Commentary

Subjective Reactivity to Smoking Cues as a Predictor of Quitting Success

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Received August 24, 2011; accepted August 30, 2011

Abstract

Introduction: Acutely increased urge to smoke, or craving, in response to smoking cues (i.e., “cue reactivity”) is often believed to identify those less able to later quit smoking. Although absolute craving level can predict smoking behavior, smoking cue reactivity per se may not predict cessation outcome.

Methods: All clinical trials of cue reactivity and cessation outcome published before 2007 were identified and supplemented with a web-based search of clinical studies published after 2006, producing one additional trial. Examined were a total of 6 studies that directly related self-reported craving in response to laboratory-presented smoking cues with subsequent ability to quit smoking.

Results: Of the 6 studies, only one found that lower cue reactivity predicted greater quitting success (with nicotine but not placebo patch). Another study found the opposite, that higher cue reactivity was related to greater, rather than less, quitting success (in an unaided attempt). The other studies showed no association between cue reactivity and cessation outcome.

Conclusions: This limited research does not clearly support self-reported craving in response to smoking cues per se as a predictor of later quitting success. Lack of consistent results may partly be due to variability in methods of smoking cue assessment, type of cessation treatment, and duration of follow-up assessment. If it is to improve our understanding of an individual's ability to quit smoking, research on cue reactivity needs to show significant and reliable associations with subsequent long-term smoking behavior.

Introduction

Self-reported urge to smoke, or craving, is often acutely associated with a greater likelihood of smoking behavior (e.g., Bagot, Heishman, & Moolchan, 2007; Killen & Fortmann, 1997). Craving is enhanced by the presentation of stimuli associated with cigarette smoking availability (cues; Tiffany, Warthen, & Goedeker, 2009). Examples of such smoking cues include pictorial stimuli of a lit or unlit cigarette, an actual pack of the preferred brand, or photos of locations where smoking commonly occurs (e.g.,

Conklin, Perkins, Robin, McClernon, & Salkeld, 2010; Tiffany et al., 2009). However, greater self-reported urge to smoke in response to smoking (vs. control) cues, often called smoking cue reactivity, has been assumed to identify smokers less likely to later quit smoking because they may have more difficulty staying quit when they inevitably face smoking cues in the natural environment (Drummond, 2000). Yet, little research shows that acute craving in response to smoking cues predicts cessation outcome.

Research on drug use has long suggested that stimuli linked (e.g., via conditioning) to that use can become potent indicators of drug availability, increasing such use (Marlatt, 1990; Wikler, 1948). Perhaps consistent with this idea, the availability of tobacco in the environment, such as the presence of other smokers in the home, is often associated with lapse or relapse after a quit smoking attempt (e.g., Hawkins, Hollingworth, & Campbell, 2010; O'Connell, Shiffman, & DeCarlo, 2011). However, the notion that greater craving during laboratory testing of smoke cue reactivity can significantly predict later difficulty quitting may not have strong supportive evidence (e.g., Niaura et al., 1999).

The validity of acute smoking cue reactivity as a predictor of cessation success is important because the frequent use of this assessment (e.g., Drummond, 2000) may produce results of limited relevance to identifying individual differences in ability to quit smoking, even if it produces other findings of importance (Tiffany et al., 2009). Clarifying the implications of smoking cue reactivity may give useful directions to future clinical trial research. If such research clearly demonstrates that smokers high in cue reactivity are more likely to relapse or are less able to quit at all, even more research attention should be paid to this individual difference in an effort to understand and control the persistence of smoking behavior (and the resulting morbidity and mortality risks). Alternatively, if smoking cue reactivity is not reliably related to later quit success, this line of clinical research may be more productive if focused on understanding other characteristics of smokers who have greater difficulty quitting. Cue reactivity research may continue to explain other factors of interest (Conklin et al., 2010; Tiffany et al., 2009), but direct prediction of cessation outcome may not be one of them.

doi: 10.1093/ntr/ntr229

Advance Access published on December 1, 2011

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Relevant Research and Results

The primary objective of this commentary was to summarize clinical trial research on the association of subjective cue reactivity with subsequent success in quitting smoking. Of interest were trials predicting cessation outcome due to self-reported craving response to smoking cues, assessed during brief laboratory (i.e., controlled) testing prior to initiating the quit attempt. Five studies published prior to 2007 (and briefly noted in Perkins, 2009) were supplemented with a web search in the ISI Web of Knowledge database of studies published since 2006 with all three keywords “smoking,” “cues,” and “cessation.” That search resulted in 175 published studies, but most were aimed at acute factors associated with self-reported craving responses to smoking cues and did not predict later quitting success. One new published study was found in this search, resulting in six studies of longitudinal clinical trials relating cue reactivity to smoking cessation outcome.

