Cue-Induced Cravings for Cigarettes

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Current Cardiovascular Risk Reports 2009, **3:**385–390
Current Medicine Group LLC ISSN 1932-9520

Cigarette craving is usually thought of as being a product of abstinence from smoking. However, cigarette craving can also be evoked through exposure to situational cues that are associated with tobacco use. Such cue-induced cravings can be reliably produced in laboratory settings, and in observational field studies, they have been found to influence smoking behavior. It is the latter finding that is perhaps most clinically relevant, as research indicates that cue-induced cravings are a contributing factor in a substantial proportion of smoking lapses during quit attempts. In this review, we examine the literature regarding smoking cue-induced craving. Particular focus is given to recent discoveries and to studies that have evaluated the effectiveness of smoking cessation interventions on treating cue-induced cravings.

Introduction

Among dependent smokers, cigarette craving is an almost universally reported symptom experienced during periods of abstinence. Craving has been defined in numerous ways [1], but the common thread with these definitions is that craving involves a strong, sometimes seemingly overwhelming desire to use a drug.

Clinically, the experience of craving is important to understand and, if necessary, to treat, primarily because craving has been found to impede cessation. Research shows that craving can be a barrier to cessation at crucial stages in the quit process. Even before starting a quit attempt, craving (or more correctly, the fear of craving) can impede cessation, with clinical experience suggesting that smokers' fear of experiencing craving is a reason for not attempting to quit. Furthermore, once a patient starts a quit effort, studies have found that the intensity of the craving experience can predict the outcome of the quit attempt [2–5]. These links between craving and cessation success, be it either a direct pathway or merely a proxy for other fears and/or symptoms of withdrawal, elevate the study of craving from an esoteric pursuit to one of clinical significance.

Among lay observers, cigarette craving is typically viewed as being the direct and simple result of nicotine abstinence. A typical physiologic model of craving would posit that smokers have become tolerant to the presence of nicotine, resulting in changes in the very physiology of the brain (eg, changes in the number and sensitivity of nicotinic receptors [6]) and, as a result of these changes, they crave nicotine when it is not available. Such a physiologic explanation of craving is supported by findings that link self-reported craving severity to blood nicotine levels (with craving increasing over time as blood nicotine levels fall [7]).

However, researchers have also found that craving can be induced without limiting access to nicotine. For example, studies show that craving varies even when smokers are smoking ad libitum [8]. Furthermore, quitters commonly experience short bouts of intense craving over the course of their attempt. Such volatility in craving is difficult to explain using a purely physiologic model of craving; if blood levels of nicotine were the only factor driving craving, then self-reported craving should be relatively consistent because circulating levels of nicotine drop in a predictable manner following the cessation of nicotine intake. A further challenge to the physiologic model of craving is that these fluctuations in craving can occur long after levels of nicotine have essentially reached zero [9].

Research has found that these episodic craving states are usually triggered by exposure to situational stimuli that may have become associated with smoking [10–14]. It is these phasic, cue-induced cravings that are the focus of this review.

The link between these situational stimuli and craving is thought to be established by learned association. These otherwise benign situational stimuli are thought to have come to induce craving through a history of repeated pairing with smoking [13]. Through this repeated pairing, the smoker brain comes to "learn" that the presence of certain stimuli signal that nicotine will soon be administered, and drug craving emerges as a result. Other researchers have reviewed the variety of theories that offer explanations for how this process of learning occurs [13]. In summary, all propose that this phenomenon requires repeated association between the stimulus and drug administration.

The most compelling evidence of a direct link between situational cues, or triggers, and craving comes from experimental laboratory studies. In a laboratory setting,

Table 1. Effect of various smoking cessation interventions on craving

Treatment	Effect on cue-induced cravings
Non-drug interventions	
Coping strategies	Hasten recovery / ?
Counseling	?
Behavioral extinction therapies	Reduce reactivity / ?
Non–nicotine-based pharmacologic interventions	
Bupropion	No effect / ?
Varenicline	No effect
Nicotine-based pharmacologic interventions	
Patch	No effect
Gum	Hasten recovery
Lozenge	Hasten recovery
Oral inhalator	?
Nasal spray	?

