cessation outcomes at both time-points. Ever having SAD was related to poorer outcomes at the 6-month but not at the 8-week follow-up. Ever having GAD predicted lower abstinence rates at 8 weeks but not 6 months post-quit (these findings were replicated when using depression as a covariate, to control for the high rate of depression in GAD). Analyses using either

past-year or prior-to-past-year diagnostic categories produced similar results to the above pattern, but some obtained relations were no longer significant due to reduced power. When all three diagnostic categories were entered into the regression models as predictors, ever meeting criteria for a panic attack was the only significant predictor of 8-week and 6-month outcome (data not shown).

We examined interactions between anxiety diagnoses (i.e. ever meeting criteria) and treatment. Treatments were collapsed into placebo, monotherapy and combination therapy conditions because sample sizes were too small (e.g. $n = 11$ with GAD in the placebo group) to permit comparisons of individual treatments. At the 6-month follow-up there was a significant interaction between ever meeting criteria for one of the three anxiety diagnoses and treatment (Wald = 6.15, $P = 0.05$; see Fig. 2). There was a similar, but not significant, pattern at 8 weeks (Wald = 4.58, $P = 0.10$). Similarly, there were significant interactions between treatment and both panic attacks (Wald = 7.32, $P = 0.03$) and SAD (Wald = 6.64, $P = 0.04$) at 6 months, but not at 8 weeks. There were no significant treatment-by-GAD interactions in predicting outcome at either 8 weeks or 6 months. This pattern of interaction effects led us to examine 6-month treatment effects within the anxiety and non-anxiety diagnosis groups. Logistic regressions, controlling for gender, revealed a significant effect of monotherapy (OR = 2.35, $P = 0.001$) and combination (OR = 3.21, $P < 0.001$) pharmacotherapy compared to placebo in the non-anxiety group, but no treatment effects in the anxiety group (OR = 0.98 and 1.11).

Table 3 Logistic regression prediction of 8-week and 6-month abstinence outcomes, comparing participants ever versus never meeting criteria for an anxiety diagnosis, controlling for treatment, gender and race.

	Outcome	% Abstinent	Wald	P	OR	95% CI
Never met criteria for an anxiety diagnosis ($n = 891$)	8 weeks	46.6				
	6 months	36.0				
Ever met criteria for a panic attack ($n = 455$)	8 weeks	39.3	6.23	0.01	0.74	0.58–0.94
	6 months	27.3	8.91	<0.01	0.68	0.53–0.88
Ever met criteria for social anxiety disorder ($n = 199$)	8 weeks	41.7	2.05	0.15	0.79	0.57–1.09
	6 months	28.6	4.00	0.05	0.70	0.50–0.99
Ever met criteria for generalized anxiety disorder ($n = 99$)*	8 weeks	34.3	5.23	0.02	0.59	0.38–0.93
	6 months	28.3	1.97	0.16	0.71	0.45–1.14
Ever met criteria for more than one anxiety disorder ($n = 150$)	8 weeks	37.3	4.37	0.04	0.68	0.47–0.98
	6 months	26.0	4.52	0.03	0.65	0.44–0.97

*When controlling for depression, generalized anxiety disorder (GAD) continued to predict 8-week outcome [Wald = 3.73, $P = 0.05$, odds ratio (OR) = 0.62, 95% confidence interval (CI) = 0.38–1.007] but not 6-month outcome.

²The results were similar after controlling for gender using an ANCOVA to predict differences in the empirical Bayes' estimates of the withdrawal parameters among diagnoses.

³The results were the same without controlling for the covariates.