As shown in Table 1, only one (Waters et al., 2004) of the six trials found that greater craving response to smoking cues (via unlit cigarette) predicted more difficulty initiating quitting and quicker smoking lapse if quitting did occur. This association was found only among smokers who were treated with the nicotine patch and not the placebo patch. Notably, unlike the others (Table 1), this study assessed cue reactivity on the quit day after patch application, rather than before attempting to quit. Results may thus better reflect cue reactivity while actually trying to quit. The other four studies published prior to 2010 failed to show that self-reported craving response to smoking cues predicted subsequent cessation. However, most did not compare responding to smoking cues versus a control condition (e.g., nonsmoking cues) in order to isolate smoking cue reactivity per se (e.g., Conklin et al., 2010). The most recent study (Powell, Dawkins, West, Powell, & Pickering, 2010; see erratum in Powell, Dawkins, West, Powell, & Pickering, 2011) reported results that were opposite of those expected (i.e., Waters et al., 2004), finding that greater reactivity to smoking cues was associated with better,

not worse, ability to quit smoking. Specifically, these authors found that greater reactivity to an unlit cigarette cue during acute placebo testing but not during acute nicotine lozenge testing was associated with better smoking cessation outcome during a subsequent unaided quit attempt.

Discussion

The lack of consistency in results among these trials suggests the need for clarification of the predictive validity of smoking cue reactivity. The most recent results, by Powell et al. (2010), clearly warrant replication because they suggest that greater reactivity may help rather than hinder an ability to quit smoking, contrary to past assumptions (Drummond, 2000) and the findings of the other significant trial (Waters et al., 2004).

On the other hand, the different procedures used to present smoking cues, assess craving, provide cessation treatment, and assess the duration of follow-up may make it difficult to compare results across these six studies (see Table 1). Most studies provided a lit or unlit cigarette (in vivo) as the smoking cue, while one provided instructions on imaginal cues. All assessed craving with a single item of urge to smoke rather than the multiitem Questionnaire on Smoking Urges (QSU; Tiffany & Drobes, 1991), which is related to abstinence status and to smoking cue exposure (e.g., Morgan, Davies, & Willner, 1999; Tiffany et al., 2009). However, other clinical research shows that craving assessed with a single item can also predict cessation outcome (e.g., Doherty, Kinnunen, Militello, & Garvey, 1995) and produces responses similar to the QSU (West & Ussher, 2010).

As far as cue assessment, three studies did not actually determine formal cue reactivity (i.e., compare responses to smoking cues per se) but measured only absolute craving levels during presentation of smoking cues. In other words, since absolute craving has been shown to predict cessation outcome

Table 1. Clinical Smoking Cessation Trials Examining Responses to Smoking Cues in the Laboratory as a Predictor of Later Quitting Success

Study	N	Cue type	Cue measure	Treatment	Cues and quitting success
Abrams, Monti, Carey, Pinto, and Jacobus (1988)	48	In vivo	One item	Counseling	NS after 6-month follow-up. Absolute craving, not CR.
Niaura, Abrams, Demuth, Pinto, and Monti (1989)	54	In vivo	One item	Counseling	NS after 3-month follow-up. Absolute craving, not CR.
Shadel et al. (1998)	183	Imaginal	One item	Self-help	NS after 1-month follow-up.
Waters et al. (2004; CR tested on quit day)	81	Unlit cig	One item	Nic patch	Lower CR = quit at 1 week.
	41	Unlit cig	One item	Plac patch	NS after 1 week.
Payne, Smith, Adams, and Diefenbach (2006)	62	In vivo	One item	Counseling	NS after 6-week treat period. Absolute craving, not CR.
Powell et al. (2010; results corrected in 2011 erratum CR tested twice, one week apart, in all 140)	140	Unlit cig, during plac	One item	No help, no meds	Higher CR = quit at 1 week, 1 month, and 3 months
		Unlit cig, during nic lozenge	One item	No help, no meds	NS at all follow-up points.

Note. Formal CR studies isolated smoking cue-related craving from nonrelated craving, while absolute craving studies did not. Significant CR predictions of cessation shown in bold. CR = cue reactivity; Plac = placebo.

(Doherty et al., 1995), smoking cue reactivity should control for other proximal causes of craving to clarify interpretation of craving responses to smoking cues per se (Conklin, Robin, Perkins, Salkeld, & McClernon, 2008; Tiffany et al., 2009). Cue reactivity can be isolated by comparing craving responses to smoking-related cues versus nonrelated or neutral cues (or with pre-session baseline craving).

Regarding cessation treatment, three studies examined non-medication counseling treatment, one tested nicotine versus placebo patch treatment (but no other medications) and two did not provide formal treatment but studied self-help approaches to quitting smoking. These six studies also varied in duration of cessation outcome assessments from 1 week to 6 months, and cue reactivity may relate to outcome during shorter cessation follow-up (Table 1).