cue-induced cravings have been explored using cue reactivity studies, also called cue exposure studies [15–17]. Cue exposure studies typically use the following procedure. First, participants report their baseline level of craving. Next, they are exposed to a smoking-relevant stimulus (eg, manipulating a lit cigarette) [18], but some researchers have used nonphysical stimuli by either showing a smoker a picture of a smoking-related cue, having participants imagine a smoking-relevant cue, or, more recently, using virtual reality computer programs [19]. Following this provocation, craving is reassessed. The key finding from these types of studies is that exposing smokers to drug-related environmental stimuli reliably provokes drug craving [13,17,20,21••,22]. A number of more recent studies using brain imaging have also documented specific patterns of brain activation associated with cue-induced craving [23,24,25], suggesting that the smoking-related cues induce particular brain states.

Importantly, cue-induced cravings are linked to treatment outcome. The aforementioned laboratory studies demonstrated a causal connection between smoking-related cues and craving; however, for the clinical implications of cue-induced craving, we need to turn our attention to naturalistic studies of smokers' quit efforts. Numerous clinical studies have, using various methodologies, attempted to investigate the causes and antecedents of cigarette slips, or lapses, during a quit effort. These studies found that lapses are often attributed by patients to high levels of craving provoked by exposure to smoking-related stimuli [10,12,14,26], suggesting that cue-induced cravings were responsible for the smoking lapses. In one particularly detailed examination of the antecedents of smoking lapses [26], roughly half of first lapses during a quit attempt were associated with exposure to smoking cues, and many more were associated with other types of smoking-related cues (eg, eating and drinking, and stress). Together, these data suggest that many lapses are provoked by increases in craving resulting from exposure to smoking-related cues. Clinically, therefore, it would be useful if treatments existed that were capable of helping smokers deal with cue-induced cravings without lapsing back to smoking.

Treatment of Cue-Induced Cravings

Conceptually, an intervention could help a smoker survive a cue-provoked spike in craving in one of two ways: either by preventing a cue-induced craving from occurring or by increasing the speed by which the craving returns to pre-spike levels following the event (a "rescue" treatment). Ideally, a preventive intervention would lower, or eliminate, the intensity of the spike in craving that occurs following exposure to a smoking-related cue, in effect eliminating the experience of cue-induced cravings altogether. A rescue treatment, on the other hand, would not (necessarily) eliminate the experience or maximum severity of a cue-provoked craving but instead would aim to reduce the amount of time that patient has to endure the elevated levels of craving by increasing the rate at which the spike in craving dissipates.

The timing of the administration of the intervention itself dictates the impact it is likely to have on cue-induced cravings. If the treatment is administered prior to the cue-induced craving occurring, such as when receiving counseling or using a nicotine patch, it is likely that the treatment will be most beneficial in reducing the occurrence of a cue-induced craving in the first place. However, interventions that can occur after a cue-induced craving has been initiated (eg, reactive, immediate coping strategies or using nicotine gum) could be useful for reducing the duration of the episode (or perhaps even the maximum intensity of the event if the intervention occurred early enough) while not impacting the overall likelihood of the cue-induced craving occurring in the first place.

Unfortunately, of the panoply of interventions that have been developed to help smokers achieve cessation, few have been evaluated in terms of their ability to either prevent cue-provoked cravings or hasten recovery from them. In the following text, we have summarized what is known about the effect of various smoking cessation interventions on cue-induced craving. For the sake of this discussion, treatment options that are available to smokers can be grouped into three broad categories: non-drug interventions, nicotine-based pharmacotherapies, and non–nicotine-based pharmacotherapies (Table 1). We examine interventions within each of these classes of treatment.

Non-drug interventions

Behavioral extinction therapy

Non-drug interventions have arguably received the fewest systematic evaluations in terms of their effects on cue-induced cravings. This is particularly surprising when one considers behavioral extinction therapies [27], which