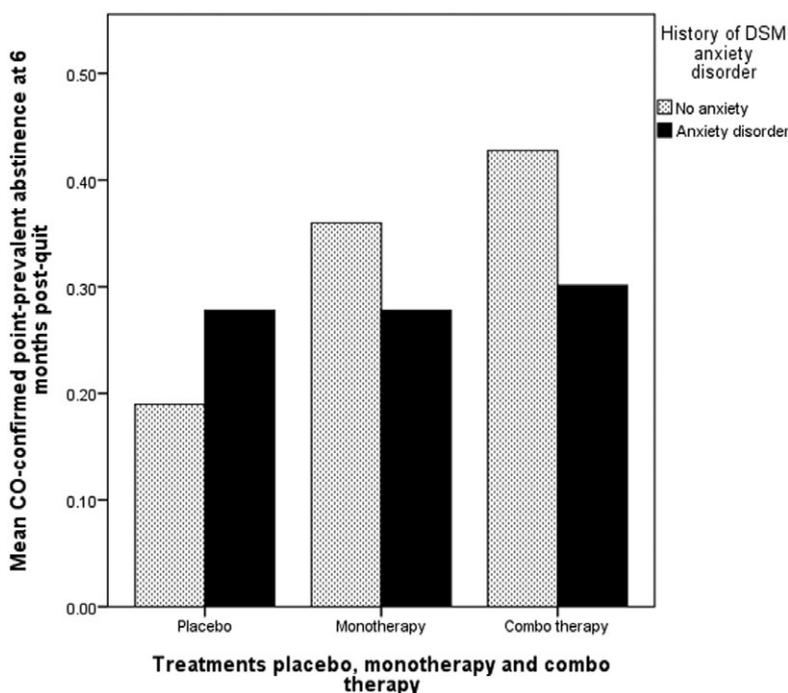


Figure 2 Abstinence rates at 6 months post-quit by treatment (combination therapy versus monotherapy versus placebo) and ever meeting criteria for an anxiety diagnosis (of panic attacks, social anxiety disorder or generalized anxiety disorder). DSM: Diagnostic and Statistical Manual; CO: carbon monoxide

DISCUSSION

This secondary data analysis found significant relations between specific anxiety diagnoses and nicotine dependence, severity of withdrawal symptoms, likelihood of cessation success and smoking cessation pharmacotherapy effectiveness. While there was some specificity between type of anxiety diagnosis and these outcomes, the weight of evidence suggested greater similarity than differences.

None of the anxiety diagnoses was related to measures of smoking heaviness, which have been associated with nicotine dependence. However, the three anxiety diagnoses tended to be associated reliably with higher self-reported measures of perceived dependence (i.e. the FTND, WISDM). Thus, while smoking heaviness is an important determinant of response to dependence questionnaires [39], it may be that these anxiety disorders increase smokers' reports of dependence-related symptoms over and above what would be expected by their level of smoking *per se*.

Examination of the PDM versus SDM WISDM composites shows that smokers with life-time anxiety diagnoses differ from other smokers principally on the SDM score. This suggests that smokers with these life-time anxiety diagnoses may be especially motivated to smoke for instrumental reasons (e.g. affect regulation, improved cognition) or that smoking serves a symptom management function. In addition, many questions on the SDM scales (and, to some extent, the FTND) elicit information about discomfort or distress, and smokers with anxiety disorders

may score more highly on distress-related questions regardless of their intended relevance to smoking. However, the associations with anxiety diagnoses were not restricted to the domain of symptom reports as they also extended to the behavioral domain (relapse/cessation).

Ever meeting criteria for any of the three anxiety diagnoses was also related to elevated real-time reports of withdrawal symptoms, especially in the pre-quit period. That these differences were seen in real-time reports suggests that differences are not due to people's global impressions, but rather reflect people's appraisal of their ongoing symptomatic experiences. While some differences were observed among the various specific disorders in withdrawal symptoms, in general the similarities were again greater than the differences (Fig. 1a). Such pre-quit differences in withdrawal symptom reports could reflect, in part, differences in tonic levels of symptoms experienced by the diagnostic groups as well as anticipation of cessation. The greater increases in cessation fatigue both before and after the quit day (see Fig. 1b) suggest that these smokers have reduced coping resources and resilience to deal with the challenge of quitting.

Smokers with the three life-time anxiety diagnoses tended to have lower likelihoods of long-term abstinence relative to smokers with no anxiety diagnoses. Ever meeting criteria for panic attacks was the only diagnostic category associated significantly with poorer outcomes at both 8 weeks and 6 months, but this appears to be due to statistical power rather than effect size. Smokers with a past-year panic attack were also less likely to achieve initial cessation. There was also a cumulative effect of

anxiety diagnosis on outcome. Specifically, smokers with more than one anxiety diagnosis constituted only 10% of participants, but they accounted for 44.4% of smokers who did not establish initial abstinence.

The present research provides strong evidence that all three anxiety disorders tested have significant relationships with smoking outcomes but does not implicate particular mechanisms in such relationships. That all three disorders were related to the outcomes suggests that factors common to anxiety disorders (e.g. subjective distress and arousal, worry, information processing biases [40]) account for the observed associations. It is tempting to forward negative affect as a potential mechanism. However, negative affect is not implicated directly and negative affect could be a proxy for numerous cognitive, behavioral and physiological phenomena associated with it [27,40–43]. For instance, relatively stable influences, such as cognitive processing biases, may be more germane [40,41,44]. Clearly, further research is needed to determine why anxiety disorders may place a smoker at higher risk for cessation failure.