Moreover, two studies associating cue reactivity with smoking cessation outcome (but in the opposite direction) differed from the other four studies by comparing reactivity or cessation as a function of nicotine versus placebo treatment. Waters et al. (2004) found that reduced cue reactivity after initial patch application predicted those better able to quit as a result of treatment with nicotine patch but not placebo. In contrast, Powell et al. (2010, but incorrect results reported; see erratum 2011) found that greater reactivity during acute placebo lozenge but not nicotine lozenge predicted later ability to quit (without any formal treatment). The non-nicotine U.S. Food and Drug Administration–approved medications of bupropion and varenicline have not been clearly shown to aid smoking cessation via reduction in cue reactivity. Yet, two recent studies of smokers not attempting to quit did show that both medications (compared with placebo) reduced subjective craving and affected brain activation in response to smoking cues (Culbertson et al., 2011; Franklin et al., 2011).

Greater consideration of medication effects during cue reactivity or cessation follow-up assessment may help determine whether and in which direction cue reactivity responses predict cessation outcome (Table 1). Providing medications during cessation treatment may lead to an association of reduced cue reactivity with quit success based on the nicotine patch results in Waters et al. (2004). On the other hand, Powell et al. (2010, 2011) found that greater cue reactivity during acute placebo lozenge (but not nicotine) predicted subsequent quit success during an unaided quit attempt. The latter outcome suggests that cue reactivity testing in the absence of medication better predicts cessation outcome during a nonmedication trial. In separate studies of unapproved medications in smokers not trying to quit, d-cycloserine, an NMDA agonist, was reported to reduce smoking cue reactivity but had no effect on amount of smoking behavior (Santa Ana et al., 2009). Similar results were seen for smoking cue reactivity in response to the dopamine antagonist olanzapine (Hutchison et al., 2004). These results may be inconsistent with the notion that medications may improve smoking cessation outcome due to their attenuation of smoking cue reactivity (although see Powell et al., 2011).

of intervening events that influence quitting success but are independent of the prior reactivity assessment. If so, cue reactivity assessment may predict short-term smoking behavior but not long-term cessation outcome. Yet, in a comprehensive study of 360 smokers, self-reported craving in response to smoking cues correlated only 0.24 with subsequent latency to initiate smoking when it was allowed, statistically significant but accounting for less than 6% of the variance (Tiffany et al., 2009). These authors concluded that cue reactivity responses on craving measures “cannot be used as a proxy for drug use” (p. 181). Similarly, in a study of smokers not trying to quit, smoking cue reactivity was only modestly related to subsequent weeklong smoking behavior, although an acute stressful imagery assessment was more strongly related to that smoking (Carpenter et al., 2009). In sum, research may not consistently show that cue reactivity per se strongly predicts subsequent acute smoking, at least in smokers not trying to quit.

The study by Powell and colleagues (Powell et al., 2010, 2011) suggests the intriguing possibility that greater cue reactivity may actually predict better ability to quit, the opposite of the association typically assumed (Drummond, 2000). These authors suggest that dopaminergic brain circuitry may mediate the salience of cues associated with smoking (see also Hutchison et al., 2004). Dopaminergic circuitry may be less active in heavier (and more dependent) smokers, helping explain why those less reactive to cues in testing also are later less able to stay quit, while lighter smokers may show greater reactivity during testing and then better cessation outcome under some conditions (Powell et al., 2011).

Other research on cue reactivity may be consistent with this counter-intuitive notion. In one study of 129 smokers, repeated treatment sessions involving extinction of smoking cues (an unlit cigarette) found that those more likely to report no change or an increase in craving across sessions subsequently had better quitting success than those reporting a decrease in craving across sessions (Niaura et al., 1999). The authors concluded that their results questioned the utility of extinguishing cue reactivity to aid smoking cessation. In other studies, greater cue reactivity was associated with a lower rather than higher level of dependence (Watson, Carpenter, Saladin, Gray, & Upadhyaya, 2010) and with lighter rather than heavier smokers tested on acoustic affective responses to smoking cues (Rehme et al., 2009). Moreover, imaging research has shown that neural activation of limbic regions during magnetic resonance imaging was greater when smokers were instructed to try to “resist” craving compared with when they were instructed to crave the cigarette (Brody et al., 2007).

Thus, one clear goal of future research on self-reported craving in response to smoking cues may be to clarify whether greater or lesser cue reactivity is reliably associated with smoking amount or cessation outcome. Results of such research may lead to a better understanding of factors that could aid or inhibit smoking cessation success and identify those in need of more intensive treatment efforts.

Future Research to Determine Clinical Utility of Cue Reactivity

Lack of consistent associations between smoking cue reactivity and subsequent cessation outcome may stem from a number

Funding

Preparation of this paper was supported by National Institutes of Health grant P50 CA143187.

Declaration of Interests

Dr. KAP has consulted with Cypress Bioscience on the development of smoking cessation medications unrelated to this paper.

Acknowledgments

This paper is based on comments presented as part of a symposium on smoking cue reactivity at the February 2011 meeting of Society for Research on Nicotine and Tobacco in Toronto, Canada.

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