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Biological challenge procedures used to study co-occurring nicotine dependence and panic disorder

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ABSTRACT

A wide array of biological challenge procedures – including carbon dioxide inhalation, hyperventilation, and breath holding – have been used to model panic in laboratory settings. Originally used to study developmental processes in panic disorder (PD), these procedures, along with nicotine patch administration and self-administered smoking, have recently been applied to help understand the etiology of co-occurring nicotine dependence and PD. The goals of the present paper are to review studies that have employed biological challenges to study the comorbid condition, identify the advantages and limitations of the various procedures, describe desirable outcome measures for use in biological challenges, and present recommendations for future challenge studies in this field. We argue that biological challenges, though in need of standardization, are useful for studying the development, maintenance, prevention, and treatment of comorbid nicotine dependence and PD.

Panic disorder (PD) and nicotine dependence are two disorders that readily lend themselves to laboratory manipulation. The explicit, discrete symptoms of panic can reliably be produced through a number of biological challenge procedures. Nicotine can be administered transdermally or by smoking, and recent smoking (or abstinence) can be biochemically verified with simple, inexpensive tests. In fact, a wide array of biological challenge procedures – including carbon dioxide (CO_2) inhalation, hyperventilation, breath holding, and stimulant administration – have been used to model panic in laboratory settings. Originally used to study developmental processes in PD, these procedures have more recently been applied to help understand the etiology of co-occurring nicotine dependence and PD. The goals of the present paper are to review studies that have employed biological challenges to study the comorbid condition, identify the advantages and limitations of the various procedures, describe desirable outcome measures for use in biological challenges, and present recommendations for future challenge studies in this field.

1. Respiratory challenge procedures

1.1. Carbon dioxide breathing challenges

Cohen and White (1950) were among the first to explore the relation between CO_2 and anxiety. They found that breathing a 4% CO_2 gas mixture for 12 min produced "anxiety attacks" among patients with "neurocirculatory asthenia" (akin to PD) though not among healthy controls. Little was made of this discovery until the 1980s when Gorman et al. (1984) reported that voluntary hyperventilation of a 5% CO_2 gas mixture (though not of room air) led to anxiety among PD patients, and, independently, Greiz and

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Vandenhout (1984) noticed that a single 35% CO_2 inhalation reliably produced anxiety in PD patients. Since then a number of other groups have reported that CO_2 inhalations induce uncomfortable somatic sensations (such as chest discomfort, dizziness, sweating, and shortness of breath) and panic attacks more often in panic patients than among healthy controls (e.g., Woods, Charney, Goodman, & Heninger, 1988). More commonly the balance of the gas mixture is pure oxygen (in part to avoid the confounding effect of hypoxia; see Li et al., 2006) although recently there has been a trend for the balance to be room air.

To clarify some terms, hypercapnia refers to having a high bloodstream level of CO_2. Respiratory acidosis occurs when hypercapnia and low blood pH levels are achieved by inhaling high concentrations of CO_2. Both breath holding challenges (discussed later) and CO_2 breathing challenges induce states of hypercapnia and respiratory acidosis. Interestingly, hyperventilation challenges (also discussed later) induce fear in individuals vulnerable to panic but do so by producing states of hypocapnia (having a low bloodstream level of CO_2) and respiratory alkalosis (in which a high blood pH level is achieved). To some, these findings indicate that the root cause of PD may be learned (fear) responses to unusual somatic sensations rather than hypercapnia per se (Barlow, 2002). A recent, alternative explanation posits that both hypercapnia and hypocapnia ultimately cause changes in pH levels, and this may be the common pathway in the similarity of their effects (Esquivel, Schruers, & Griez, 2008).

There are several reasons, though, why CO_2 challenges have become the most widely used means to induce lab panic. The procedure is easy to execute, non-invasive, and medically safe. Carbon dioxide readily crosses the blood-brain barrier, yet induced symptoms are brief. Panic attacks experienced are similar to naturally occurring ones with respect to symptoms, duration, and severity (Perna et al., 1994; Van den Hout, Van der Molen, Griez, Lousberg, & Nansen, 1987). Responses to the challenge within patients are consistent across time (Perna et al., 1994), and hypersensitivity to CO_2 exists in those with or at risk for PD, the first-degree relatives of those with PD, and individuals with one of a few other disorders (e.g., situational phobia, post-menstrual dysphoric disorder; Griez & Schruers, 1998).