were originally developed to break the conditioned associations between environmental stimuli and smoking behavior. Typically, behavioral extinction therapies involved repeatedly exposing a patient to drug-related cues (either in vivo or using the guided imagery procedures) without the coadministration of nicotine, the goal of which was to break the learned association between these cues and smoking. Despite being in regular use for the treatment of addictive drugs for over three decades [28], there is little evidence that behavioral extinction therapies can decrease cue-induced cravings. However, for the most part, this is a case of lack of evidence as opposed to evidence of non-effect. The studies that have been conducted to evaluate behavioral smoking extinction therapies have focused on their effect on cessation rather than on whether they impact the experience of cue-induced cravings [27]. Outside the cigarette smoking literature, we know of one study of cue exposure in cocaine users that examined the effect of treatment on cue reactivity [29]. Over the course of repeated behavioral extinction sessions, cue-induced craving could be reduced in cocaine users; however, outside the laboratory, patients who showed no reactivity in the laboratory still reported experiencing cue-induced cravings in their daily lives. This finding suggests that cue-exposure may reduce reactivity but only in a very specific context [30]. Research into these treatments is ongoing [31,32], but for the moment, no data exist that suggest these treatments may be useful in the treatment of cue-induced cravings.

Cognitive and behavioral therapy

One non-drug intervention that has shown promise in the treatment of cue-induced cravings is the use of cognitive and behavioral coping strategies during a quit attempt. Quit studies have found that high-risk "relapse crisis" situations are more likely be to survived without lapsing if a patient reports using a coping strategy during the experience [11,14,26]. The type of coping appears to be irrelevant, as both cognitive (eg, relaxation techniques) and behavioral (eg, changing location, taking part in a distracting activity) coping responses appear to be equally effective at helping patients to avoid lapsing during these highly tempting situations [33]. Although these findings suggest that coping strategies are useful for dealing with cue-induced cravings, they do not shed light on how coping mechanisms convey this benefit. It is possible that utilizing a coping intervention helps to increase the speed with which craving returns to its normal levels, a mechanism that has found some support in the literature [34]. However, it is also plausible that coping interventions do just that—they help patients to cope with the experience of a cue-induced craving while not directly impacting on the magnitude or the duration of these cravings. Detailed research is required in order to determine the exact mechanism.

Quit smoking advice and/or counseling

We could not find studies that had evaluated the effect that quit smoking advice and/or counseling has on the experience of cue-induced craving. It is possible that these interventions have an independent effect on cue-reactivity (ie, that they directly reduce the intensity of cue-induced cravings) or they promote the use of alternative interventions (eg, coping strategies), which in turn impact the experience of cue-induced cravings. However, additional research is needed to determine if either of these proposed mechanisms is accurate.

Non–nicotine-based pharmacologic interventions

There are currently two non–nicotine-based pharmacologic interventions that are approved by the US Food and Drug Administration for the treatment of nicotine dependence: bupropion and varenicline. Both compounds are effective at helping patients quit smoking [35]. As both bupropion and varenicline are steady-state treatments (with patients typically dosing twice per day), research has focused on whether these treatments can prevent the occurrence of cue-induced craving (as opposed to the speed of recovery from them).

Bupropion

One study systemically tested the effect of bupropion on cue-induced cravings. In a laboratory-based cue-reactivity study, patients on bupropion (300 mg/d) showed just as much cue-induced craving as patients taking a placebo, suggesting that active bupropion does not guard against the experience of cue-induced cravings [36]. A second small, open-label preliminary study conducted in a similar fashion found that patients treated with bupropion had smaller increases in craving and smaller changes in brain activation after provocation with a smoking-related cue compared with untreated patients [37]; however, the interpretation of this finding is difficult because the treatment and control groups differed in terms of the length of abstinence they had achieved prior to testing [38]. Thus, the evidence suggests that bupropion likely does not reduce the experience of cue-induced craving. Additional studies are warranted to confirm this conclusion, however.

Varenicline

Varenicline, a mixed nicotinic receptor agonist/antagonist, is the newest arrow in the quiver for smokers seeking cessation. Although it appears to be highly efficacious [35], like bupropion, varenicline does not appear to guard against the experience of cue-induced cravings. In the one cue exposure study that has tested the drug, varenicline did not protect participants against a spike in craving following cue provocation [39]. Thus, current data do not indicate that varenicline reliably reduces or protects against cue-induced cravings.

