Brain imaging studies examine how anti-smoking medications may curb cravings

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The smoking cessation medications bupropion and varenicline may both be associated with changes in the way the brain reacts to smoking cues, making it easier for patients to resist cravings, according to two reports posted online today that will appear in the May print issue of *Archives of General Psychiatry*.

"Environmental cues associated with nicotine reinforcement induce cigarette craving, which propagates smoking habits in smokers and relapse in abstinent individuals," the authors write as background information in one of the articles. "Human brain imaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography scanning have provided insight into brain regions associated with cue-induced cigarette craving. Nicotine-dependent smokers exhibit activation in brain regions related to attention (prefrontal cortex), emotion (amygdala), reward (ventral tegmental area) and motivation (striatum) while viewing cigarette-related cues."

Bupropion, originally marketed as an antidepressant, was found to enhance smoking cessation in patients with depression and is now one of the most common therapies for smoking cessation in the world. It is known to reduce cravings in response to smoking cues, but its mechanism for doing so is not well understood. In one study, Christopher S. Culbertson, Ph.D., of University of California, Los Angeles, and colleagues assessed changes in brain activation in response to smoking cues among 30 smokers who were randomly assigned to take either bupropion or placebo for eight weeks.

Participants underwent fMRI scans within one week of joining the study and again at the end of the eight-week treatment period. During the scans, they were shown 45-second videos that contained either smoking cues-actors and actresses smoking in a variety of settings-or neutral cues, with similar settings but no smoking behaviors. Participants also used a response box with five buttons on it to report how strongly they craved cigarettes immediately after watching each video.

Patients who were treated with bupropion reported less craving in response to smoking cues than did patients who received placebo. Those taking bupropion also showed reduced activation in areas of the brain known to be associated with cravings, including limbic and prefrontal regions. Among all the participants, regardless of treatment, reports of cravings aligned with fMRI images-that is, those who showed reduced activation in craving-related areas also reported feeling fewer cravings.

"These results demonstrate that treatment with bupropion is associated with an improved ability to resist cue-induced craving and a reduction in cue-induced activation of limbic and prefrontal brain regions," the authors conclude.

In another article, Teresa Franklin, Ph.D., of University of Pennsylvania, Philadelphia, and colleagues studied brain responses to varenicline, a first-line smoking cessation medication. Varenicline reduces withdrawal symptoms and the reinforcement received from nicotine while smoking. The researchers studied whether it would also aid in reducing brain and craving responses when smokers are exposed to smoking cues. They used a neuroimaging technique called perfusion fMRI, which allows the measurement of longitudinal changes induced by a medication during smoking cue exposure and also in the brain in the resting condition.

Twenty-two smokers received either varenicline or placebo in a three-week randomized medication regimen. The brains of smokers were

imaged before and after the medication regimen, while 'at rest' and while viewing 10-minute video clips that contained either smoking cues or non-smoking cues, and they also reported their cravings. Smokers were still smoking during the medication regimen to explicitly examine varenicline effects on cue reactivity independent of withdrawal, which also affects brain activity.

In scans performed before the medication regimen, smoking cues activated brain areas involved in drug-motivation, such as the ventral striatum and medial orbitofrontal cortex, and also elicited reports of craving. After the medication regimen, similar patterns of activity persisted in patients who had taken placebo, whereas those who received varenicline experienced a reduction in brain activity in those regions and in self-reported craving.

In participants who took varenicline, brain activity in the resting condition was selectivity increased in a region known as the lateral orbitofrontal cortex, which is implicated in inhibiting behavior that predicts reward (such as smoking cues). Importantly, increased activation in this area predicted the blunted response in the medial orbitofrontal cortex and ventral striatum, explicitly demonstrating the mechanism underlying varenicline's property to reduce the effects of smoking cues on both the brain and craving.

"The results of our study reveal a distinctive new action that likely contributes to its clinical efficacy," the authors conclude. "Unsuccessful smoking cessation is more prevalent in individuals with psychiatric illness, suggesting that they have greater difficulty quitting. Varenicline and other medications that can reduce both withdrawal and cue reactivity may be of special benefit to these subgroups who may also be more vulnerable to relapse in the presence of smoking cues."

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