Further, CO_2 challenges allow for the assessment of cognitive factors as they impact panic vulnerability. For example, whether participants are informed about the onset, duration, and potential symptoms/harmfulness of CO_2 breathing (i.e., predictability factors) can be experimentally manipulated (e.g., Abelson, Weg, Nesse, & Curtis, 1996). To assess the importance of control factors in provoking panic, participants can be given offset control (Van den Bergh, Vandendriessche, de Broeck, & Van de Woestijne, 1993), a dial that adjusts the inhaled CO_2 level (Abelson et al., 1996), or even a sham CO_2 control dial (Sanderson, Rapee, & Barlow, 1989). Applied to co-occurring nicotine dependence, researchers could vary the instructional set to further our understanding of how control, predictability, and expectancies affect panic vulnerability among smokers.

There are three primary techniques by which CO_2 is delivered in lab settings:

Single- or Double-Breath Inhalation. With this technique, participants take one or two vital capacity (maximum volume) inhalations of a 35% CO_2 gas mixture through a mask covering the nose and mouth. Compared with other CO_2 delivery techniques (described next), this technique produces the highest systemic CO_2 exposure (hypercapnia) but for the briefest duration. In fact the high CO_2 levels very rapidly produce hyperventilation and hence hypocapnia and respiratory alkalosis (Zandbergen, Pols, de Loof, Lousberg, & Greiz, 1989). Because this technique is the simplest and quickest of the three, more participants can be run in a fixed time period, premature challenge termination rarely occurs, and there is a lower possibility of losing participants to machine malfunction.

Steady-State Breathing. With this technique participants continuously breathe a steady-state level (typically 5 or 7%) of CO_2 for a fixed amount of time (e.g., 10 or 20 min) or until a panic attack occurs. The CO_2 can be delivered with a respiratory canopy in which a clear plastic hood is placed over the participant's head or though a gas mask with continuous positive air pressure that fits over the participant's nose and mouth. Of note, exit interviews have shown that the canopy itself leads some participants to feel "suffocated" or "trapped" (Sanderson & Wetzler, 1990). This could be considered advantageous if the goal is to produce panic attacks or examine the role of external danger cues; however, this could be considered disadvantageous if the aim is to isolate the specific anxiogenic properties of CO_2. With either delivery system, the participant experiences a state of hypercapnia and respiratory acidosis.

Rebreathing. With the Read rebreathing technique (named after its designer; Read, 1967), participants rebreathe (breathe in and out of a closed system) a gas mixture that typically starts with 5–7% CO_2 (e.g., Abrams et al., in press). The percentage of CO_2 in the system gradually increases as the individual continuously inhales from and exhales into the system through an oral mask, typically reaching levels 2–3% higher within 5 min (e.g., Abrams et al., in press). Of note, whether the gas mixture is initially 5% or 7% has a significant impact on panic rates. For example, Gorman and colleagues found that an initially-5% CO_2 gas mixture produced panic attacks in 29% of PD patients and 6% of controls whereas an initially-7% CO_2 gas mixture produced panic attacks in 68% of panic patients and 12% of controls (Gorman et al., 1988).

Supplies needed for this technique include a non-diffusing gas bag and a mouth-breathing, nasal-occluding, non-rebreathing (to ensure the gas circulates) face mask. Such a mask has little dead space, does not allow the participant to smell the gas mixture, and precludes the need for an anxiety-provoking noseclip (Askanazi, Foster, Hyman, Milic-Emili, & Kinney, 1980). As with steady-state breathing, participants reach a state of hypercapnia and respiratory acidosis.

To allow the identification of the specific effects of the gas mixture (vs. of environmental factors), participants can breathe room air through the mask before the experimenter remotely changes the inhalation source to the gas bag (e.g., through the inflation and deflation of balloon valves). With an advanced instrumentation module, respiratory measures, such as tidal volume, respiratory rate, and end-tidal partial pressure of CO_2 ($etpCO_2$, a measure of the concentration of CO_2 in exhaled air), can be assessed at fixed intervals and instantly downloaded onto a computer. Recording $eptCO_2$, though not absolutely necessary, allows the experimenter to check that the desired levels of CO_2 were administered and to use $etpCO_2$ values as a within-subject independent variable.

The primary advantage of the Read method is that participants are exposed to a wide range of CO_2 levels in a single experimental session and hence graphs showing changes in physiological, psychological, and behavioral parameters against changes in $etpCO_2$ can be constructed. A disadvantage of the technique is that, with increasing levels of CO_2, early termination becomes more likely, which can make comparisons of pre- to post-challenge change scores across participants challenging to interpret.