Cessation pharmacotherapy appeared to be ineffective for smokers with anxiety diagnoses [14]. Relative to placebo treatment, combination pharmacotherapy doubled smokers' chances of success—unless the smoker had ever had an anxiety diagnosis. Neither monotherapy nor combination pharmacotherapy benefited smokers who had ever met criteria for one of the three anxiety diagnoses. Lack of power prevented a meaningful investigation of the relations of anxiety diagnoses and the effects of specific cessation medications, but an inspection of success rates across specific medications suggested a stable pattern; no medication treatment appeared to benefit individuals appreciably who received one of the three anxiety diagnoses.⁴

It is unclear why the medications did not benefit the individuals diagnosed with these disorders. However, recent evidence shows that the study medications produce relatively modest effects on negative affect, and that such effects do not mediate their effects on cessation outcomes [45,46] (cf. [47]). Perhaps individuals with a history of anxiety disorder might benefit from either drug or counseling treatments that address affect more effectively. Interestingly, the anxiety-diagnosed patients may have benefited more from counseling than did other smokers (cf. placebo condition in Fig. 2), encouraging exploration of special or more intensive counseling approaches with this population [48–50].

The association of anxiety diagnosis with a failure to respond to cessation pharmacotherapy warrants replica-

tion. If this null finding is replicated consistently it would contradict the 2008 PHS Clinical Practice Guideline on the Treatment of Tobacco Use and Dependence [51], which concluded that most smoking cessation treatments were similarly effective across different types of patients.

These findings have considerable clinical relevance. This work suggests that clinicians and researchers should assess anxiety disorder status if they wish to predict patients' withdrawal and likelihood of achieving abstinence. This research also suggests that relevant assessment need not focus upon recency of symptoms or on type of anxiety disorder, although number of anxiety disorders does seem to make a difference.

These findings must be interpreted in light of certain limitations. This research used smokers who were highly motivated to quit and willing to participate in an intensive smoking cessation trial. The study's structured clinical interview did not assess current symptomatology, which perhaps would have yielded stronger relations with some dependent measures. Many analyses used participants who never met criteria for one of the three assessed anxiety disorders as the comparison condition; however, these smokers may have met criteria for other (anxiety and non-anxiety) diagnoses that may have influenced dependence, withdrawal, treatment or outcome. Other anxiety disorders (specific phobias, obsessive-compulsive disorder and post-traumatic stress disorder) were not assessed, making it impossible to rule out additional comorbidity with these anxiety disorders. Finally, because patients were not assigned randomly to diagnostic categories, it is impossible to draw conclusive causal inferences about anxiety disorder effects.

In conclusion, this research found that ever meeting criteria for panic attacks, SAD or GAD was common among smokers participating in a smoking cessation clinical trial. Such diagnoses were not associated with smoking heaviness but were associated with self-reported tobacco dependence motives and elevated withdrawal symptoms prior to the quit day and elevated cessation fatigue while quitting. Finally, ever meeting criteria for one of these anxiety disorders was associated with heightened relapse risk and reduced benefit from smoking cessation pharmacotherapies.

Clinical trial registration

Smoking Cessation Medications: Efficacy, Mechanisms and Algorithms: NCT00332644. Available at: <http://clinicaltrials.gov/ct2/show/NCT00332644?term=NCT00332644&rank=1>

⁴Among smokers ever diagnosed with one of the three anxiety disorders, 6-months post-quit abstinence rates by treatment were: 27.8% (placebo), 26.4% (bupropion), 24.8% (lozenge), 32.6% (patch), 25.7% (bupropion + lozenge), and 34.5% (patch + lozenge); cf. Figure 2.

Declarations of interest

Megan E. Piper, Jessica W. Cook and Tanya R. Schlam have no potential conflicts of interest to disclose. Douglas E. Jorenby has received research support from the National Institute on Drug Abuse, the National Cancer Institute, Pfizer, Inc., Sanofi-Synthelabo and Nabi Biopharmaceuticals. He has received support for educational activities from the National Institute on Drug Abuse and the Veterans Administration, and consulting fees from Nabi Biopharmaceuticals. Timothy B. Baker has served as an investigator on research projects sponsored by pharmaceutical companies including Sanofi-Synthelabo, Pfizer, Inc. and Nabi Biopharmaceuticals.

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