Nicotine-based pharmacologic interventions

Nicotine replacement therapies (NRTs) come in a number of forms (patch, gum, lozenge, oral inhalator, and nasal spray), all of which have been proven to increase quit rates [35,40]. In terms of examining the effect of each form of

NRT on cue-induced craving, it is useful to divide the products into two groups based on dosing schedule: the nicotine patch (the only NRT that is designed for once-daily dosing) and all other forms (which are designed to be administered at multiple times over the course of the day). This distinction is useful for two reasons. First, the pharmacokinetic profile of the two classes of NRT products is very different [41]. Secondly, the dosing of the products in relation to cue-induced cravings differs. Only the multiple-dosing forms of NRT have the potential to be used as acute "rescue" medications to help relieve acute cravings after they have been induced.

Nicotine patch

Five cue reactivity studies have found that a nicotine patch does not protect smokers from cue-induced cravings [42–46]. In each case, an active patch had no effect on cue-induced cravings provoked by exposure to smoking-related cues or on the rate at which the craving dissipated [45]. Thus, the nicotine patch literature suggests that it is not an effective treatment for cue-induced cravings. Interestingly, however, a study that compared patients on a 24-hour nicotine patch to those on a 16-hour patch found that the 24-hour patch significantly reduced the occurrence of "temptation" episodes (characterized by spikes in craving) [47]. One interpretation of this finding, in light of the laboratory findings mentioned earlier, is that a nicotine patch may have no effect on relatively strong, direct smoking cues (ie, the types of smoking cues that are used in cue-reactivity experiments), but it may prevent responses to more subtle cues from growing to the level of a temptation episode. Further research is needed to evaluate this hypothesis.

Other NRTs

Other NRTs that are designed to be dosed multiple times per day have the potential to be used as rescue medications (ie, to be taken after the onset of a cue-induced craving with the aim of hastening the reduction in craving to pre-spike levels). To assess the effectiveness of oral NRT in regard to this task, researchers again turned to cue-reactivity experiments. After provocation with a smoking cue, participants were instructed to use a piece of gum or a lozenge, and their craving was then monitored over time. The evaluation of a rescue medication strategy assesses the speed with which craving is reduced over time following administration of the intervention. Using such a design, researchers have found that both nicotine gum [48,49] and a nicotine lozenge [50] can increase the speed with which cue-induced craving is reduced following provocation compared with placebo. These findings suggest that both gum and lozenge can assist smokers in recovering from a cue-induced craving. No studies have tested the other acute-dose NRT products; however, given that the pharmacokinetics of the oral nicotine inhaler [41] and the nicotine nasal spray [51] resemble that of nicotine gum, it seems plausible that these products will also prove effective at reducing cue-induced craving.

Conclusions

This review examined cue-induced cigarette cravings. The clinical relevance of cue-induced cravings was established by reviewing data that suggest cue-induced cravings are associated with lapses of smoking after quitting. We then examined which among the currently available smoking cessation interventions were effective in treating cue-induced cravings. We could find no evidence that any currently available smoking cessation intervention was effective at reducing the occurrence of cue-induced cravings, although there is some suggestion that a nicotine patch may help when patients are exposed to particularly mild smoking-related cues. Acutely administered nicotine medications, such as nicotine gum and lozenges, however, did demonstrate promise as rescue medications, given their ability to rapidly relieve cue-induced cravings. The clinical relevance of these findings is unknown, but helping to reduce the duration of time during which smokers are exposed to an intense cue-induced craving would seem likely to impact on the likelihood that the smoker would lapse. Further research is needed to confirm this.

In summary, the available evidence, collected over a number of years and across a range of difference types of studies, suggests that cue-induced cravings are important for understanding the occurrence of smoking relapse. Given what is currently known about the relationship between the occurrence of cue-induced cravings and the outcome of smoking cessation attempts, patients should be encouraged to utilize interventions. These interventions can include coping strategies and/or acutely administered NRT products (eg, gum or lozenges) as part of the cessation attempt in order to reduce the likelihood that experiencing such cravings will result in the resumption of smoking.

Acknowledgment

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Disclosure

Dr. Ferguson serves as a consultant to GlaxoSmithKline Consumer Healthcare on an exclusive basis regarding matters relating to smoking cessation through his work at Pinney Associates.

Dr. Shiffman serves as a consultant to GlaxoSmithKline Consumer Healthcare on an exclusive basis regarding matters relating to smoking cessation through his work at Pinney Associates. He also has a financial interest in a venture to develop a new rapid-delivery nicotine replacement medication.

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