Relevant Panic/Smoking Studies. At least two studies have utilized CO_2 challenges in the investigation of panic and smoking. In one, heavy smokers who were physically and psychologically healthy were divided into those who in the past were able to quit for at least seven days ($n = 10$) and those who were unable to quit for that long ($n = 12$; Zvolensky, Feldner, Eifert, & Brown, 2001). All were administered a steady-state 20% CO_2 gas mixture for 25 s. Those unable to quit for long periods experienced heightened cognitive and affective (though not physiological) reactivity to the challenge.

In a study employing the Read rebreathing method, Abrams et al. (in press) examined 24 heavy smokers in nicotine withdrawal and 24 non-smokers on subjective and physiological reactivity to a 4-minute CO_2 challenge. Results indicated that, despite decreased respiration during the challenge, smokers experienced a significantly greater increase in self-reported panic symptoms than non-smokers. Such findings are consistent with the idea that smoking may promote fearful responding to somatic sensations and hence may be a panic vulnerability factor.

1.2. Breath holding challenges

Breath holding, of course, is a simple procedure requiring no specialized equipment. The duration of maximal breath holding had been thought to reflect tolerance to CO_2 or physical sensations, with shorter times reflecting lower tolerance. However, given that duration is highly influenced by initial arterial CO_2 levels (which tend to be low in those who chronically hyperventilate, such as panic patients), $etpCO_2$ at the first exhalation following maximal breath holding is now thought to better reflect tolerance to CO_2. For example, Rassovsky and colleagues found that, among PD patients, $etpCO_2$ after maximal breath holding but not duration of the breath holding predicted anxiety from a subsequent CO_2 rebreathing challenge (Rassovsky, Kushner, Schwarze, & Wangensteen, 2000). This group later showed that panic patients had lower $etpCO_2$ levels at maximal breath holding than healthy controls, indicating a lower tolerance to CO_2 (Rassovsky, Abrams, & Kushner, 2006).

It has been argued that, beyond assessing tolerance to CO_2 and/or bodily sensations, breath holding challenges also assess differences in stoicism and motivation. For example, in one study PD patients demonstrated the same breath holding duration as those with mood disorders and a shorter duration than healthy controls, reflecting perhaps the relevance of motivation (Van der Does, 1997). To eliminate the impact of stoicism and motivation, Roth and colleagues asked patients with PD, patients with generalized anxiety disorder, and healthy controls to hold their breath for fixed (standardized) durations (i.e., for 30 s 12 times, separated by 60 s of normal breathing; Roth, Wilhelm, & Trabert, 1998). The three groups reacted quite similarly across a range of affective and physiological measures. Because the panic group had lower baseline $etpCO_2$ levels, the authors concluded that breath holding for fixed durations, while minimizing motivational factors, may not adequately test CO_2 tolerance in those with PD.

Relevant Panic/Smoking Studies. Brown and colleagues found that smokers' maximum breath holding duration positively correlated with duration of past quit attempts (Brown, Lejuez, Kahler, & Strong, 2002), while Zvolensky and colleagues found no relationship between these variables (Zvolensky et al., 2001).

1.3. Hyperventilation challenges

Hyperventilation involves breathing in excess of metabolic needs (Rassovsky, Hurliman, Abrams, & Kushner, 2004) and leads to a state of hypocapnia and respiratory alkalosis (Nunn, 1987). When used as a biological challenge procedure, participants are typically instructed to breathe every 2 s for durations ranging from 3 min (Zvolensky et al., 2004) to 15 min (Gorman et al., 1988). Audiotaped instructions can be used to standardize the breathing tempo, and compliance can be examined through direct observation or physiological measurement (Zvolensky et al., 2004).

Voluntary hyperventilation may result in dyspnea, dizziness, faintness, paresthesia, tachycardia, sweating, and feelings of unreality (Hornsveld, Garssen, & van Spiegel, 1995). Although individuals with PD are more sensitive to hyperventilation challenges than those with GAD or social phobia (Rapee, Brown, Antony, & Barlow, 1992), there is substantial evidence that hyperventilation is a less potent anxiogen and panicogen than CO_2 breathing (Papp et al., 1997; Zandbergen, Pols, de Loof, & Griez, 1991). In one study voluntary hyperventilation produced panic attacks in 16% of PD patients while 66% of patients panicked in response to a 35% CO_2 challenge (Goetz, Klein, Papp, Martinez, & Gorman, 2001). One proposed explanation for the milder impact of hyperventilation is that it slowly results in respiratory alkalosis whereas CO_2-breathing rapidly results in respiratory acidosis (Zandbergen et al., 1991).

Because of its milder effects, hyperventilation may be more useful as a method of testing fear proneness than panic proneness. Additionally, because hyperventilation may be perceived as less aversive than CO_2 challenges, participant recruitment may be easier. Another advantage is the simplicity of the procedure.

Relevant Panic/Smoking Studies. At least two studies have utilized voluntary hyperventilation to study the relationship between panic and smoking. In one, researchers found that, among psychologically healthy smokers, acute nicotine withdrawal symptoms predicted anxiety reactivity to a three-minute hyperventilation challenge beyond other established predictors (negative affectivity, anxiety sensitivity, and nicotine dependence; Zvolensky et al., 2005). This study demonstrated that greater levels of nicotine withdrawal lead to greater perceived intensity of panic-relevant physical symptoms.

In another study, smokers with PD, smokers without PD, and non-smokers with PD engaged in a hyperventilation challenge (Zvolensky et al., 2004). Smokers with PD experienced greater increases in anxiety and bodily distress at post-challenge and recovery than the other two groups. There were no significant differences in autonomic responding to the challenge among the three groups. The authors concluded that hyperventilation promotes anxiety among smokers not through the production of more autonomic sensations but rather through cognitive and affective channels.

2. Pharmacologic challenge procedures

2.1. Nicotine patch challenges

Being administered transdermal nicotine results in slower absorption than smoking tobacco. In placebo-controlled challenge studies, one advantage of using patches over cigarettes is that it is easier initially to keep participants blind to condition. On the other hand, patches may cause nausea and vomiting in nicotine-naïve individuals resulting in premature patch removal (Cosci, Abrams, Schruers, Rickelt, & Griez, 2006).

Relevant Panic/Smoking Studies. In one study researchers examined whether nicotine promotes heightened reactivity to a CO_2 challenge in healthy non-smokers. The 35 participants underwent a single-breath 35% CO_2 challenge after the administration of a 10-mg nicotine patch on one test day and of a placebo patch on another test day (Cosci et al., 2006). Results indicated that nicotine, relative to the placebo, led to greater pre-challenge sympathetic activation (increases in blood pressure, heart rate, and physiological panic symptoms) though not pre-challenge subjective anxiety. Nicotine did not affect physiological or psychological reactivity to the CO_2 challenge itself. Future studies could repeat the protocol with more psychologically-vulnerable individuals (e.g., non-smokers with high anxiety sensitivity, high suffocation fear, or PD) to examine whether nicotine promotes CO_2 hypersensitivity in particular subgroups.

Another study examined, among 52 undergraduate smokers, the role of nicotine in attenuating anxiety and urge to smoke in response to imagined anxiety and smoking cues (Morissette, Palfai, Gulliver, Spiegel, & Barlow, 2005). Participants were administered a 21-mg nicotine or placebo patch and then deprived of smoking for 4 h. Not surprisingly, participants reported a greater urge to smoke during the absorption period when administered a nicotine (vs. placebo) patch. However, nicotine did not attenuate anxiety during the absorption period nor did it attenuate anxiety or urge to smoke in response to imagined cues. Thus, the study findings were inconsistent with the hypothesis that smokers in withdrawal are hypersensitive to anxiety- and smoking-relevant cues.

2.2. Smoking challenges

Recently-developed technology has enabled the measurement of various aspects of smoking topography. Cigarettes can be mounted onto mouthpieces containing pressure transducers, and pressure changes caused by inhalation permit the recording of puff volume, duration, and inter-puff interval (Breland, Evans, Buchhalter, & Eissenberg, 2002). As some evidence exists that anxiety influences smoking topography (Pomerleau & Pomerleau, 1987), this technology remains ripe for future research on smoking and panic. For example, to examine the extent to which somatic sensations promote and maintain smoking, smokers with PD and smokers without PD could undergo a placebo-controlled CO_2 challenge followed by a self-administered smoking period. More smoking in response to the CO_2 (vs. placebo) challenge would suggest that uncomfortable bodily sensations do promote or maintain smoking behavior.

3. Measures

When studying lab panic, it is desirable to utilize physiological, subjective, and behavioral measures of anxiety. Additionally, the judicious use of baseline variables (as potential moderator variables) can often assist with data interpretation.

3.1. Outcome measures

3.1.1. Physiological

The primary physiological measures used in studies of lab panic are respiratory. Minute ventilation is the product of respiratory rate and tidal volume. All three variables can be plotted against time or, to control for differences in CO_2 exposure, etpCO_2. Some researchers have found that changes in respiratory rate predict lab panic better than changes in tidal volume (e.g., Papp et al., 1997). Additionally, high breathing variability and low baseline pCO_2 (reflecting chronic hyperventilation) have been found to be potent predictors of panic (Papp et al., 1997). The Approximate Entropy Index, a nonlinear measure of breathing irregularity and useful outcome measure, was developed based on this knowledge (e.g., Caldirola, Bellodi, Cammino, & Perna, 2004). Smokers and PD patients show higher entropy in baseline respiratory patterns than healthy non-smokers.

Salivary cortisol, which is elevated during spontaneously occurring panic attacks (Bandelow et al., 2000), is sometimes used as a proxy for HPA activity. Smoking itself leads to a surge in cortisol activity (Kirschbaum and Strasburger, 1992), while acute withdrawal leads to a drop (Broocks et al., 2002). As such, it may be desirable for researchers who are not specifically studying the impact of withdrawal to have smoking participants smoke prior to challenge sessions in a controlled manner to minimize confounded data.

Skin conductance has been infrequently measured in panic challenge paradigms. To date, the evidence that this variable reliably correlates with panic vulnerability factors is mixed. For example, studies have variously found that skin conductance does not distinguish between those with PD, those with generalized anxiety disorder, and healthy controls during a breath holding challenge (Roth et al., 1998) but does distinguish those with PD from those with social phobia and healthy controls during a hyperventilation challenge (Wilhelm, Gerlach, & Roth, 2001). Heart rate is often studied as an outcome measure in panic studies. However, when using smokers in withdrawal in lab challenges, changes in heart rate are unlikely to parallel other measures of fear because nicotine withdrawal results in dampened heart rate (Hughes, Higgins, & Hatsukami, 1990).

3.1.2. Subjective

Symptom checklists, such as the Acute Panic Inventory (Gorman et al., 1984), are often used post-challenge to assess participants' subjective experience of anxiety and panic (e.g., Rassovsky et al., 2004). To continuously assess subjective breathlessness levels during lab challenges, researchers have utilized dials (e.g., ranging from "no breathlessness" to "maximal breathlessness"; Rassovsky et al., 2004) and computerized Borg-type scales (e.g., ranging from "no air hunger" to "intolerable air hunger"; Li et al., 2006). Questions have been raised, though, about the reliability and validity of self-report data on internal states during challenges. It has been hypothesized that scores may be influenced by education, intelligence, emotional insightfulness, panic history, and demand characteristics (Rassovsky & Kushner, 2003).

3.1.3. Behavioral

One behavioral measure of anxiety sometimes employed in lab studies is premature termination of the challenge itself. However, while premature termination should be recorded, it may be influenced by motivational factors and hence may not be a valid measure of anxiety (Ehlers, Margraf, & Roth, 1987). Other potential behavioral measures include the use of videotaping or motion sensors to detect participant movement or avoidance-type behaviors (e.g., eye contact with the CO_2 delivery apparatus). Alternatively, if participants are permitted to smoke either in anticipation of or following a panic challenge, several measures of smoking topography, including puff volume, duration, and inter-puff interval, can be electronically recorded.

3.1.4. Panic

The lack of standardization for defining lab panic has impaired comparison of panic rates across labs. Strict DSM-IV criteria (i.e., intense fear plus at least four other symptoms) may be overly inclusive in lab settings because most individuals exposed to CO_2 challenges experience discomfort and a number of physiological symptoms (Sanderson & Wetzler, 1990). As such, some researchers have required the presence of at least one cognitive symptom (e.g., the fear of losing control or going crazy) to establish lab panic (e.g., Gorman et al., 1988). Such a requirement can be justified as the vast majority of individuals with PD report cognitive symptoms during naturally occurring attacks (Barlow et al., 1985). Others have required an experimentally-observed "clear and sudden increase" in anxiety (Gorman et al., 1994) or an acknowledgment that the induced panic attack was "very similar or identical" to spontaneously occurring ones (Bradwejn & Koszycki, 1991). Barlow, Brown, and Craske (1994) proposed what is perhaps the most comprehensive set of requirements for lab panic: intense fear, terror, or discomfort; a crescendo of symptoms within 5 min; a measurable autonomic surge; and an urge to escape. Despite the comprehensiveness of this definition, it has not been widely employed in other labs. Finally, the issue of whether lab panic should be considered a categorical or dimensional construct has been raised (Rassovsky & Kushner, 2003).

3.2. Moderator variables

A number of individual difference variables have been found to or theorized to affect sensitivity to biological challenges. Including measures of them for use as potential moderator variables during data analysis is recommended. These variables can be roughly divided into the categories of smoking-related and anxiety-related.

3.2.1. Smoking-related variables

Rapidly lapsing after quitting smoking and having poor perceived health (e.g., as a result of smoking) are both associated with heightened anxiety in response to bodily sensations (Zvolensky et al., 2001). Additionally, level of nicotine dependence (measured by cigarettes smoked per day or a standardized dependence questionnaire such as the Fagerstrom Test of Nicotine Dependence; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) has been hypothesized to correlate with sensitivity to challenge tests (Abrams et al., in press). Smoking expectancies (e.g., sedation) and nicotine withdrawal expectancies (e.g., loss of control) may also affect sensitivity (Zvolensky et al., 2005), although these hypotheses await further testing.

3.2.2. Anxiety-related variables

Two anxiety-related characteristics are associated with hypersensitivity to biological challenges. Anxiety sensitivity, typically measured by the Anxiety Sensitivity Index (Reiss, Peterson, Gursky, & McNally, 1986), is the tendency to catastrophically interpret somatic manifestations of stress and anxiety. Suffocation fear, typically measured by the Suffocation Fear Scale (Rachman & Taylor, 1994), is the tendency to interpret benign changes in air quality and quantity as signaling impending suffocation. Elevated levels of anxiety sensitivity and suffocation fear predict heightened reactivity to CO_2 challenges in PD patients (Rassovsky et al., 2000). Additionally, among smokers, high anxiety sensitivity predicts early lapsing during quit attempts (Brown, Kahler, Zvolensky, Lejuez, & Ramsey, 2001). An argument has been made that trait anxiety or neuroticism should be measured in addition to anxiety sensitivity and suffocation fear to gauge whether higher-order or lower-order dimensions of negative affectivity confer the greater risk for CO_2 sensitivity (Zvolensky et al., 2001).

4. Future directions

Biological challenge procedures have the potential to shed light on etiologic and maintenance factors of the comorbid condition as well as on the efficacy of prevention and treatment approaches.

4.1. Etiology and maintenance

While smokers in withdrawal are more sensitive to bodily sensations and hence at greater risk for experiencing panic attacks than non-smokers (Abrams et al., in press), the mechanism(s) linking smoking to panic (e.g., chronic nicotine use, acute withdrawal, etc) needs to be further explicated. Toward this end, smokers in various stages of smoking and withdrawal (e.g., no withdrawal, acute withdrawal, prolonged abstinence) could be compared on CO_2 sensitivity. Additionally, nicotine and placebo patch groups could be included to help differentiate the psychological and pharmacologic effects of nicotine on CO_2 sensitivity. To examine maintenance (vs. etiologic) factors of the comorbid condition, these challenge studies could include smokers with PD and non-smokers with PD (Zvolensky et al., 2005).

4.2. Prevention and treatment

One model for a prevention study would be to provide standard smoking cessation to a group of panic-free smokers, while keeping others on a wait list, and examine between-group differences on CO_2 sensitivity as a measure of panic vulnerability. Treatment studies could involve the provision of cognitive, behavioral, and/or pharmacologic therapies to smokers with PD with short-term outcome measures including sensitivity to and the extent of smoking following a biological challenge. If a treatment were found to be successful, component analysis could be helpful for identifying the critical features of treatment. Preliminary studies suggest that exposure to somatic sensations associated with panic and with smoking withdrawal could be beneficial (Zvolensky et al., 2005). A longstanding and still unresolved issue is whether the two conditions should be treated serially, in parallel, or in an integrated fashion (Zvolensky, Schmidt, & Stewart, 2003).

4.3. Challenge methodology

Future research could also aim to improve the external validity of the challenge procedures themselves. Studies could compare the utility of various challenge paradigms including, for CO_2 studies, the dose of CO_2, length of the challenge, and whether breathing occurs in an open or closed system. Researchers could also examine the utility of various outcome measures (described earlier).

5. Conclusion

Respiratory and pharmacologic challenge procedures offer great potential for illuminating factors that cause and maintain the co-occurrence of PD and smoking. Judicious use of dependent and moderator variables is necessary to maximize a given study's potential. Greater standardization of equipment, protocol, and measures, including the definition of lab panic, would allow the comparison of findings across laboratories to be made with greater ease.

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